

# STUDIENKURZPROTOKOLLE

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## Impressum

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(siehe Seite 2!)

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## Arbeitsgruppe CUP-Syndrom

### CUP – palliative Therapie, 1st-line

**AIO-CUP-0117/ass: A Phase II, Active-Controlled, Multicenter Study Comparing The Efficacy & Safety of Targeted Therapy or Cancer Immunotherapy Guided by Genomic Profiling vs. Platinum Based Chemotherapy in Patients with Cancer of Unknown Primary Site who Have Received Three Cycles of Platinum Doublet Chemotherapy, MX39795**

#### AIO-assozierte Studie

Studiennummer:	AIO-CUP-0117/ass - CUPsequential
Status:	in Rekrutierung
Rekrutierungszeitraum	2017 – 2019
Weitere Zentren:	Ggfs. auf Anfrage
Letzte Aktualisierung	Oktober 2017

Art der Studie:	randomisierte Phase-II-Studie
Verantwortlicher Studienleiter nach AMG	Prof. Dr. Alwin Krämer
Kontaktadresse/ Kontaktperson:	Prof. Dr. Alwin Krämer Klinische Kooperationseinheit Molekulare Hämatologie/Onkologie Deutsches Krebsforschungszentrum und Medizinische Klinik V, Universität Heidelberg Im Neuenheimer Feld 581, 69120 Heidelberg Tel: +49-6221-42-1440 Fax +49-6221-42-1444.
Studienziele	Primary Endpoint: PFS - Progression Free Survival (from randomization to first occurrence of disease progression) Secondary Endpoints: Overall survival (OS), Overall Response Rate (ORR), Duration of Clinical Benefit (DCB)
Patientenzahl	790 patients.
Rekrutierung	Start: 2017
Weitere Zentren erwünscht?	Anfragen ggfs. an Prof. Krämer
Einschlusskriterien	<ul style="list-style-type: none"> <li>• Histologic or cytologic proven, non-resectable carcinoma of unknown primary (adenocarcinoma or poorly differentiated carcinoma or squamous cell carcinoma)</li> <li>• Measurable tumor lesion(s) according to RECIST criteria</li> <li>• WHO PS 0 to 1</li> <li>• Signed written informed consent</li> <li>• ≥18 years of age</li> <li>• Sufficient tumor tissue sample (for NGS-testing)</li> <li>• No prior lines of chemotherapy</li> <li>• Life expectancy &gt;= 12 weeks</li> <li>• Effective contraception for both male and female subjects if the risk of conception exists</li> <li>• Adequate hematologic and organ function</li> </ul>
Ausschlusskriterien	<ul style="list-style-type: none"> <li>• CNS-metastases or leptomeningal disease</li> </ul>

	<ul style="list-style-type: none"> <li>• Spinal cord compression not definitely treated</li> <li>• Non epithelial cancer</li> <li>• Patients belonging to subsets of CUP with good prognosis: <ul style="list-style-type: none"> <li>○ Women with axillary node metastasis as predominant tumor site</li> <li>○ Women with papillary adenocarcinoma of the peritoneal cavity</li> <li>○ Men with poorly diff. ca. with midline distribution</li> <li>○ Squamous cell carcinoma in cervical lymph nodes</li> <li>○ Poorly diff. neuroendocrine tumors</li> <li>○ Men with blastic bone metastases and elevated PSA</li> <li>○ Isolated inguinal adenopathy</li> <li>○ Single, potentially resectable tumor site</li> </ul> </li> <li>• Investigational agents or participation in clinical trials within 28 days before treatment start in this study</li> <li>• Clinically relevant coronary disease, renal disease, (dialysis), HIV, active tuberculosis, major surgery within 4 weeks before study entry, severe allergic reaction to study drugs</li> </ul>
Therapieschema	<ul style="list-style-type: none"> <li>• 3 cycles platinum doublet (carboplatin/paclitaxel or cisplatin/gemcitabine) (During this time: molecular genomic profiling)</li> <li>• If CR, PR, SD: randomize 3:1: molecular guided therapy or inv. choice vs. platinum doublet continuation</li> <li>• If PD: molecular guided therapy or inv. choice</li> </ul>
Tumorevaluierung	According to RECIST-criteria 1.0

## Arbeitsgruppe Endokrine Tumoren

### Nebennierenrindenkarzinom – adjuvante Therapie

#### Adjuvante Mitotanetherapie bei Patienten mit Nebennierenkarzinom und niedrigem/mittlerem Rezidivrisiko (ADIUVO-Studie)

##### AIO-assozierte Studie

Studiennummer/-Code:	ADIUVO
Status:	in Rekrutierung
Rekrutierungszeitraum	2011 - 2020
Weitere Zentren:	leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Studiendesign	Randomisierte, prospektive, kontrollierte, nicht-geblindete Multicenterstudie
Studienleiter:	Prof. Massimo Terzolo University Hospital of Turin, Italien terzolo@usa.net
Internat. Studienkoordinator	Prof. Dr. Martin Fassnacht (Leiter d. klin. Studie Deutschland) Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie Universitätsklinikum Würzburg Oberdürrbacherstr. 6, 97080 Würzburg Tel 0931-201-39021, Fassnacht_m@ukw.de
Statistiker	Prof. Gianni Ciccone, University of Turin, Italy Prof. Dr. Hans-Helge Müller, LMU München, Germany
Protokoll-Komitee:	Massimo Terzolo, Alfredo Berruti, Martin Fassnacht, Eric Baudin, Harm Haak
Sponsor	Universität Turin, Italy
Ziel	Beleg der Effizienz einer adjuvanten Mitotane-Therapie in Bezug auf Verlängerung des erkrankungsfreien Überlebens bei Patienten mit Nebennierenkarzinom mit niedrig bis mittlerem Rezidivrisiko.
Teilnehmerzahl	200 Patienten (100 in jeder Gruppe) Eingeschlossene Patienten: 78 (Stand Oktober 2017)
Rationale	Mitotane hat sich in den letzten Jahren zur Standardtherapie bei Patienten mit Nebennierenkarzinom entwickelt. Dies gilt auch bei Patienten mit komplett reseziertem Tumor. Es ist allerdings unklar, ob wirklich alle Patienten von einer solchen (nebenwirkungsbehafteten) Therapie profitieren. Aus diesem Grund wird der Stellenwert der Mitotanetherapie in diesem speziellen Studienkollektiv der „Niedrig-Risiko-Patienten“ untersucht.
Studiendauer	Januar 2011 - 2020
Weitere Zentren erwünscht:	Nein Aktueller Stand der Studienzentren: Berlin, Dresden, Düsseldorf, Hamburg, München, Würzburg
Einschlusskriterien	<ul style="list-style-type: none"> <li>• Histologisch gesichertes Nebennierenrinden Karzinom (NN-Ca)</li> <li>• Z.n. kompletter Resektion des Tumors ohne Hinweis auf Fernmetastasen</li> <li>• Niedriges/mittleres Rezidivrisiko definiert als: histologisch belegte komplette Resektion (R0) und Ki67 <math>\leq</math> 10%</li> <li>• Akzeptabler körperlicher Zustand (ECOG performance status 0-2)</li> </ul>

	<ul style="list-style-type: none"> <li>• Alter &gt; 18 Jahre</li> <li>• Adäquate Knochenmarksreserve</li> <li>• Effektive Kontrazeption bei Männern und bei prämenopausalen Frauen</li> <li>• Vorliegen der unterschriebenen Patienteneinverständnis</li> </ul>
Ausschlusskriterien	<ul style="list-style-type: none"> <li>• Zeitraum zwischen Operation und Randomisierung &gt; 3 Monate</li> <li>• Operation wegen Rezidiv des NN-Ca</li> <li>• Nachweis einer autonomen adrenocorticalen Hormonproduktion (auch ohne Nachweis der Erkrankung in der Bildgebung)</li> <li>• Eigenanamnese anderer Neoplasien mit Ausnahme definitiv kurerter Malignome mit einer mehr als 3 Jahre dauernden erkrankungsfreien Zeit</li> <li>• Frühere Therapie mit Mitotane oder andere Tumorthérapien für das NN-Ca (incl. Bestrahlung)</li> <li>• Gravierende Niereninsuffizienz oder Lebererkrankung</li> <li>• Schwangerschaft oder Stillen</li> <li>• Andere schwerwiegende klinische Situationen, die nach Einschätzung des lokalen Untersuchers den Patienten einem erhöhten Risiko aussetzen</li> </ul>
Endpunkte	<p>Primärer Endpunkt: Rezidivfreies- und erkrankungsfreie Überleben</p> <p>Sekundäre Endpunkte:</p> <ul style="list-style-type: none"> <li>• Quality of life (Lebensqualität)</li> <li>• Gesamtüberleben</li> <li>• Toxizität (nach NCI-CTC-Kriterien)</li> </ul>
Behandlungsplan	<p>Patienten erhalten randomisiert:</p> <p>I) Orale adjuvante Mitotanegebe (Dosistrierung nach Blutspiegel (Ziel 14-20 mg/l) und Verträglichkeit für 2 Jahre</p> <p>II) Keine adjuvante Therapie</p> <p>Evaluation mittels CT/MRT von Abdomen und Thorax bis zum Nachweis eines Rezidivs bzw. Ende der Studie: in den ersten 2 Jahren alle 3 Monate, im Jahr 3+4 alle 6 Monate, danach jährlich.</p>
Statistische Analyse	<p>Die Auswertung des primären Endpunkts erfolgt als "Intention-to-treat" Analyse. Für jede Studiengruppe wird das Rezidiv-freie-, erkrankungsfreie- und das Gesamtüberleben anhand der Kaplan-Meier-Methode berechnet. Mittels Cox's Proportional Hazardmodell werden die Hazard Ratios mit 95% Konfidenzintervallen berechnet. Die konfirmatorische Analyse erfolgt hierarchisch für die o.g. Überlebenszeiten jeweils mit einem Signifikanzlevel von 0.05. Der Zeitpunkt der Hauptanalyse erfolgt nach 96 Events (Rezidive). Bei signifikanten Ergebnissen erfolgt eine verlängertes Follow-up für weitere 4 Jahre um robuste Gesamtüberlebensdaten zu erhalten. Zwei Interimanalysen ohne (alpha-spending) sind geplant.</p>
Studiendauer	9 Jahre
Deutsche Studienzentren	<p>Berlin: Klinische Endokrinologie, Charite, Campus Mitte</p> <p>Dresden: Medizinische Klinik III, Universitätsklinikum</p> <p>Hamburg: ENDOC Praxis</p> <p>München: Medizinische Klinik IV, Klinikum der Universität München</p> <p>Würzburg: Medizinische Klinik I, Universitätsklinikum</p>
Unterstützung der Studie	<ul style="list-style-type: none"> <li>• European Network for the Study of Adrenal Tumors (ENSAT)</li> <li>• Arbeitsgemeinschaft Internistische Onkologie (AIO) – AG Endokrine Tumoren</li> <li>• Förderung durch die Europäische Union im Rahmen des FP-7 Programms</li> </ul>

Malignes Phäochromozytom / Paragangliom – palliative Therapie**First International Randomised Study in Malignant Progressive Pheochromocytoma and Paraganglioma (FIRST-MAPPP) – Sunitinib vs. Placebo****AIO-assozierte Studie**

Studiennummer/-Code:	FIRST-MAPP
Status:	in Rekrutierung
Rekrutierungszeitraum	2011 - 2018
Weitere Zentren:	leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Art der Studie	Randomisierte, prospektive, kontrollierte, placebo-kontrollierte, doppelgeblindete Multicenterstudie
Sponsor	Institut Gustav Roussy, Villeneuve, Frankreich
Studienleiter:	Prof. Eric Baudin Institut Gustav Roussy, Villeneuve, Frankreich
Kontaktadresse/ Kontaktperson:	Prof. Dr. med. Martin Fassnacht (Leiter der klinischen Prüfung) Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie Universitätsklinikum Würzburg Oberdürrbacherstr. 6, 97080 Würzburg Tel 0931-201-39021, Fassnacht_m@ukw.de
Studienziele	<b>Primäres Studienziel:</b> <ul style="list-style-type: none"> <li>• Progressionsfreies Überleben</li> </ul> <b>Sekundäre Studienziele: (Auswahl)</b> <ul style="list-style-type: none"> <li>• Overall Survival</li> <li>• Quality of life (Lebensqualität)</li> <li>• Gesamtansprechrate, Dauer des Ansprechens</li> </ul>
Patientenzahl	Mehrstufiges Studiendesign mit 34 bis 144 Patienten Aktuell (Okt 2017: 68)
Rationale	Aktuell gibt es keinerlei zugelassene Medikation zur Behandlung des metastasierten Phäochromozytoms. Präklinische Daten und einige Case Reports lassen Sunitinib als vielversprechende Substanz erscheinen, die nun in einer weltweit ersten randomisierten Studie getestet werden soll.
Für weitere Zentren offen:	Nein
Studienstart:	Dezember 2011 (Frankreich), Juni 2013 (Deutschland)
Einschlusskriterien	<ul style="list-style-type: none"> <li>• Unequivocal diagnosis of malignant PPGL</li> <li>• Metastatic disease not amenable to radical surgical resection</li> <li>• Evaluable disease according to RECIST 1.1 criteria</li> <li>• Progressing disease within 18 months prior to randomisation according to RECIST 1.1</li> <li>• Age <math>\geq</math> 18 years</li> </ul>
Ausschlusskriterien	<ul style="list-style-type: none"> <li>• History of prior malignancy</li> <li>• Severe renal or hepatic insufficiency, or bone marrow impairment</li> <li>• Major cardiovascular events within the last 12 months</li> <li>• Uncontrolled hypertension despite therapy</li> <li>• Prior systemic treatment with any tyrosine kinase inhibitors or anti VEGF angiogenic inhibitors. However, patients who have received other</li> </ul>



	systemic therapies such as 131-I-MIBG or cytotoxic therapies are accepted.
Therapieschema	Patienten erhalten randomisiert: <ul style="list-style-type: none"> <li>• Sunitinib 37.5 mg oral einmal täglich</li> <li>• Placebo</li> </ul>
Tumorevaluierung	Die Evaluation des Ansprechens erfolgt alle 12 Wochen.
Statistik	<p>PPGL is a rare disease which lacks a therapeutic gold standard. This clinical dilemma calls for a placebo controlled trial that is, however, challenged by limitations of patient recruitment. To meet these requirements a seamless phase IIa/IIb study design will be applied: Two interim analyses with futility stop rules (considering efficacy of therapeutic intervention as well as study feasibility based on patient accrual) will dictate the flow of the trial. This design avoids prolonged recruitment in order to reach statistical power, while enabling sufficient patient accrual within a reasonable timeframe for an evidence-based medicine approach to improving the care and treatment of patients with malignant PPGL.</p> <p><b>Efficacy:</b> The 12 months-PFS and PFS time will be assessed on the Intent to Treat population and data set will be based upon central imaging review.</p> <p><b>Description of the primary efficacy:</b></p> <p><b>Phase IIa:</b> The optimal two-stage design [Simon, Controlled Clinical Trials 1989] has been adopted (<math>\alpha=10\%</math>, power = 90%). We assume a gain of 20% in PFS (from 20% to 40%) at 12 months upon sunitinib treatment. In the first stage, 34 patients will be randomised with 17 in each group. If 4 or more patients of the sunitinib group (<math>n=17</math>) are without progression at 12 months, 40 additional patients will be randomised to achieve a total number of 74 patients (37 in each group). If 11 or more patients in the sunitinib group show no progression at 12 months, sunitinib will be considered effective (Simon design conclusion)</p> <p><b>Phase IIb:</b> At the time of the second interim analysis (12 months after recruitment of the 74th assessable patient) two conditions have to be fulfilled to continue the trial as a phase III trial: the first 74 patients have been enrolled in <math>\leq 58</math> months and hazard ratio (HR) for PFS <math>\geq 1.33=1/0.75</math> (placebo vs. sunitinib). For the statistical analysis, for both groups the median PFS will be estimated using the Kaplan-Meier method. The two-sided logrank test at a 0.05 significance level will be used to test the PFS time null hypothesis assuming proportional hazards. For the HR a point estimate and a 95% confidence interval will be provided. To detect a clinically meaningful HR of <math>1.667=1/0.60</math> with a power of 80%, 123 observed events are needed by use of an optimised group sequential design incorporating a futility stop. Thus at least 144 patients are required. When assuming a drop-out rate of <math>&lt; 10\%</math> 144 - 150 patients have to be randomised.</p> <p><b>Safety:</b> Adverse and serious adverse events will be assessed using standard descriptive statistical methods. 24-h blood pressure profiles will be compared between the two groups (analysing each patient baseline vs. on treatment).</p> <p><b>Secondary endpoints:</b> Analysis of Quality of Life, objective tumour response rate, and overall survival will be descriptive.</p>
Deutsche Studienzentren	Berlin: Klinische Endokrinologie, Charite, Campus Mitte Dresden: Medizinische Klinik III, Universitätsklinikum Lübeck: Universitätsklinikum, Medizinische Klinik München: Medizinische Klinik IV, Klinikum der Universität München Würzburg: Medizinische Klinik I, Universitätsklinikum
Unterstützung der Studie	<ul style="list-style-type: none"> <li>• Bundesministerium für Bildung und Forschung (BMBF)</li> <li>• Förderung durch die Europäische Union im Rahmen des FP-7 Programms (European Network for the Study of Adrenal Tumors (ENSAT-CANCER))</li> <li>• Sunitinib und Placebo werden von der Firma Pfizer zur Verfügung gestellt</li> <li>• Arbeitsgemeinschaft Internistische Onkologie (AIO) – AG Endokrine Tumoren</li> </ul>

Metastasiertes Schilddrüsenkarzinom - Zweitlinientherapie

**AIO-ENC-0316/ass: A phase II study exploring the safety and efficacy of nintedanib (BIBF1120) as second line therapy for patients with either differentiated or medullary thyroid cancer progressing after first line therapy ( EORTC protocol 1209-EnTF)**

**AIO-assozierte Studie**

Studiennummer/-Code:	AIO-ENC-0316/ass / EORTC protocol 1209-EnTF
Status:	in Rekrutierung
Rekrutierungszeitraum	2016 - 2018
Weitere Zentren:	leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Martin Fassnacht (Leiter d. klin. Studie Deutschland) Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie Universitätsklinikum Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg Tel 0931-201-39021, Fassnacht_m@ukw.de
Gesamtstudienleiter	Prof. Dr. Martin Schlumberger, Institute Gustave Roussy, Frankreich
Studienziele/ Objectives	The primary objective is to explore the efficacy of nintedanib (as measured by progression free survival) as second line therapy for patients with either differentiated or medullary thyroid cancer progressing after first line therapy. Primary end-point ◆ Progression free survival (RECIST 1.1) Secondary end-points ◆ Response Rate (RECIST 1.1) ◆ Toxicity profile ◆ Duration of response ◆ Exploration of the molecular mechanisms of action of drug Safety CTCAE version 4.0 will be used for adverse event reporting
Studiendesign	Randomized blinded, placebo controlled phase II trial. A 2:1 randomization in favor of the experimental arm will be used in both subpopulations: differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC)
Patientenzahl Number of patients	Geplant: DTC: 75 Patienten (DTC Arm komplett rekrutiert) MTC: 68 Patienten
Rekrutierungszeitraum von/bis	Seit 2015, in Deutschland seit Sept. 2016 Rekrutierung DTC-Arm beendet Rekrutierung MTC-Arm voraussichtlich bis Ende 2018
Weitere Zentren?	Nein
Haupt-Einschlusskriterien / Key inclusion criteria	◆ Histologically confirmed differentiated or medullary thyroid cancer by local pathologist. ◆ Available tumor tissue at the time of initial diagnosis for histology review. The provision of tumor tissue for histology review is mandatory for every site. ◆ Locally advanced or metastatic disease deemed incurable by surgery, radiotherapy and/or RAI. ◆ No current symptomatic brain metastases ◆ Patients must have measurable lesion with documented progression during the 12 months prior to randomization, according to RECIST V.1.1.

- ◆ Patients must have received one or 2 prior line of treatment (but no more than two) and must be off treatment for at least 4 weeks prior to randomization. For patients with MTC If it is available and reimbursed in the respective country one of the prior lines of treatment needs to be with Vandetanib as long as there is no contraindication or the patient refuses the treatment with Vandetanib.”
- ◆ Age  $\geq 18$  years
- ◆ Performance status (PS) 0-1
- ◆ Life expectancy of more than 12 weeks
- ◆ No history of other malignancy within the last 5 years, except for adequately treated carcinoma in situ of the cervix or basal cell or spinocellular carcinoma of the skin
- ◆ No ongoing treatment related toxicity due to prior treatment  $>$ grade I (except alopecia).
- ◆ Adequate organ function, evidenced by the following laboratory results within 3 weeks prior to randomization:
  - ◆ Absolute neutrophil count  $> 1500$  cells/mm<sup>3</sup>
  - ◆ Platelet count  $> 100,000$  cells/mm<sup>3</sup>
  - ◆ Hemoglobin  $> 8.5$  g/dL
  - ◆ Total bilirubin within normal limits
  - ◆ SGOT (AST), SGPT (ALT), and alkaline phosphatase  $\leq 1.5 \times$  ULN (or  $\leq 2.5 \times$  ULN in the case of presence of liver metastases)
  - ◆ Glomerular Filtration Rate (GFR)  $\geq 45$  ml/min according to Cockcroft and Gault Formula
  - ◆ Proteinuria CTC-AE  $< 2$
- ◆ Coagulation parameters: International normalized ratio (INR)  $\leq 2$ , prothrombin time (PT) and partial thromboplastin time (PTT)  $\leq 1.5 \times$  institutional ULN
- ◆ No history of significant cardiac disease defined as: Symptomatic CHF, high-risk uncontrolled arrhythmias, i.e. atrial tachycardia with a heart rate  $> 100$ /min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block), no prolongation of corrected QT interval (QTc)  $> 480$  msec, history of myocardial infarction within 12 months prior to randomization, clinically significant valvular heart disease, no angina pectoris requiring anti-angina treatment
- ◆ No current uncontrolled hypertension (persistent systolic  $> 180$  mmHg and/or diastolic  $> 100$  mmHg) (with or without medication). Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry.
- ◆ No evidence of active bleeding or bleeding diathesis.
- ◆ No cerebrovascular accident at any time in the past, transient ischemic attack, deep venous thrombosis (DVT) or pulmonary embolism in the past 6 months
- ◆ Therapeutic anticoagulation( except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous device) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid  $< 325$ mg per day) is not allowed
- ◆ No hypersensitivity to nintedanib, peanut or soya, or to any of the excipients of nintedanib.
- ◆ No history of clinically significant gastrointestinal disorders including: malabsorption syndrome, major resection of the stomach or small bowel that could affect the absorption of study drug, active peptic ulcer disease, known intraluminal metastatic lesions with risk of bleeding, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation. No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.
- ◆ No current severe, uncontrolled systemic disease that can hamper compliance with the protocol, according to physicians' judgment.
- ◆ No major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment and/or presence of any non-healing wound, fracture, or ulcer.
- ◆ No history of receiving any investigational treatment within 28 days prior to

	<p>randomization</p> <ul style="list-style-type: none"> <li>◆ Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment.</li> <li>◆ Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 3 months after the last dose of study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.</li> </ul>
<p>Therapieschema Scheme of therapy</p>	<p>Treatment cycles are defined as a four week period to facilitate scheduling of visits and assessments. Treatment should start within 2 days from randomization.</p> <p>Patients will receive drug in a blinded fashion. Nintedanib should be administered orally at a dose of 200 mg twice daily. It should be swallowed unchewed, preferably together with a glass of water of about 250 mL. The doses should be taken with a dose interval of approximately 12 hours.</p> <p>Treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal.</p>
<p>Tumorevaluierung Criteria for evaluation</p>	<p>Every 8 weeks</p>
<p>Statistik (optional)</p>	<p>Sample size is applicable for each sub-study separately (DTC, MTC). A 2:1 randomization is used with double of patients in the experimental arm. Despite data on median PFS in the secondary setting is little; it will be assumed that median PFS in the control arm is 5 months in both settings, DTC and MTC. The sample size is based on the hypothesized hazard ratio (HR) of the primary endpoint, progression free survival (PFS) and an assumption that the median PFS in the control arm is 5 months for both settings (DTC and MTC). Using 1-sided alpha = 10%, to detect a 50% reduction of risk of progression or death, i.e. HR = 0.5 with 85% power, 50 events (progression or death) are required.</p> <p>In DTC sub-population, assuming the median PFS in control arm is 5 months, an accrual rate of 5 patients randomized per month and adding an extra 5% patients to take into account patients lost to follow up, a total of 75 eligible patients are needed within 21 months of accrual. In addition 7.3 months of follow-up time is required to have the required number of events.</p> <p>In MTC sub-population, assuming the median PFS in control arm is 5 months, an accrual rate of 3.3 patients randomized per month and adding an extra 5% patients to take into account patient lost to follow up, a total of 67 eligible patients are needed within 27 months of accrual. In addition 7.4 months of follow-up time is required to have the required number of events.</p>
<p>Studienzentren</p>	<p>Uniklinikum Würzburg (Prof. Fassnacht, PD Dr. Kroiss) LMU München – Großhadern (Prof. Spitzweg) Klinikum Augsburg (PD Dr. Kreissl)</p>

Nebennierenkarzinom, "salvage therapy"**AIO-ENC-0114/ass: Phase-I-Studie zur Sicherheit und Verträglichkeit von ATR-101 bei Nebennierenrindenzkarzinom****AIO-assoziierte Studie**

Studiennummer/-Code: AIO-ENC-0114/ass

Status: vorübergehende Rekrutierungspause von 2015-2017, Wiederbeginn nach Protokollamendment für Q1 2018 geplant

Rekrutierungszeitraum 2013 - 2018

Weitere Zentren: leider nicht möglich

Letzte Aktualisierung Oktober 2017

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Martin Fassnacht (Leiter d. klin. Studie Deutschland) Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie Universitätsklinikum Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg Tel 0931-201-39021, Fassnacht_m@ukw.de
Studienziele/ Objectives	<b>Primär:</b> Die primäre Zielsetzung dieser Studie ist es, die Sicherheit und Verträglichkeit von oral verabreichtem ATR-101 bei Patienten mit Nebennierenrindenzkarzinom (ACC) zu ermitteln <b>Sekundär:</b> Ermittlung der maximal verträglichen Dosis (MTD) von ATR-101 (innerhalb des verabreichten Bereichs); Ermittlung der Pharmakokinetik (PK) von ATR-101 mithilfe einer validierten Prüfung; Beschreibung von Veränderungen der pharmakodynamischen Biomarker nach der Behandlung mit ATR-101 Beschreibung von Veränderungen objektiver Messungen der Tumorgroße nach der Behandlung mit ATR-101; Beschreibung von Veränderungen der Steroidsynthese und Metabolismusprofile nach der Behandlung mit ATR-101. Ermittlung einer empfohlenen Phase-II-Dosis.
Studiendesign	Diese Studie ist eine multizentrische, offene Kohortenstudie mit ansteigender Dosierung. Ein klassisches 3 + 3 Design wird befolgt. Die Dosisescalation erfolgt durch Verdopplung der vorherigen Dosis, wenn 0 oder 1 dosislimitierende Toxizität (DLT) beobachtet wurde. Die Dosisescalation wird geändert, wenn bestimmte Toxizitäten auftreten. Weitere Studienteilnehmer (bis zu 20) erhalten eine Dosis, wenn eine Dosierung wirksam für die Steroid- oder Tumorkontrolle zu sein scheint.
Patientenzahl Number of patients	Geplant: 31 - 59 Patienten Stand: Okt. 2017: 52
Rekrutierungszeitraum von/bis	Start: USA: 15.7.2013, Deutschland (Uniklinik Würzburg): 1.1.15 2017 vorübergehende Pause, Wiederbeginn nach Protokollamendment für Q1 2018 geplant
Weitere Zentren?	Nein
Haupt-Einschlusskriterien / Key inclusion criteria	Alter $\geq$ 18 Jahre; Klinisch bestätigtes Nebennierenrindenzkarzinom, das lokal fortgeschritten oder metastatisch ist und nicht durch chirurgische Entfernung behoben werden kann; Vorhergehende (adjuvante oder therapeutische) Mitotantherapie und platinbasierte Chemotherapie hat versagt oder wurde abgelehnt; Vorliegen der unterschriebenen Patienteneinverständnis
Haupt-Ausschlusskriterien / Key exclusion criteria	Vorliegen von anderen Tumorerkrankungen als ACC in den letzten 2 Jahren. Ausnahmen sind Basalzellkarzinom oder Plattenepithelkarzinom der Haut;

	Zervixkarzinom in situ; duktales Karzinom in situ der Brust; nicht-muskelinvasives Urothelkarzinom; organbegrenzt niedriggradiges (Gleason-Summe < 6) Prostatakarzinom. Instabiler medizinischer Zustand, der im Ermessen des Prüfarztes die Studienverfahren oder Dateninterpretation beeinträchtigen kann.
Therapieschema Scheme of therapy	ATR-101 täglich oral einzunehmen. Die Anfangsdosis beträgt 1,6 mg/kg Körpergewicht
Tumorevaluierung Criteria for evaluation	Alle 8 Wochen
Rationale	In präklinischen Studie wirkte ATR-101 zytotoxisch auf Nebennierenzellen und hemmte dosis-abhängig die Cortisol-Sekretion. In Hunden führte die Gabe von ATR-101 zu Nekrosen der Nebennieren.
Statistik (optional)	Die hauptsächlich verwendete statistische Methode sind beschreibende Statistiken, die für kontinuierliche und kategoriale Daten geeignet sind, da die Zielsetzung dieser First-in-human-Studie der Nachweis (der Abwesenheit) von DLT und MTD ist. Grundlegende pharmakokinetische und pharmakodynamische Parameter werden berechnet.
Deutsches Studienzentrum	Würzburg: Medizinische Klinik I, Universitätsklinikum

Registerstudie - Medulläres und dedifferenziertes (anaplastisches und radiojodrefraktäres) Schilddrüsenkarzinom

**AIO-YMO/ENC-0216: Multicenter registry for patients with rare malignant tumors of the thyroid (ThyCa)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/ENC-0216 - ThyCa
Rekrutierungszeitraum:	retrospektiv 2000 – 2013, prospektiv ab 2014
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	Oktober 2016

Art der Studie Study Type	Retrospective and prospective registry study
Kontakt	PD Dr. Dr. Matthias Kroiß Medizinische Klinik und Poliklinik I Schwerpunkt Endokrinologie/Diabetologie Oberdürrbacher Str. 6, 97080 Würzburg Tel.: 0931/201-39740 Email: Kroiss_M@ukw.de Universitätsklinikum Würzburg
Die Synopse ist zu finden unter den Kurzprotokollen der Young Medical Oncologists.	

Registerstudie**Europäisches Nebennierenkarzinom Register (ENSAT ACC registry and biobank)****AIO-assoziierte Studie**

Studiennummer/-Code:	ENSAT
Status:	in Rekrutierung
Rekrutierungszeitraum	seit 2011 fortlaufend
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	Okt 2017

Studienleiter	Prof. Dr. Martin Fassnacht (Head of the ACC working group of ENSAT) Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie Universitätsklinikum Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg Tel 0931-201-39021, Fassnacht_m@ukw.de
Kontaktadresse/ Kontaktperson:	Frau Michaela Haaf (Study Nurse) Schwerpunkt Endokrinologie und Diabetologie, Medizinische Klinik I, Universtitätsklinik Würzburg, Oberdürrbacher Str. 6, 97080 Würzburg Tel.: 0931 – 201 39717, Fax: 0931 – 201 639716 haaf_m@medizin.uni-wuerzburg.de
Studienziele	Das Nebennierenkarzinom (NN-Ca) ist ein seltener hochmaligner Tumor mit schlechter Prognose. Die Therapie des NN-Ca ist aufgrund der geringen Fallzahl der Erkrankung nicht durch Studien evidenz-basiert gesichert. So liegt bisher keine einzige Phase-III-Studie vor, die prospektiv unterschiedliche Behandlungsoptionen verglichen hat. Ziel des Deutschen Nebennieren-Karzinom-Registers war es, strukturelle Verbesserung in der Betreuung von Patienten mit Nebennieren-Karzinom herbeizuführen. Durch die bundesweite Erfassung möglichst vieler Patienten werden Daten zur Prognose und zu den Erfolgsaussichten unterschiedlicher Therapieregime gewonnen. Diese sollen zur Planung prospektiver Studien herangezogen werden. Durch das Register wird die Rekrutierung für Prospektive Studien entscheidend erleichtert. Das 2003 etablierte Register war so erfolgreich, dass es 2011 zu einem Europäischen Register ausgebaut wurde.
Studienablauf	In das Europäische Nebennieren-Karzinom-Register werden europaweit Patienten mit histologisch gesichertem Nebennierenkarzinom aufgenommen. Die Daten werden zentral in einer digitalen Datenbank gesammelt und ausgewertet. Das Register wird durch die Working Group des europäischen Nebennierentumor-Netzwerks ENSAT koordiniert. Die Daten aus Deutschland können weiterhin vom behandelnden Arzt an die Studienzentrale nach Würzburg übermittelt werden und werden dann von hier zentral eingegeben. Die weitere Auswertung erfolgt pseudonymisiert. Anfangs werden die Patienten retrospektiv analysiert. Mit dem Zeitpunkt der Erstaufnahme in das Register erfolgt eine prospektive Beobachtung. Parallel zu den klinischen Daten werden Bioproben (Tumor, Blut und Urin) von den Patienten gesammelt und ausgewertet.
Erfasste Patienten	Oktober 2017: 2914 (davon > 1300 aus Deutschland)
Fragestellungen	In den letzten Jahren konnten auf Basis der Daten dieses Registers viele klinische drängende Fragen beantwortet werde; u.a. zur adjuvanten Therapie (Fassnacht JCEM 2006, Terzolo NEJM 2007), zu Operationsverfahren (Brix Eur Urol 2010; Reibetanz Ann Surg 2012) oder zur Therapie beim Rezidiv (Erdogan JCEM 2013) oder Salvage Therapie (Quinkler JCEM 2008, Weismann EJE 2009, Kroiss Horm Cancer 2016). Zusätzlich wurde eine neue TNM-Klassifikation vorgeschlagen, die inzwischen allgemein akzeptiert wird

	(Fassnacht et al. Cancer 2009). Weitere Informationen und bisherige Publikationen unter: <a href="http://www.nebennierenkarzinom.de">www.nebennierenkarzinom.de</a> ; <a href="http://www.ensat.org">www.ensat.org</a>
Förderung	Initial über die Deutsche Krebshilfe Seit 2011 Förderung durch die Europäische Union im Rahmen des FP-7 Programms



## Arbeitsgruppe Geriatrische Onkologie

### AIO-GER-0115: A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine +/- nab-paclitaxel in elderly pancreatic cancer patients (GrantPax)

#### AIO-Studie

Studiennummer/-Code: AIO-GER-0115 - GrantPax

Status: Aktiv rekrutierend

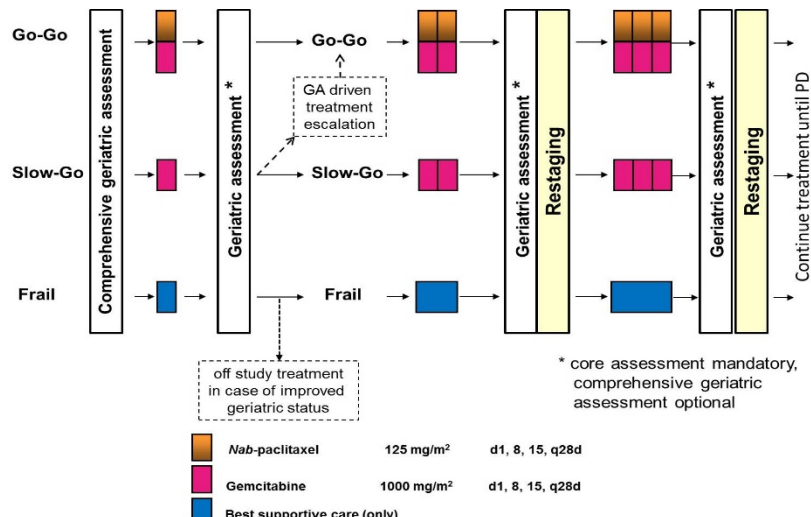
Rekrutierungszeitraum: 2016 - 2018

Anzahl initiiertes Zentren: 6

Weitere Zentren: leider nicht möglich

Anzahl eingeschlossene Patienten: 27 von 145

Letzte Aktualisierung: 10. April 2018

Coordinating Investigator	Prof. Dr. med. Matthias Ebert Universitätsmedizin Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim Phone: +49621 383 3284, Fax: +49621 383 3905 E-Mail: Matthias.Ebert@umm.de
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49-30 – 8145 344 31, Fax: +49-30 – 322932926 E-Mail: info@aio-studien-ggmbh.de
Study design	Multicenter, open label phase IV interventional study with stratified parallel treatment groups.   <p>* core assessment mandatory, comprehensive geriatric assessment optional</p>
Anticipated start date	Q2/2016
Duration of study	3 years
Indication	Metastatic ductal adenocarcinoma of the pancreas, first-line
Primary objective	The primary objective is that CGA-stratified patients do not decline in their CGA performance in response to chemotherapy measured as a loss of five points or less in the Barthel's ADL, (ADL1 vs. ADL2 during core CGA assessment).
Secondary objectives	<ul style="list-style-type: none"> <li>Evaluation of the predictive value of the CGA (CGA 1+2) containing testings (CRASH-Scores, IADL, ADL, G8-Questionnaire etc.) for the incidence of <math>\geq</math> grade 3 hematological and/ or non-hematological</li> </ul>

	<p>toxicities;</p> <ul style="list-style-type: none"> <li>• Predictive value of the assessed geriatric tests for treatment discontinuation;</li> <li>• Response rates;</li> <li>• Safety (<i>nab</i>-paclitaxel/gemcitabine combination and gemcitabine alone);</li> <li>• Survival rates (PFS, OS);</li> <li>• Percentage of patients receiving therapy in each treatment group;</li> <li>• Percentage of patients improving in the CGA during therapy;</li> <li>• QoL (plus time to QoL deterioration)</li> </ul>
Planned sample size	135 patients are to be enrolled to reach 43 analyzable patients and account for a 5% drop-out rate (n=2) in each CGA-driven treatment arm.
Inclusion Criteria 1 – Chemotherapy arms (Go-Go, Slow-Go):	<ol style="list-style-type: none"> <li>1. Patients <math>\geq 70</math> years of age.</li> <li>2. Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas.</li> <li>3. At least one measurable lesion of disease according to RECIST 1.1 criteria.</li> <li>4. No prior chemotherapy (except fluoruracil or gemcitabine in an adjuvant setting at least <math>&gt; 6</math> months prior enrollment).</li> <li>5. Adequate end organ function: <ul style="list-style-type: none"> <li>• renal function: serum creatinine <math>\leq 1.5 \times</math> ULN or GFR <math>\geq 30</math> mL/min.</li> <li>• hematopoietic function: white blood cell (WBC) count <math>\geq 3000/\mu\text{L}</math>, absolute neutrophil count (ANC) <math>\geq 1500/\mu\text{L}</math>, platelets <math>\geq 105/\mu\text{L}</math>, hemoglobin level <math>&gt;9.0</math> g/dL</li> <li>• liver function: total bilirubin <math>\leq 1.5 \times</math> ULN, AST / ALT <math>\leq 3.0 \times</math> ULN</li> </ul> </li> <li>6. Cooperation and willingness to complete all aspects of the study</li> </ol> <ul style="list-style-type: none"> <li>• Written informed consent to participate in the study</li> </ul>
Inclusion Criteria 2 – Frail patients (FRAIL arm):	<ol style="list-style-type: none"> <li>1. Patients <math>\geq 70</math> years of age.</li> <li>2. Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas.</li> <li>3. No prior chemotherapy (except fluoruracil or gemcitabine in an adjuvant setting at least <math>&gt; 6</math> months prior enrollment).</li> <li>4. Cooperation and willingness to complete all aspects of the study</li> </ol> <p>Written informed consent to participate in the study</p>
Exclusion Criteria 1 (Go-Go, Slow-Go):	<ol style="list-style-type: none"> <li>1. Patients <math>&lt;70</math> years of age.</li> <li>2. Papillary cancer, cholangiocellular carcinoma, neuro-endocrine tumors.</li> <li>3. Patient has a severe and/or uncontrolled medical disease (i.e. uncontrolled active infection, uncontrolled hypertension/ diabetes or cardiac disease).</li> <li>4. Patient has received any other investigational product within 28 days prior study entry.</li> <li>5. Patient is <math>&lt; 5</math> years free of another primary malignancy (except: not currently clinically significant nor requiring active intervention)</li> <li>6. Hypersensitivity against gemcitabine or nab-paclitaxel.</li> <li>7. Major surgery <math>\leq 28</math> days prior to study entry.</li> <li>8. Patient has a known diagnosis of human immunodeficiency virus (HIV) infection.</li> <li>9. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.</li> <li>10. Any other chemotherapy at start.</li> <li>11. Any psychiatric illness that would affect the patient's ability to understand the demands of the clinical trial.</li> <li>12. Parallel participation in another clinical trial or participation in another clinical trial within the last 30 days or 7 half-lives of a study medication,</li> </ol>

	<p>whichever is of longer duration, prior study start.</p> <p>13. Patient has already been recruited in this trial.</p> <p>14. Patients who do not understand the nature, the scope and the consequences of the clinical trial.</p> <p>15. Patient who might be dependent on the sponsor, the study site or the investigator.</p> <p>16. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 Nr. 4 AMG.</p>
Exclusion criteria 2 – (FRAIL study subjects):	<ol style="list-style-type: none"> <li>1. Patients &lt;70 years of age.</li> <li>2. Papillary cancer, cholangiocellular carcinoma, neuro-endocrine tumors.</li> <li>3. Patient has received any other investigational product within 28 days prior study entry.</li> <li>4. Patient is &lt; 5 years free of another primary malignancy (except: not currently clinically significant nor requiring active intervention)</li> <li>5. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.</li> <li>6. Any chemotherapy at study start.</li> <li>7. Any psychiatric illness that would affect the patient's ability to understand the demands of the clinical trial.</li> <li>8. Parallel participation in another clinical trial or participation in another clinical trial within the last 30 days or 7 half-lives of a study medication, whichever is of longer duration, prior study start.</li> <li>9. Patient has already been recruited in this trial.</li> <li>10. Patients who do not understand the nature, the scope and the consequences of the clinical trial.</li> <li>11. Patient who might be dependent on the sponsor, the study site or the investigator.</li> <li>12. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 Nr. 4 AMG.</li> </ol>
Investigational Agent	<p><i>Nab</i>-paclitaxel (Abraxane®) Gemcitabine</p>
Treatment schedule	<p><b>GO-GO arm:</b> <i>Nab</i>-paclitaxel 125 mg/m<sup>2</sup> i.v. over 30 minutes followed by gemcitabine infusion 1000 mg/m<sup>2</sup> on days D1, D8, D15 of a 28-day cycle.</p> <p><b>SLOW-GO arm:</b> Gemcitabine 1000 mg/m<sup>2</sup> i.v. on days D1, D8, D15 of a 28-day cycle.</p> <p><b>FRAIL arm:</b> Best supportive care as determined by the investigator. Treatment until PD, withdrawal of consent, intolerable toxicity or death</p>
Primary endpoint	<p>Loss of five points or less in the Activity of Daily Living (Barthel's ADL; assessed during 2<sup>nd</sup> CGA) after first cycle of chemotherapy (or after 4 weeks in BSC group) compared to the initial ADL for each treatment groups.</p>
Secondary endpoints	<ul style="list-style-type: none"> <li>• CGA scores before and after 1<sup>st</sup> treatment cycle (CGA1+2; further CGA scores 3+4 – if available ) or after 28 days of BSC</li> <li>• Response rates: CR, PR, DCR, ORR</li> <li>• AEs/SAEs</li> <li>• PFS</li> <li>• OS</li> <li>• Percentage of patients receiving at least one chemotherapy in each treatment group and percentage of patients escalating treatment;</li> <li>• Duration of treatment</li> </ul>

	<ul style="list-style-type: none"> <li>• Cumulative dose</li> <li>• QoL (time to QoL deterioration [loss of 10 points in QLQ-C30])</li> <li>• Discrepancy between CGA strata estimation by the investigator and true CGA assessment.</li> </ul>
Comprehensive geriatric assessment (CGA)	<p>Full CGA [baseline only]:</p> <ol style="list-style-type: none"> <li>1. Functional testing: IADL (Lawton/Browdy), ADL (Barthel)</li> <li>2. Screening tests: G8-Questionnaire, non-hematological CRASH Score (toxicity)</li> <li>3. Comorbidity assessment: Charlson Comorbidity Index</li> <li>4. Cognition tests: MMSE</li> <li>5. Depression scale: GDS15</li> <li>6. Nutritional assessment: MNA</li> <li>7. Biological testing: chair stand test</li> <li>8. Evaluation of geriatric syndromes</li> </ol> <p>CGA core assessment for initial treatment decision, treatment escalation and all follow-up Assessments:</p> <ol style="list-style-type: none"> <li>1. ECOG</li> <li>2. ADL (Barthel)</li> <li>3. IADL (Lawton/Browdy)</li> <li>4. G8-Questionnaire</li> </ol>
Stratification & Treatment escalation	<p><b>Treatment assignment according to core CGA</b></p> <p><u>I. Baseline CGA (CGA 1):</u></p> <p><b>GO-GO:</b> ECOG 0-1 and G8-Questionnaire &gt; 14 points and ADL(Barthel) = 100 and IADL = 8 (f) / = 5 (m);</p> <p><b>SLOW-GO:</b> ECOG ≤ 2 and G8-Questionnaire ≤ 14 points and/or ADL ≤ 100 and/or IADL ≤ 8 (f) / ≤ 5 (m);</p> <p><b>FRAIL:</b> ECOG ≥ 3 and G8-Questionnaire &lt; 14 points and ADL &lt; 100 and IADL &lt; 8 (f) / &lt; 5 (m)</p> <p>Definitive assignment is going to be confirmed by investigators decision (CGA result).</p> <p><u>II. Assessment after first cycle of chemotherapy (core CGA 2):</u></p> <p><b>Cross over from SLOW-GO to GO-GO arm (escalation):</b></p> <p>Core CGA improved and treatment related toxicity ≤ grade 1 according to CTCAE V4.03-criteria. Note: Within the GrantPax study the escalation option is only available for SLOW-GO study subjects. FRAIL subjects, who become eligible for a mono-chemotherapy are withdrawn from the study and may commence any chemotherapy at the discretion of the treating physician.</p> <p>The indication to escalate is going to be confirmed by investigator's decision (CGA result).</p> <ul style="list-style-type: none"> <li>• A central CGA review will be conducted by telephone conference with the study coordinator/ coordinating investigator to relay</li> </ul>

	changes in the CGA2 results, in particular CGA differences which result in treatment modifications.
Rationale	<p>Recent studies convincingly demonstrated that <i>nab</i>-paclitaxel in combination with gemcitabine is an effective treatment regimen for metastatic PDAC.</p> <p>Unpublished data of the MPACT trial indicated that <i>nab</i>-paclitaxel/gemcitabine is not feasible in PDAC patients <math>\geq 75</math> years. However the MPACT trial lacked a geriatric assessment to properly evaluate the health status and functional reserve of elderly pancreatic cancer patients. There is rising evidence that comprehensive geriatric assessments (CGAs) as well as condensed geriatric screening tools are able to predict treatment-related toxicity and outcome.</p> <p>The aim of this study is to determine whether CGAs can predict the benefit from combined <i>nab</i>-paclitaxel/gemcitabine therapy for elderly patients. A stratified treatment approach shall result in patient groups with a stable or improving CGA performance during the first cycle of treatment.</p>
Interim analyses	Not planned
Safety Data	AEs and SAEs, standard laboratory safety data (hematology, biochemistry), vital signs (blood pressure, heart rate, body temperature, weight), physical and neurological examinations.
Sample size calculation	<p>The expected proportion of patients with ADL decline in each treatment group is 6%. Under this assumption it shall be shown with 80% power at one-sided significance level alpha of 0.05 that the proportion of patients with functional decline (Barthel's ADL) is less than 20%. This requires the inclusion of 43 patients with a maximum number of 2 patients with ADL decline per group.</p> <p>→ n = 43 patients in each treatment group; <math>\alpha = 0.05</math>; Power= 0.80</p>
QoL measurements	EORTC QLQ-C30 V3.0, QLQ-ELD14
Study plan	<p>First Patient In (FPI): Q2/2016</p> <p>Last Patient In (LPI): Q2/2018</p> <p>Last Patient Last Visit (LPLV): Q2/2019</p> <p>Study report: Q1/2020</p>

## Arbeitsgruppe Hepatobiliäre Tumoren

### Frühes HCC, kurativ / Erstlinie

#### **AIO-HEP-0417/ass: A phase II trial of immunotherapy with pembrolizumab in combination with local ablation for patients with early stage hepatocellular carcinoma (HCC) (IMMULAB)**

#### AIO-Studie

Studiennummer/-Code:	AIO-HEP-0417/ass
Status:	in Vorbereitung Vollständiges Protokoll von MSD freigegeben, Vorbereitung der Einreichung
Rekrutierungszeitraum:	Studienstart noch offen (geplant: Q2/2018, 12 Monate Rekrutierung)
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	09.04.2018

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover
CONDITION	Early stage hepatocellular carcinoma (HCC)
OBJECTIVE(S)	Primary: Overall response rate (ORR) before local ablation Secondary: Time to recurrence (TTR), recurrence free survival, and overall survival (OS) Safety and tolerability Identification of predictive molecular biomarkers
INTERVENTION(S)	pembrolizumab 200mg IV Q3W on D1C1 and D1C2 RFA / MWA will be performed on D1C3 pembrolizumab 200mg IV administration on D3C3 pembrolizumab 200mg IV Q3W for up to one year total treatment duration
KEY EXCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Extrahepatic disease</li> <li>• Fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC</li> <li>• Tumor thrombus involving main trunk of portal vein</li> <li>• Patient is awaiting liver transplantation (LTx)</li> <li>• Prior history of Grade <math>\geq 2</math> hepatic encephalopathy</li> <li>• Pericardial effusion, uncontrollable pleural effusion, or clinically significant ascites</li> <li>• Autoimmune disease requiring systemic treatment</li> </ul>
KEY INCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Histologically confirmed diagnosis of HCC</li> <li>• Child-Pugh Classification score <math>\leq 6</math></li> <li>• Candidate for local ablation (via either RFA or MWA)</li> <li>• High risk patient (Presence of <math>\leq 5</math> tumor nodules with diameters <math>\leq 5</math>cm [longest axis] each and not a candidate for resection)</li> <li>• No prior systemic therapy for HCC (TACE <math>&gt;8</math> weeks before study allocation permitted)</li> <li>• Measurable disease based on RECIST</li> <li>• Archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion</li> </ul>

	<ul style="list-style-type: none"> <li>• ECOG performance status 0 to 1</li> </ul>
OUTCOME(S)	<p>Efficacy :</p> <ul style="list-style-type: none"> <li>• We hypothesize that treatment with pembrolizumab before RFA / MWA will allow conversion / downstaging of borderline candidates for local ablation. This will be displayed by an ORR of 30% (measured before RFA / MWA, compared to baseline).</li> <li>• We hypothesize that peri-interventional treatment with pembrolizumab will increase TTR, recurrence free survival and overall survival after RFA / MWA.</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• We hypothesize that combination of RFA / MWA with peri-interventional administration of pembrolizumab is safe and well tolerated.</li> </ul>
STUDY TYPE	Interventional, single-arm, open-label, multicenter
STATISTICAL ANALYSIS	<p>This is an explorative phase II study. There is no formal sample size calculation. The primary endpoint is ORR and the number of 30 patients will allow to observe the expected ORR of 30% (0.3) with 90% confidence interval (CI) extending from 0.18 to 0.45 and 95% confidence interval extending from 0.16 to 0.48.</p> <p>There is no full interim analysis planned for this study, due to the small sample size and the relatively short recruitment period. However, single objectives may be analyzed as soon as sufficient events are available for analysis as detailed in the Statistical Analysis Plan (SAP).</p>
SAMPLE SIZE	n=30
TRIAL DURATION	<p>max. 42 months from FPI to LPO (consisting of 12 months recruitment, 12 months treatment after LPI, and 18 months FU for OS after LPLT)</p>
PARTICIPATING CENTERS	10 sites planned

### HCC, periinterventionelle Studie, Erstlinie

#### **AIO-HEP-0217: A Phase II single-arm, open-label study of transarterial chemoembolization (TACE) in combination with nivolumab performed for intermediate stage hepatocellular carcinoma (IMMUTACE)**

<b>AIO-Studie</b>	
Studiennummer:	AIO-HEP-0217 - IMMUTACE
Status:	Einreichung und Bearbeitung bei PEI und Ethikkommissionen
Rekrutierungszeitraum:	2018 - 2019
Weitere Zentren:	Geplante Anzahl Zentren erreicht. Interessierte Zentren können sich auf die Warteliste setzen lassen
Letzte Aktualisierung	09. April 2018

National Coordinating Investigator (LKP)	<p>Prof. Dr. med. Arndt Vogel Klinik für Gastroenterologie, Hepatologie und Endokrinologie Medizinische Hochschule Hannover Carl-Neuberg-Str. 1, 30625 Hannover Tel: +49 511-532-9590</p>
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Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431 Fax +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Study design	Open label, multicenter phase II trial
Anticipated start date	Q1/2018
Duration of study	Enrollment: 12 months total study duration max. 42 months (incl. follow-up of LPI)
Indication	Multinodular hepatocellular carcinoma (HCC)
Target population	Patients with histologically diagnosed, intermediate stage HCC, aged $\geq 18$ years. Limited metastatic disease may be considered (see inclusion/ exclusion criteria).
Total number of sites	10
Primary objective	The aim of the study is the assesement of the clinical activity of the anti-programmed-death-1 antibody (anti-PD-1) nivolumab in combination with transarterial chemoembolization (TACE) in patients with multinodular or solitary large hepatocellular carcinoma (HCC) as first line systemic therapy.
Secondary objectives	To assess the 1.) efficacy by PFS, TTP, TTFS, DoR and OS and 2.) safety and tolerability of nivolumab in combination with TACE in patients with intermediate stage HCC. 3) Quality of Life
Planned sample size	N=49 enrolled to receive TACE followed by nivolumab mono-therapy
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>2. Age <math>\geq 18</math> years at time of study entry</li> <li>3. Multinodular or large, solitary HCC, not eligible for resection or local ablation, Tumor burden below 50% of liver volume.</li> <li>4. Histologically confirmed diagnosis of HCC.</li> <li>5. At least one measurable site of disease as defined by modified RECIST (mRECIST) criteria with spiral CT scan or MRI.</li> <li>6. Child-Pugh A, performance status (PS) <math>\leq 2</math> (ECOG scale).</li> <li>7. Subjects with chronic HBV infection must have HBV DNA viral load <math>&lt; 100</math> IU/mL at screening. In addition, they must be on antiviral therapy per regional standard of care guidelines prior to initiation of study therapy.</li> <li>8. Life expectancy of at least 12 weeks.</li> <li>9. Adequate blood count, liver-enzymes, and renal function: <ul style="list-style-type: none"> <li>• Haemoglobin <math>\geq 8.5</math> g/dL, absolute neutrophil count <math>\geq 1,500</math> /L, platelets <math>\geq 70 \times 10^3</math>/L;</li> <li>• Total bilirubin <math>\leq 3x</math> upper normal limit;</li> <li>• AST (SGOT), ALT (SGPT) <math>\leq 5</math> x upper normal limit;</li> <li>• International normalized ratio (INR) <math>\leq 1.25</math>;</li> <li>• Albumin <math>\geq 31</math> g/dL;</li> <li>• Serum Creatinine <math>\leq 1.5</math> x institutional ULN or creatinine clearance (CrCl) <math>\geq 30</math> mL/min (if using the Cockcroft-Gault formula below):</li> </ul> </li> </ol>



Female CrCl =  $(140 - \text{age in years}) \times \text{weight in kg} \times 0.85$   
 $72 \times \text{serum creatinine in mg/dL}$

Male CrCl =  $(140 - \text{age in years}) \times \text{weight in kg} \times 1.00$   
 $72 \times \text{serum creatinine in mg/dL}$

10. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial.
11. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational products (nivolumab). Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception).
12. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

#### Exclusion criteria

#### Methodological or clinical criteria:

1. Diffuse HCC or presence of vascular invasion or extrahepatic spread with the following exceptions:
  - a) Invasion of a segmental portal vein or hepatic veins
  - b) Limited extrahepatic metastases with one organ system manifestations, e.g. lymphnodal, pulmonary, osseous metastases. For lymphnodal metastases maximum three metastases, maximum 2 cm in the longest diameter, and for all other metastases only solitary metastases, maximum 2 cm in the longest diameter, are allowed.
2. Patients on a liver transplantation list or with advanced liver disease as defined below:
  - a) Encephalopathy;
  - b) Untreatable ascites.
3. Any contraindications for hepatic embolization procedures:
  - a) Known hepatofugal blood flow;
  - b) Known porto-systemic shunt;
  - c) Impaired clotting test (platelet count  $<70 \times 10^3/L$ , INR  $>1.25$ );
  - d) Renal failure/ insufficiency requiring hemo- or peritoneal dialysis;
  - e) Known severe atheromatosis;
  - f) Total thrombosis or total invasion of the main branch of the portal vein.
4. History of cardiac disease:
  - a) Congestive heart failure  $>$ New York Heart Association (NYHA) class 2;
  - b) Active coronary artery disease (CAD) (myocardial infarction  $\geq 6$  months prior to study entry is allowed);
  - c) Cardiac arrhythmias ( $>$ Grade 2 NCI-CTCAE Version 3.0) which are poorly controlled with anti-arrhythmic therapy or requiring pace maker;
  - d) Uncontrolled hypertension;
  - e) Clinically significant gastrointestinal bleeding within 4 weeks prior to start of study treatment (TACE + nivolumab)
5. Thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months prior to the first dose of study drug with the exception of thrombosis of a segmental portal vein.
6. Prior systemic anti-cancer therapy OR endocrine- OR immunotherapy

7. Prior treatment with TACE
8. RFA and resection administered less than 4 weeks prior to study treatment start.
9. Radiotherapy administered less than 4 weeks prior to study treatment start.
10. Major surgery within 4 weeks of starting the study treatment OR subjects who have not recovered from effects of major surgery.
11. Patients with second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix.
12. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).
13. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lives of previously used trial medication, whichever is longer.
14. Previous treatment in the present study (does not include screening failure).
15. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to:
  - a) history of interstitial lung disease
  - b) HBV and HCV coinfection (i.e. double infection)
  - c) known acute or chronic pancreatitis
  - d) active tuberculosis
  - e) any other active infection (viral, fungal or bacterial) requiring systemic therapy
  - f) history of allogeneic tissue/solid organ transplant
  - g) diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of nivolumab-monotherapy treatment.
  - h) Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Exceptions: Subjects with vitiligo, hypothyroidism, diabetes mellitus type I or resolved childhood asthma/atopy are an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with Hashimoto thyroiditis, hypothyroidism stable on hormone replacement or psoriasis not requiring treatment are not excluded from the study.
  - i) Live vaccine within 30 days prior to the first dose of nivolumab-monotherapy treatment or during study treatment.
  - j) History or clinical evidence of CNS metastases

Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:

- a. are asymptomatic and
- b. have no requirement for steroids 6 weeks prior to start of nivolumab-monotherapy treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases

Drug related criteria:

16. Medication that is known to interfere with any of the agents applied in the trial.
17. Has known hypersensitivity to nivolumab or any of the constituents of the products.

18. Any other efficacious cancer treatment except protocol specified treatment at study start.
19. Patient has received any other investigational product within 28 days of study entry.
20. Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-Programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

Safety criteria:

21. Female subjects who are pregnant, breast-feeding or male/female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner]. Women of childbearing potential must have a negative pregnancy test (serum  $\beta$ -HCG) at screening.

Regulatory and ethical criteria:

22. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.
23. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
24. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

Investigational agents

- nivolumab

Treatment schedule

So far, there are only few standards regarding the most appropriate intervals of TACE treatments, maximum number of sessions and whether radiological response is necessary for TACE continuation. Differing techniques of TACE are used depending on tumour load, distribution and vascularisation. Taking this heterogeneity of TACE techniques in clinical practice into account, recommendations on the preferable TACE techniques for both cTACE and DEB-TACE are as follows:

The embolization position for cTACE and DEB-TACE should be as selective as reasonably achievable to prevent unintentional embolization of non-tumour liver tissue. The use of intraprocedural cone-beam CT imaging for the work-up of the intrahepatic vascular anatomy is strongly recommended. A coaxial technique with microcatheters should be adopted.

Conventional TACE (cTACE) can be performed with 10 mL of lipiodol together with doxorubicin and mitomycin. If hypervascularity persists up to 10 mL of additional lipiodol can be administered. In cases of extensive hypervascularity microspheres can be considered.

Drug eluting bead TACE (DEB-TACE) can be performed with doxorubicin loaded beads. The size of the beads should address the presumed selectivity of the embolization position and the hypervascularity of the tumour. In cases where a superselective position cannot be achieved and flow-direction is not compensating for it larger particles should be used

The actual TACE technique will be investigators choice.

Treatment will be divided into 4-week cycles from the starting date of TACE. The second TACE will be repeated on day 1 ( $\pm$  4 days) of cycle 3 (after 8

	<p>weeks ± 4 days). As there are no standards regarding the duration of treatment with TACE, patients will be allowed one optional TACE treatment, if deemed necessary by the investigator.</p> <p>Nivolumab will be initiated on day 2-3 after the first TACE session. Nivolumab will be administered every two weeks (240mg fixed dose] IV) until disease progression for up to two years.</p> <p>Patients are allowed to continue with the study, if a progressive or new lesion can successfully be treated with one additional local therapy (TACE, radiofrequency ablation [RFA]/ microwave ablation [MWA] or resection).</p> <p>Study assessments:</p> <ul style="list-style-type: none"> <li>• Safety Lead-in: These patients will be observed for the first 4 week cycle with weekly safety visits.</li> <li>• Main part: Safety visits every 2 weeks, efficacy assessment by CT or MRI abdomen and CT thorax for radiological response 7 weeks after the first TACE and then every 8 weeks.</li> </ul>
<p>Primary endpoint</p>	<p>ORR according to modified RECIST for HCC</p>
<p>Secondary endpoints</p>	<p>Additional secondary endpoints:</p> <ul style="list-style-type: none"> <li>• tumor response according to RECIST 1.1</li> <li>• PFS</li> <li>• TTP</li> <li>• Time-to-Failure-of-Strategy (TTFS):</li> </ul> <p>Progression according to mRECIST for HCC with the exception of new intrahepatic lesions, which are assessed to be treatable with one additional locoregional therapy (TACE, RFA/ MWA or resection). Progression following one additional locoregional treatment of such lesions according to mRECIST would be equivalent to failure of strategy.</p> <ul style="list-style-type: none"> <li>• Duration of response</li> <li>• Duration of treatment</li> <li>• OS</li> <li>• QoL (EORTC QLQC30 and HCC-18)</li> <li>• AEs/SAEs</li> </ul>
<p>Translational research: Exploratory objectives and endpoints</p>	<p>Biomarker assessment:</p> <ul style="list-style-type: none"> <li>• Tumour blocks or slides of all patients confirming diagnosis of HCC according to the inclusion criterion prior to treatment will be collected.</li> <li>• Standardized histopathological examination will be performed.</li> <li>• DNA, RNA, miRNA will be extracted from tumours and subjected to molecular analysis using immunohistochemistry, RT-PCR analysis, RNA seq and Panel seq.</li> <li>• CTC and ctDNA will be collected before therapy, 4 weeks after the first TACE, 3 months after first TACE and at end of nivolumab treatment/ following the last infusion of nivolumab.</li> </ul> <p>Central Review of radiological response:</p> <ul style="list-style-type: none"> <li>• Parametric response mapping – a novel postprocessing approach for response assessment established for TACE in HCC - will be performed and tested against the established criteria regarding the potential to predict further response to treatment and OS earlier on, addressing the need for better and earlier prognostic information on treatment response to utilize for the proposed treatment migration concept.</li> </ul> <p>QoL-adjusted cost-effectiveness analysis:</p> <ul style="list-style-type: none"> <li>• QoL assessment based on established techniques (EORTC QLQ-C30 / HCC-18) will be performed as a secondary outcome measure and in order to make the study data available for following analyses addressing quality-adjusted cost-effectiveness issues.</li> </ul>
<p>Rationale and Hypothesis</p>	<p>1.) Hepatocellular carcinoma is one of the most lethal and prevalent cancers worldwide [1]. The prognosis of patients with HCC is dismal and the mortality</p>

rates are almost the same as the incidence rates. In the year 2008, 748,300 new HCC and 695,900 deaths have been registered (<http://www.iarc.fr>). When potentially curative treatments are not indicated at an intermediate or advanced disease stage anymore, a palliative treatment is offered. TACE is commonly used to act locally in the intermediate disease stage and is the most common first-line treatment in patients with HCC. Early randomized trials and more recent reviews and meta-analyses reported improved survival rates of patients with unresectable lesions managed with TACE so that TACE has been accepted as the standard treatment for intermediate stage disease [2-4]. However, outcome of patients treated with TACE in real-life cohorts is still very poor with median overall survival (OS) of 20 months or less [2-5]. According to the stage migration concept proposed by BCLC, patients treated with TACE are supposed to shift to systemic therapies - currently the multikinase inhibitor sorafenib - upon progression. However, treatment with systemic therapy following TACE is complicated by a deteriorating hepatic function during treatment with TACE and/or rapid tumor progression [3, 5, 6]. Consequently, the use of systemic treatments is lower than 20% in the subsequent treatment lines ([7], Kirstein MM et al. unpublished data).

2.) In order to increase the outcome of TACE, several trials have analyzed the combination of TACE with sorafenib and other anti-angiogenic agents. However, none of the trials have reported an improved overall survival for patients treated with the combination of TACE and sorafenib [8-10]. Sorafenib may not represent the ideal combination partner for TACE as its efficacy as monotherapy in patients with advanced HCC is very modest [11]. There is clearly an unmet need for novel systemic therapies with more effective mechanisms for HCC to be combined with TACE.

3.) Monoclonal antibodies (mAbs) that target the immune checkpoints cytotoxic T- lymphocyte-associated antigen 4 (CTLA-4) and programmed-death-1 (PD-1) and its ligand (PD-L1) are currently on the rise and are encouragingly active in a variety of malignancies, such as metastatic melanoma and non-small-cell lung cancer (NSCLC) [12].

PD-L1 expression has also been reported in HCC. As assessed in resected tumour specimen from 240 HCC patients and validated in further 124 patients, overexpression of PD-L1 was significantly associated with tumour recurrence [13]. In addition, combined PD-L1low/ human leukocyte antigen class I (HLA class I) high expression in human HCC was confirmed to be prognostic for recurrence-free and overall survival [14]. Together, these results suggest a prognostic role for and a rationale to target PD-1 in HCC. Preliminary data from the CheckMate-040 trial strongly suggest that nivolumab has clinical activity and is tolerable in patients with HCC, including those with hepatitis B or hepatitis C virus (HCV) infection [15].

4.) Doxorubicin has been shown to trigger immunogenic cell death [16]. In addition, TACE induces local tumor destruction with subsequent antigen release suggesting an efficient synergistic effect of TACE with anti-PD-1 antibodies. Early clinical data already support a safe combination of immune checkpoint inhibition with TACE [17].

Therefore, the aim of this study is to evaluate the safety and efficacy of TACE in combination with nivolumab in patients with intermediate stage HCC.

Research hypothesis:

We hypothesize that the combination of nivolumab with TACE, which induces local tumor destruction with subsequent antigen burst, is safe and effective. The aim of this phase II study is to determine the safety and efficacy of the combination of nivolumab with TACE.

Safety data

- AEs, SAEs and treatment emergent adverse events according to CTCAE 4.03
- Frequency of clinically significant abnormal laboratory parameters

Sample size estimation and

The primary objective is to estimate best ORR per mRECIST for HCC. Considering a historical ORR of 35% [9], a ORR of 55% is estimated for the

Statistical analysis considerations	<p>nivolumab+ TACE combination. A Fleming single-stage Phase II design will be used to test the null-hypothesis that (i) the true ORR in study subjects is <math>\leq 35\%</math> (P0) against a one-sided alternative that the ORR <math>\geq 55\%</math> (PA).</p> <p><math>H_0 : P \leq P_0 \quad H_A : P \geq P_A</math></p> <p>A study requires 41 subjects to decide whether the proportion responding, P, is less than or equal to 0.35 or greater than or equal to 0.55. If the number of responses is 20 or more, the null-hypothesis that <math>P \leq 0.35</math> is rejected with a one-sided target error rate of <math>\alpha=0.05</math> (actual alpha 0.05). If the number of responses is 19 or less, the alternative hypothesis that <math>P \geq 0.55</math> is rejected with a target error rate of <math>\beta=0.2</math> (Power = 80%; actual beta 0.17).</p> <p>Considering a rate of uninformative drop-out of approx. 15% a total of N=49 subjects are to be recruited (incl. study subjects of the lead-in phase).</p>	
Study plan / time lines	<p>First Patient In (FPI):</p> <p>Last Patient In (LPI):</p> <p>Last Patient Last treatment (LPLT):</p> <p>End of follow-up period after LPI:</p> <p>Study report:</p> <p>Publication:</p>	<p>Q1/2018</p> <p>after approx. 12 months</p> <p>after approx. 20 - 36 months</p> <p>after approx. 26 - 46 months</p> <p>after approx. 35 - 51 months</p> <p>after approx. 35 - 51 months</p>

### HCC, definitive Therapie im intermediären Stadium

**AIO-HEP-0317/ass: TACE followed by systemic therapy compared to continuous TACE in intermediate stage hepatocellular carcinoma (HCC) (TACEnd) – a randomized multicentre phase III trial of the AIO**

#### **AIO-assozierte Studie**

Studiennummer/-Code:	AIO-HEP-0317/ass / TACEnd
Status:	in Vorbereitung / Förderantrag bei DFG
Rekrutierungszeitraum:	Studienstart noch offen
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	06.10.2017

Antragsteller / Leiter der klinischen Prüfung	<p>Sponsor / Antragsteller: Krankenhaus Nordwest gGmbH, Institut für Klinisch-Onkologische Forschung</p> <p>Leiter der klinischen Prüfung (LKP): Prof. Dr. med. Arndt Vogel (Medizinische Hochschule Hannover Klinik für Gastroenterologie, Hepatologie und Endokrinologie Tel.: 05115329590; Fax: 05115328392; <a href="mailto:vogel.arndt@mh-hannover.de">vogel.arndt@mh-hannover.de</a>)</p>
Statistiker	Dipl.-Stat. Michael Scholz, Trium Analysis Online GmbH, München
Co-Antragsteller	<p>Dr. med. Martha Kirstein, Gastroenterologie, MHH Tel.: 05115329590; Fax: 05115328392; <a href="mailto:kirstein.martha@mh-hannover.de">kirstein.martha@mh-hannover.de</a></p> <p>PD Dr. med. Thomas Rodt, Institut für Diagnostische und Interventionelle Radiologie, MHH Tel.: 05115323421; Fax: 05115329421; <a href="mailto:rodt.thomas@mh-hannover.de">rodt.thomas@mh-hannover.de</a></p>
Titel der Studie (German)	TACE gefolgt von systemischer Therapie im Vergleich zu kontinuierlicher TACE beim intermediären hepatozellulären Karzinom - eine randomisierte multizentrische Phase-III Studie der AIO - AIO-HEP-0317
Hypothese	Unsere Hypothese lautet, dass bei Patienten mit hepatozellulärem Karzinom

	(HCC) im intermediären Stadium ein früher Wechsel von einer Induktionstherapie mit TACE zu systemischen Therapien (Sorafenib oder eine andere systemische Behandlung entsprechend der Entscheidung des Prüfarztes) im Vergleich zur Weiterführung der Behandlung mit TACE zu einer Verbesserung des Gesamtüberlebens führt.
Studienteilnehmer/ Studienpopulation	<p>Haupt-Einschlusskriterien:</p> <ul style="list-style-type: none"> <li>• Diagnose eines histologisch und/oder durch Bildgebung gesicherten hepatozellulären Karzinoms (HCC)</li> <li>• HCC im intermediären Stadium definiert durch: <ul style="list-style-type: none"> <li>➢ Child-Pugh-Score A, B7</li> <li>➢ Kein Kandidat für eine potentielle kurative Operation oder lokale Ablation</li> </ul> </li> <li>• Mindestens eine messbare Läsion nach mRECIST</li> <li>• Alter ≥ 18 Jahre</li> <li>• Eastern Cooperative Oncology Group performance status (ECOG-PS) 0-1</li> <li>• Vorausgehende Behandlung mit 2 TACE-Sitzungen (eine oder zwei Zielregionen) nach denen noch an mindestens einer Zielregion vitale Resttumormasse vorhanden ist</li> </ul> <p>Haupt-Ausschlusskriterien:</p> <ul style="list-style-type: none"> <li>• Kontraindikation für TACE oder für systemische Therapien mit Tyrosinkinase-Inhibitoren und Antikörpern wie Immun-Checkpoint-Inhibitoren oder Ramucirumab.</li> <li>• Extrahepatische Erkrankung</li> <li>• Vaskuläre Invasion des Hauptstamms der Pfortader</li> <li>• Vorangegangene systemische Therapie</li> <li>• Erwartete Lebertransplantation</li> <li>• Sekundäre Malignität innerhalb der letzten 3 Jahre</li> </ul>
Studiendesign	Interventionelle klinische Prüfung: Randomisierte multizentrische Phase III-Studie
Behandlung / Untersuchungen	<p>Experimentelle Intervention:</p> <p>Patienten mit stabiler Erkrankung (SD) oder partiellem Ansprechen (PR) nach modifizierten Response-Kriterien in soliden Tumoren (mRECIST) werden nach 2 Behandlungen mit TACE (entweder an einer oder zwei verschiedenen Zielregionen) zu systemischen Behandlungen (Sorafenib oder eine andere systemische Behandlung entsprechend der Entscheidung des Prüfarztes) gewechselt. Bildgebung (Computertomographie [CT]/Magnetresonanztomographie [MRT] und Laborkontrollen werden alle 10-12 Wochen ± 5 Tage durchgeführt. Bei Patienten mit progredienter Erkrankung (PD) oder Unverträglichkeit wird die Studientherapie abgebrochen.</p> <p>Kontroll-Intervention:</p> <p>Patienten mit SD oder PR nach mRECIST werden nach 2 Behandlungen mit TACE (entweder an einer oder zwei verschiedenen Zielregionen) weiterhin mit TACE behandelt. Behandlungsintervalle und maximale Anzahl der TACE-Sitzungen unterliegen der Entscheidung des Prüfarztes. Bildgebung (CT/MRI) und Laborkontrollen werden alle 10-12 Wochen ± 5 Tage nach TACE durchgeführt. Bei Patienten mit PD oder Unverträglichkeit wird die Studientherapie abgebrochen.</p> <p>Follow-up pro Patient:</p> <p>Während der Nachbeobachtung werden bis zum Zeitpunkt der Tumorprogression alle 3 Monate der Tumorverlauf und die Lebensqualität sowie das Gesamtüberleben erfasst. Die Dokumentation der Folgetherapie erfolgt alle 3 Monate bis zum Tod oder dem Ende der Studie.</p> <p>Dauer der Intervention pro Patient:</p> <p>Die Studientherapie dauert bis zur Progredienz der Erkrankung (PD) oder Unverträglichkeit (ca. 21 Monate).</p>
Endpunkt(e)	Primärer Endpunkt:

	<ul style="list-style-type: none"> <li>• Medianes Gesamtüberleben (mOS)</li> </ul> <p>Sekundäre Endpunkte:</p> <ul style="list-style-type: none"> <li>• Medianes progressionsfreies Überleben (mPFS)</li> <li>• Gesamt-Ansprechrates (ORR)</li> <li>• Lebensqualität (QoL)</li> <li>• Toxizitäten</li> <li>• Verschlechterung der Leberfunktion unter der Behandlung</li> <li>• 'Parametric response mapping'</li> </ul> <p>Erfassung der Sicherheit:</p> <ul style="list-style-type: none"> <li>• Toxizitäten werden nach 'CTC adverse events criteria version 4.03' eingeteilt.</li> </ul>
Studiendauer	<p>'First patient in' bis 'last patient out' (Monate): 5 Jahre (60 Monate) The study can be analyzed earlier or later depending on the number of events (N=145). Gesamt-Studiendauer (Monate): Die Gesamt-Studiendauer beträgt 5 Jahre (60 Monate). Rekrutierungszeitraum (Monate): 36 Monate</p>
Statistische Analyse	<p>Statistische Methoden für den Vergleich der Behandlungsgruppen hinsichtlich der primären und sekundären Zielkriterien: Kaplan-Meier (KM)-basierte Bewertung des mOS und der Überlebensraten. Methoden für zusätzliche Analysen wie Subgruppen-Analysen und angepasste Analysen: QoL: Mittlere Änderung in EORTC QLQ-C30 und HCC-18 vor und 14 Tage nach Behandlung in der Kontrollgruppe und an entsprechenden Zeitpunkten in der experimentellen Gruppe. Erfassung des Ansprechens durch Bildgebung basiert auf mRECIST/EASL Kriterien und 'parametric response mapping'</p>
Fallzahl	<p>Auf Studien-Eignung gescreent: (n =231) In die Studie eingeschlossen: (n =178) Analysiert: (n = 169)</p>
Teilnehmende Zentren	<p>Anzahl der beteiligten Städte: Ca. 25 Anzahl der beteiligten Zentren: Bis zu 30 Zentren Namen der Städte und Prüfzentren: Charité, Berlin; Kliniken Essen-Mitte, Essen; Krankenhaus Nordwest, Frankfurt; Universitätsklinikum Frankfurt, Frankfurt; Universitätsklinikum Freiburg, Freiburg; Universitätsklinik Hamburg, Hamburg; Medizinische Hochschule Hannover, Hannover; Universitätsklinikum des Saarlandes, Homburg; UKSH Kiel, Kiel; Klinikum Landshut, Landshut; Klinikum Leverkusen, Leverkusen; Medizinische Fakultät Universität Leipzig, Leipzig; Klinikum Magdeburg gGmbH, Magdeburg; Universitätsmedizin Johannes-Gutenberg Universität, Mainz; Klinikum rechts der Isar, München; Krankenhaus Barmherzige Brüder, Regensburg; Elblandklinikum, Riesa; Leopoldina Krankenhaus, Schweinfurt; SRH Krankenhaus, Sigmaringen; Universitätsklinik Würzburg, Würzburg</p>



Cholangiokarzinom, Erstlinie**AIO-HEP-0117: A randomized phase II trial of durvalumab and tremelimumab with gemcitabine or gemcitabine and cisplatin compared to gemcitabine and cisplatin in treatment-naïve patients with cholangio- and gallbladder carcinoma (IMMUCHEC)****AIO-Studie**

Studennummer/-Code:	AIO-HEP-0117 - IMMUCHEC
Status:	Genehmigt durch PEI und Ethikkommissionen
Erwarteter Studienstart:	Q2/2018
Weitere Zentren:	Geplante Anzahl Zentren erreicht. Interessierte Zentren können sich auf die Warteliste setzen lassen
Letzte Aktualisierung	09. April 2018

EudraCT No.	2017-001538-25
National Coordinating Investigator	Prof. Dr. med. Arndt Vogel Klinik für Gastroenterologie, Hepatologie und Endokrinologie Medizinische Hochschule Hannover Carl-Neuberg-Str. 1, 30625 Hannover, Germany Tel: +49 511-532-9590 , FAX.: +49-511-532-8392 E-Mail: vogel.arndt@mh-hannover.de
Sponsor	AIO-Studien-gGmbH Dr. Aysun Karatas Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, Fax +49 30 322932926 info@aio-studien-ggmbh.de
Study design	phase II, open-label, three-arm, 1:1:1 randomized, non-comparative, calibrated, multi-centre clinical trial
Anticipated start date	Q1/2018
Duration of study	Enrollment: 18 month + 6 month treatment + 6 month FU Total study duration: ~30 months
Indication	Advanced or metastatic CCA
Total number of sites	15
Primary objective	To determine the efficacy in terms of objective response rate (ORR) of the combination of durvalumab and tremelimumab in addition with gemcitabine or in addition with gemcitabine and cisplatin in treatment-naïve patients with advanced, unresectable and/or metastatic cholangio- and gallbladder carcinoma.
Secondary objectives	To determine 1.) the efficacy of the combination of durvalumab and tremelimumab in addition with gemcitabine or in addition with gemcitabine and cisplatin in treatment-naïve patients with advanced, unresectable and/or metastatic cholangio- and gallbladder carcinoma in terms of median overall survival (OS), median progression-free survival (PFS) and duration of response, 2.) to determine the safety/toxicity within a first safety stage and during the whole study, and 3.) quality of life (QOL).
Exploratory objectives	Prognostic and predictive biomarkers in the serum and in tumor tissue and correlation with response to treatment and survival for the treatment of durvalumab and tremelimumab in combination with gemcitabine or with gemcitabine and cisplatin.
Planned sample size	<b>N=63 total</b>
Inclusion criteria	1. Fully-informed written consent and locally required authorization (European Union [EU] Data Privacy Directive in the EU) obtained from

	<p>the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.</p> <ol style="list-style-type: none"> <li>2. Age <math>\geq</math> 18 years.</li> <li>3. Histologically documented diagnosis of cholangiocarcinoma or gall bladder carcinoma and available tumor tissue (block or at least 10 slides) for translational research.</li> <li>4. Performance status (PS) <math>\leq</math> 1 (ECOG scale).</li> <li>5. At least one measurable site of disease as defined by RECISTv1.1 criteria.</li> <li>6. Adequate bone marrow and renal function including the following: Hemoglobin <math>\geq</math> 9.0 g/dL; absolute neutrophil count <math>\geq</math> <math>1.5 \times 10^3</math>/L; platelets <math>\geq 100 \times 10^9</math> /L; Creatinine <math>\leq</math> 1.5 x upper normal limit.</li> <li>7. Calculated creatinine clearance <math>\geq 40</math> mL/min as determined by the Cockcroft-Gault equation</li> <li>8. Adequate hepatic function (with stenting for any obstruction, if required) including the following: Total bilirubin <math>\leq</math> 2x upper normal limit; AST (SGOT), ALT (SGPT) <math>\leq</math> 5 x upper normal limit; prothrombin time <math>\geq</math> 60%; albumin <math>\geq</math> 30 g/L.</li> <li>9. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial.</li> <li>10. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply: <ul style="list-style-type: none"> <li>- Women <math>&lt; 50</math> years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).</li> <li>- Women <math>\geq 50</math> years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses <math>&gt; 1</math> year ago, had chemotherapy-induced menopause with last menses <math>&gt; 1</math> year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).</li> </ul> </li> <li>11. The patient is willing and able to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations.</li> </ol>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study, or during the follow-up period of an interventional study</li> <li>2. Participation in another clinical study with an investigational product within 21 days prior to the first dose of the study treatment.</li> <li>3. Prior immunotherapy or use of other investigational agents, including prior treatment with an anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T-lymphocyte associated antigen-4 (anti-CTLA-4) antibody, therapeutic cancer vaccines.</li> <li>4. Prior chemotherapy with gemcitabine and cisplatin (exception: gemcitabin in the adjuvant setting, last infusion has to be <math>\geq</math> 6 months prior randomization).</li> <li>5. Any unresolved toxicity NCI CTCAE Grade <math>\geq 2</math> from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria <ul style="list-style-type: none"> <li>o Patients with Grade <math>\geq 2</math> neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.</li> <li>o Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.</li> </ul> </li> <li>6. Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for</li> </ol>

	<p>cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions for palliative intent is acceptable (eg, local radiotherapy).</p> <ol style="list-style-type: none"><li>7. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drugs.</li><li>8. Major surgery (as defined by the Investigator) within 4 weeks prior to the first dose of the IMP of starting the study and patients must have recovered from effects of major surgery. Note: Local non-major surgery for palliative intent (eg, surgery of isolated lesions, per-cutaneous biliary drainage or biliary stenting) is acceptable.</li><li>9. History of allogenic organ transplantation.</li><li>10. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], celiac disease, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:<ul style="list-style-type: none"><li>○ Patients with vitiligo or alopecia</li><li>○ Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement</li><li>○ Any chronic skin condition that does not require systemic therapy</li><li>○ Patients without active disease in the last 5 years may be included but only after consultation with the study physician</li></ul></li><li>11. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent</li><li>12. History of another primary malignancy except for:<ul style="list-style-type: none"><li>○ Malignancy treated with curative intent and with no known active disease <math>\geq 5</math> years before the first dose of IP and of low potential risk for recurrence</li><li>○ Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease</li><li>○ Adequately treated carcinoma in situ without evidence of disease</li></ul></li><li>13. History of leptomeningeal carcinomatosis</li><li>14. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have a CT/ MRI of the brain prior to study entry.</li><li>15. History of active primary immunodeficiency</li><li>16. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen [HBsAg] result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.</li><li>17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:<ul style="list-style-type: none"><li>○ Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)</li><li>○ Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent</li><li>○ Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)</li></ul></li></ol>
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	<p>18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IMP. <b>Note:</b> Patients, if enrolled, should not receive live vaccine whilst receiving IMP and up to 30 days after the last dose of IMP.</p> <p>19. Body weight <math>\leq 30</math> kg.</p> <p>20. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of tremelimumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy.</p> <p>21. Known allergy or hypersensitivity to any of the IMPs or any of the constituents of the product.</p> <p>22. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.</p> <p>23. Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the patient's participation in the study.</p> <p>24. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>25. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p>
Investigational medical products	<ul style="list-style-type: none"> <li>• Durvalumab (MEDI4736)</li> <li>• Tremelimumab</li> </ul> <p>Standard chemotherapy:</p> <ul style="list-style-type: none"> <li>• Cisplatin</li> <li>• Gemcitabine</li> </ul>
Treatment schedule	<p><b>Experimental arm 1 (arm A)</b></p> <ul style="list-style-type: none"> <li>• Gemcitabine will be administered at a dose of 1000 mg/m<sup>2</sup> as an IV infusion over 30 minutes, on day 1 and 8 of each 3-week cycle for up to a total of 24 weeks (8 cycles) according to the ABC-02 study.</li> <li>• Tremelimumab will be administered at a fixed dose of 75 mg as an IV infusion over 1 hour on day 1, to be repeated every 3 weeks for up to a total of 12 weeks (4 cycles) together with the durvalumab infusion. Tremelimumab may be reinduced for another 4 cycles upon PD.</li> <li>• Durvalumab will be administered at a fixed dose of 1500 mg as an IV infusion over 1 hour, on day 1, to be repeated every 3 weeks together with the tremelimumab infusion, provided tremelimumab will be administered, otherwise alone. After completion of chemotherapy durvalumab will be maintained at a dose of 1500 mg to be repeated every 3 weeks (see comment above).</li> </ul> <p><b>Experimental arm 2 (arm B)</b></p> <ul style="list-style-type: none"> <li>• Cisplatin will be administered over 1 hour at a dose of 25 mg/m<sup>2</sup> as an IV on day 1 and 8 of each 3-week cycle.</li> <li>• Gemcitabine will be administered at a dose of 1000 mg/m<sup>2</sup> as an IV infusion over 30 minutes, on day 1 and 8 of each 3-week cycle.</li> <li>• Both, gemcitabine and cisplatin, will be administered for up to a total of 24 weeks (8 cycles) according to the ABC-02 study.</li> <li>• Tremelimumab will be administered at a fixed dose of 75 mg as an IV infusion over 1 hour on day 1, to be repeated every 3 weeks for up to a total of 12 weeks (4 cycles) together with the durvalumab infusion. Tremelimumab may be reinduced for another 4 cycles upon PD.</li> <li>• Durvalumab will be administered at a dose of 1500 mg as an IV infusion over 1 hour, on day 1, to be repeated every 3 weeks together with the tremelimumab infusion, provided tremelimumab will</li> </ul>

	<p>be administered, otherwise alone. After completion of chemotherapy durvalumab will be maintained at a dose of 1500 mg to be repeated every 3 weeks.</p> <p><b>Standard Arm (Arm C)</b></p> <ul style="list-style-type: none"> <li>• Cisplatin will be administered over 1 hour at a dose of 25 mg/m<sup>2</sup> as an IV on day 1 and 8 of each 3-week cycle.</li> <li>• Gemcitabine will be administered at a dose of 1000 mg/m<sup>2</sup> as an IV infusion over 30 minutes, on day 1 and 8 of each 3-week cycle.</li> <li>• Number of cycles will be left to the investigator's discretion.</li> </ul> <p>Treatment until progressive disease, unacceptable toxicity, withdrawal of consent or death.</p>
Primary endpoint	Objective response rate (ORR) according to RECIST 1.1
Secondary endpoints	<ul style="list-style-type: none"> <li>• PFS</li> <li>• OS</li> <li>• Duration of Response</li> <li>• AEs / SAEs and Treatment Emergent Adverse Events according to CTC 4.03</li> <li>• Health related Quality of Life (HR-QoL) – EORTC-QLQ-C30</li> </ul>
Randomization procedure	1:1:1
Rationale	<p>The aim of this study is the assessment of the clinical activity of the combination of durvalumab and tremelimumab and of the combination of durvalumab and tremelimumab with gemcitabine and cisplatin compared to gemcitabine and cisplatin in treatment-naïve patients with locally advanced, unresectable or metastatic cholangio- and gallbladder carcinoma.</p> <p>Patients with CCA have poor outcomes, as a consequence of the very aggressive nature of the disease, and the limited treatment options. Thus there is a significant unmet medical need for additional treatment options for use in this patient population. Providing rationale to consider immunotherapy in the treatment of CCA, within a small study of 18 patients, lymphocytic infiltrates were seen in resected cholangiocarcinoma suggesting immune response as a relevant anti-cancer mechanism in CCA (Sabbatino F et al. 2016). In addition, previous biomarker studies on biliary tract tumor samples have shown a high rate of expression of PD-L1 in these tumors (Sabbatino F et al. 2016, Ye et al 2009, Suleimann Y et al. 2015). Within another small study expression of PD-L1 was found to be up-regulated in intrahepatic CCA compared with the cancer adjacent tissues and elevated expression was associated with poor histological differentiation and advanced tumor-nodal-metastatic (TNM) stage (Ye Y et al. 2009). Moreover, in a related immune therapy approach, tumor regression was achieved using adoptive transfer of tumor-infiltrating lymphocytes from a patient with CCA providing pivotal evidence that T-cells can control tumor growth and induce remission in CCA (Tran E et al. 2014). Mismatch repair (MMR) deficient tumors harbor hundreds to thousands of mutations that may produce neoantigens that can be recognized and targeted by T cells and have been shown to be highly sensitive to immunotherapeutic approaches. In two small phase-II trials, MMR deficient CCA patients have been treated successfully with pembrolizumab and nivolumab (Dung et al. J Clin Oncol 34, 2016 (suppl 4S; abstr 195) and Dung et al. J Clin Oncol 33, 2015 (suppl; abstr LBA100). Moreover, in the KEYNOTE-028, an ongoing, multicohort, phase 1b trial of pembrolizumab monotherapy for patients with PD-L1-positive advanced solid tumors, patients with biliary cancer were included if they had PD-L1-positive adenocarcinoma of the gallbladder or biliary tree (Bang et al. EJC 51, 2015 (suppl 3; abstr 525)). Out of 89 patients with biliary tract cancer 37 (42%) had PD-L1-positive tumors. As their best response, 4 (17%) patients had partial response, 4 (17%) stable disease, and 12 (52%) progressive disease. Importantly, 5 patients, including all responders, remained on treatment</p>

	<p>(duration of treatment: 40+ to 42+ weeks).          Considering, the combination of durvalumab and tremelimumab with chemotherapy, in the CCTG phase 1 study over 80 patients have been enrolled and treated with platinum doublet chemotherapy. There were no dose limiting toxicities (DLTs) at the highest dose levels providing evidence for a safe combination of durvalumab and tremelimumab with a chemotherapy doublet. The provisional objective response rate was 52.9% (95%CI: 28 – 77%) (Jeurgens et al. 2016).          As in most other tumor entities however, only a fraction of patients respond to immunotherapy alone. Evidence suggests that those patients might preferentially have tumors that have favorable mutational landscapes, express the PD-L1 and/ or contain pre-existing tumor-infiltrating CD8+ T cells that are inhibited locally, e.g., by PD-1 engagement. In order to increase the proportion of patients who could ultimately benefit from immunotherapies, it is important to develop strategies that can be employed for converting tumor microenvironments lacking T cell infiltration to ones displaying antitumor T-cell immunity and therefore to sensitize tumors to checkpoint inhibition therapy.          One approach to achieve this goal might involve the induction of immunogenic conditions in the tumor microenvironment. There is increasing evidence that chemotherapeutics such as gemcitabine can influence the tumor-host interactions and to stimulate T-cell immunosurveillance and therapy enhancing efficacy of immunotherapies (Pfirschke et al. 2016). The immune effects of gemcitabine have been studied perhaps more than for any other drug used in gastrointestinal cancer. Gemcitabine is a nucleoside analog that is part of the standard treatment of pancreaticobiliary malignancies. Its effects on the immune system are diverse including increased cross-presentation of antigen to CD8 cells resulting in their increased proliferation and functionality, an increase in MHC-I expression in tumor cells, resulting in increased killing by T cells and enhanced immunogenicity indirectly by depleting Tregs or myeloid derived suppressor cells (MDSCs) (Duffy and Greten 2014).          While it is important to delineate as much as possible the immune effects of individual chemotherapeutics, the reality is that most drugs are used in combination, particularly in the first-line setting. Few studies however have so far studied the net effect on the immune system for drug combinations. Some investigators have however shown that oxaliplatin/ irinotecan/5-FU combinations can be given to patients with vaccines without abrogation of the immune response (Harrop R et al. 2008). Currently, there are several ongoing clinical trials testing the potential of chemotherapy to enhance the efficacy of immune checkpoint blocking agents against various cancer types (Apetoh L et al. 2015). Based on these preclinical and preliminary clinical efficacy and safety data observed in patients with solid tumors (including CCA), the current study is conducted to evaluate the activity of durvalumab and tremelimumab in combination with chemotherapy compared to the standard of care in the first-line setting, gemcitabine and cisplatin, in treatment-naïve patients with CCA. In one experimental arm durvalumab and tremelimumab will be combined with gemcitabine and cisplatin. In the other experimental arm durvalumab and tremelimumab will be combined only with gemcitabine based on the assumption that gemcitabine mono might be sufficient to sensitize tumors to immune checkpoint inhibition in favor of a reduced toxicity.</p> <p><b>Hypothesis:</b>          We hypothesize that the combination of durvalumab and tremelimumab in addition with gemcitabine or in addition with gemcitabine and cisplatin is more effective compared to gemcitabine and cisplatin in treatment-naïve patients with advanced, unresectable and/or metastatic cholangio- and gallbladder carcinoma.</p>
<p>Safety data</p>	<ul style="list-style-type: none"> <li>• AEs / SAEs /Treatment Emergent Adverse Events according to CTCAE 4.03</li> <li>• Frequency of abnormal laboratory parameters</li> <li>• Immune related (ir)AEs of special interest will require additional</li> </ul>

	reporting (e.g. colitis, hepatitis, hypophysitis, uveitis or pneumonitis, pancreatitis)												
Sample size estimation	<p>The study is projected as an open label 1:1:1 randomized, three-arm, non-comparative phase II study, which investigates the efficacy of durvalumab and tremelimumab in addition with gemcitabine or in addition with gemcitabine and cisplatin in patients with locally advanced or metastatic CCA. The primary objective is to estimate best ORR per investigator assessment in both experimental treatment arms. The sample size estimation is based on the following assumptions:</p> <ol style="list-style-type: none"> <li>the objective response rate of the standard cisplatin+gemcitabine treatment is 20% (historical control)</li> <li>the objective response rates of each of the experimental treatments is 50%.</li> </ol> <p>A Fleming single-stage Phase II design will be used to test the null-hypothesis that (i) the true ORR in experimentally treated subjects is <math>\leq 20\%</math> (<math>P_0</math>) against a one-sided alternative that the ORR <math>\geq 50\%</math> (<math>P_A</math>). The test will be performed for each experimental treatment arm.</p> $H_0 : P \leq P_0 \quad H_A : P \geq P_A$ <p>Each experimental arm requires N=17 subjects to decide whether the proportion responding, P, is less than or equal to 0.2 or greater than or equal to 0.5. If the number of responses is 7 or more, the null-hypothesis that <math>P \leq 0.2</math> is rejected with a one-sided target error rate of <math>\alpha=0.05</math> (actual <math>\alpha</math> 0.04). If the number of responses is 6 or less, the alternative hypothesis that <math>P \geq 0.5</math> is rejected with a target error rate of <math>\beta=0.2</math> (Power = 80%; actual <math>\beta</math> 0.17).</p> <p>The efficacy analysis of the primary endpoint ORR is to be performed in all randomized subjects (ITT principle) as well as in the Per-Protocol-Population. The total sample size estimate is therefore adjusted according to the following assumption. Approx. 20 % of all randomized subjects do not qualify for the Per-Protocoll-population (i.e. subjects did not receive at least 3 treatment cycles and no post base-line tumor assessment has been performed). Hence, the number of subjects to be randomized in each treatment arm is N=21 to ensure sufficient evaluable subjects for the hypothesis testing. The total number of randomized study subjects is <b>N=63</b>.</p>												
QoL measurements	EORTC-QLQ-C30												
Study plan / time lines	<table> <tr> <td>First Patient In (FPI):</td> <td>Q1/2018</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 18 month</td> </tr> <tr> <td>Last Patient Last Visit (LPLV):</td> <td>after approx. 24 month</td> </tr> <tr> <td>End of follow-up period after LPLV:</td> <td>after approx. 30 month</td> </tr> <tr> <td>Study report:</td> <td>after approx. 39 month</td> </tr> <tr> <td>Publication:</td> <td></td> </tr> </table>	First Patient In (FPI):	Q1/2018	Last Patient In (LPI):	after approx. 18 month	Last Patient Last Visit (LPLV):	after approx. 24 month	End of follow-up period after LPLV:	after approx. 30 month	Study report:	after approx. 39 month	Publication:	
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Publication:													

**AIO-YMO/HEP-0315: Nal-IRI with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary-tract cancer - An open label, non-comparative, randomized, multicenter phase II trial (NIFE)**

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/ - Code	AIO-YMO/HEP-0315 - NIFE
Status:	6 Patienten rekrutiert, 5 randomisiert, Initiierungen laufen noch
Rekrutierungszeitraum:	2017 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung:	April 2018

Coordinating Investigator	Prof. Dr. med. Thomas Seufferlein Dr. med. Thomas Ettrich
Condition	Locally advanced or metastatic adenocarcinoma of the biliary tract including intrahepatic and extrahepatic bile ducts, gallbladder, and ampulla of Vateri
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Tel.: 030-322932934, FAX:030-322932926 E-Mail: info@aio-studien-ggmbh.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologists!	

*Cholangiozelluläres Karzinom, Zweitlinie*

**AIO-HEP-0116: A randomized phase II trial of nal-IRI and 5-Fluorouracil compared to 5-Fluorouracil in patients with cholangio- and gallbladder carcinoma previously treated with gemcitabine -based therapies (NALIRICC)**

<b>AIO- Studie</b>	
Studiennummer/-Code:	AIO-HEP-0116 - NALIRICC
Status:	Rekrutierung (18 Patienten rekrutiert, 16 randomisiert)
Rekrutierungszeitraum	2017 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

National Coordinating Investigator	Prof. Dr. med. Arndt Vogel Klinik für Gastroenterologie, Hepatologie und Endokrinologie Medizinische Hochschule Hannover Carl-Neuberg-Str. 1, 30625 Hannover, Germany Phone: +49 511-532-9590, FAX.: +49-511-532-8392 E-Mail: vogel.arndt@mh-hannover.de
Co-Coordinator:	Dr. med Martha Kirstein Klinik für Gastroenterologie, Hepatologie und Endokrinologie Medizinische Hochschule Hannover Carl-Neuberg-Str. 1, 30625 Hannover, Germany Phone:+49-511-532-0 Fax:+49-511-532-8392



	E-mail: kirstein.martha@mh-hannover.de
Sponsor	AIO-Studien-gGmbH Represented by Dr. Aysun Karatas (CEO) Kuno-Fischer-Straße 8, 14057 Berlin, Germany Phone: +49 30 814534435, Fax +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Study design	open label, randomized, multicenter phase II trial
Anticipated start date	Q4/2017
Duration of study	Enrollment: 24 months, total study duration ~32 months (incl. follow-up)
Indication	Advanced, unresectable and metastatic cholangio- and gallbladder carcinoma (CCA) after failure of gemcitabine-based therapies.
Target population	Patients with advanced, unresectable and metastatic cholangio- and gallbladder carcinoma eligible for treatments after failure to respond to a gemcitabine-based treatment.
Total number of sites	20
Primary objective	To assess the efficacy of nal-IRI in gemcitabine pre-treated patients with CCA.
Secondary objectives	To assess further efficacy variables as well as safety, tolerability and quality of life measures of nal-IRI for CCA.
Planned sample size	N=100 total (n=50 per treatment arm)
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Written informed consent incl. participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>2. Age <math>\geq</math> 18 years at time of study entry</li> <li>3. Histologically or cytologically confirmed, non-resectable, locally advanced or metastatic cholangiocarcinoma or gall bladder carcinoma</li> <li>4. Measurable or assessable disease according to RECIST 1.1</li> <li>5. Documented disease progression after prior gemcitabine or gemcitabine containing therapy, in locally advanced or metastatic setting. Examples of permitted therapies include, but are not limited to: <ol style="list-style-type: none"> <li>a) Single agent gemcitabine</li> <li>b) Any one gemcitabine-based regimen, with or without maintenance gemcitabine</li> </ol> </li> <li>6. ECOG performance status 0-1</li> <li>7. Adequate blood count, liver-enzymes, and renal function: <ul style="list-style-type: none"> <li>• ANC &gt; 1,500 cells/<math>\mu</math>L without the use of hematopoietic growth factors; and</li> <li>• Platelet count <math>\geq</math> 100 x 10<sup>9</sup>/L (&gt;100,000 per mm<sup>3</sup>) and</li> <li>• Hemoglobin &gt; 9 g/dL (blood transfusions are permitted for patients with hemoglobin levels below 9 g/dL)</li> <li>• Serum total bilirubin <math>\leq</math> 3x upper normal limit (ULN) (biliary drainage is allowed for biliary obstruction; elevated bilirubin should be caused by obstruction not impaired liver function as assessed by albumin and INR values): <ul style="list-style-type: none"> <li>• Albumin levels <math>\geq</math> 3.0 g/dL</li> <li>• Patients not receiving therapeutic anticoagulation must have an INR &lt; 1.5 ULN and PTT &lt; 1.5 ULN within 7 days prior to randomization. The use of full dose anticoagulants is allowed as long as the INR or PTT is</li> </ul> </li> </ul> </li> </ol>

	<p>within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose for anticoagulants for at least three weeks at the time of randomization</p> <ul style="list-style-type: none"> <li>• AST (SGOT)/ALT (SGPT) <math>\leq 5</math> x institutional upper limit of normal</li> <li>• Serum Creatinine <math>\leq 1.5</math> x ULN and a calculated glomerular filtration rate <math>\geq 30</math> mL per minute</li> </ul> <p>8. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of treatment.</p> <p>9. Subject is willing and able to comply with the protocol (including contraceptive measures) for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.</p>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Active CNS metastases (indicated by clinical symptoms, cerebral oedema, steroid requirement, or progressive disease); patient should have been off steroids for at least 28 days prior to starting study therapy</li> <li>2. Clinically significant gastrointestinal disorder including bleeding, inflammation, occlusion, or diarrhoea &gt; grade 1</li> <li>3. History of any second malignancy in the last 5 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years.</li> <li>4. Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes or an unexplained fever &gt; 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumour fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome.</li> <li>5. Premalignant hematologic disorders, e.g. myelodysplastic syndrome</li> <li>6. Pre-existing lung disease</li> <li>7. Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment</li> <li>8. History of hypersensitivity to any of the study drugs or any excipient (nal-IRI, other liposomal products, fluropyrimidines or leucovorin)</li> <li>9. Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy</li> <li>10. Severe non-healing wounds, ulcers or bone fractures</li> <li>11. Evidence of bleeding diathesis or coagulopathy</li> <li>12. Major surgical procedures, except open biopsy, nor significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgical procedure during the course of the study except for surgery of central intravenous line placement for chemotherapy administration.</li> <li>13. Medication that is known to interfere with any of the agents applied in the trial.</li> <li>14. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner].</li> <li>15. Known Gilbert-Meulengracht syndrome</li> <li>16. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient</li> </ol>

	<p>safety or study results</p> <p>17. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 5 half-lives of previously used trial medication, whichever is of longer duration.</p> <p>18. Previous enrollment or randomization in the present study (does not include screening failure).</p> <p>19. Previous enrollment in the NIFE trial [AIO-YMO/HEP-0315]</p> <p>20. Involvement in the planning and/or conduct of the study (applies to both Baxalta staff and/or staff of sponsor and study site)</p> <p>21. Patient who might be dependent on the sponsor, site or the investigator</p> <p>22. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>23. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p>
Investigational agents and active comparators	<ul style="list-style-type: none"> <li>• IRINOTECAN LIPOSOME (MM-398, nal-IRI)</li> <li>• 5-Fluorouracil,</li> <li>• leucovorin (calcium folinate)</li> </ul>
Treatment schedule	<p><u>Experimental intervention (Arm A):</u></p> <ul style="list-style-type: none"> <li>• nal-IRI 80 mg/m<sup>2</sup> as a 1.5 hour infusion</li> <li>• 5-FU 2400 mg/m<sup>2</sup> as 46 hour infusion</li> <li>• leucovorin 400 mg/m<sup>2</sup> as 0.5 hour infusion</li> <li>• Cycle q2w</li> </ul> <p><u>Control intervention – standard arm (Arm B):</u></p> <ul style="list-style-type: none"> <li>• 5-FU 2400 mg/m<sup>2</sup> as 46 hour infusion</li> <li>• leucovorin 400 mg/m<sup>2</sup> as 0.5 hour infusion</li> <li>• Cycle q2w</li> </ul> <p>In both study arms treatment continues until progressive disease or intolerable toxicity or withdrawal of consent.</p> <p><b>Key study procedures (and routine procedures):</b></p> <ul style="list-style-type: none"> <li>• Tumor assessment according to standard of care Q6W</li> <li>• Monitoring of serum tumor markers (Ca19-9, CEA, CRP) before and during therapy.</li> <li>• Blood sampling of 35 mL Q6W for translational research</li> </ul>
Primary endpoint	Progression-free survival
Secondary endpoints	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Objective response rate (ORR)</li> <li>• Safety (type, grade and frequency of AEs/SAEs)</li> <li>• QoL – EORTC QLQ C30</li> </ul>
Exploratory objectives and endpoints	<p>To assess prognostic biomarker in the serum and in tumor tissue and correlation with survival and response to treatment:</p> <ul style="list-style-type: none"> <li>• Ca-19-9, CEA, CRP serum levels before the beginning of treatment and during treatment.</li> <li>• Immunohistochemistry of Carboxylesterase (CES) 1 and 2 before treatment</li> <li>• Whole blood and plasma will be collected to potentially identify factors that may correlate with tumour response, sensitivity or resistance to nal-IRI.</li> </ul>

Randomization procedure	<p>1:1</p> <p>Stratified permuted block randomization will be applied to ensure balanced prognostic groups.</p> <p>The stratification parameter will be tumor localization:</p> <ul style="list-style-type: none"> <li>• Intrahepatic CCA (ICCA)</li> <li>• Extrahepatic CCA (ECCA)</li> <li>• Gallbladder CA (GB)</li> </ul>
Rationale Hypothesis	<p>Cholangio-/ Gallbladdercarcinoma (CCA) is an epithelial cancer originating from the bile ducts with features of cholangiocyte differentiation. CCA are rare tumours comprising only 3% of gastrointestinal tumours and having an overall incidence of less than 2/100 000 (Berquist A et al. 2015). However, they are the second most common primary hepatic malignancies, accounting for approximately 20% of the deaths from hepatobiliary cancer, which cause 13% of the total cancer mortality worldwide. Epidemiologic studies suggest its incidence is clearly increasing in Western countries during the last decades (Plentz RR et al. 2015, Berqqist A et al. 2015).</p> <p>The only curative option for patients with CCA is surgical resection. Unfortunately, most CCA remain clinically silent until the advanced stages. At advanced stage, CCA has a devastating prognosis. There are only limited numbers of studies about the systemic treatment options for biliary cancers. The combination of cisplatin with gemcitabine is the standard first-line chemotherapy for patients with unresectable CCA (Valle J et al. 2010; Okusaka T et al. 2010).</p> <p>So far, no standardized second-line therapy has been established due to the lack of prospective, randomized controlled trials. However, a systematic review and meta-analysis of phase II data and retrospective analyses recently provided weak evidence for second-line chemotherapy to prolong median progression-free (PFS) and overall survival (OS) (Lamarca A et al. 2014). In clinical practice, a combination of 5-fluorouracil (5-FU)-based chemotherapy alone or in combination with either irinotecan or oxaliplatin is most commonly administered rather than best supportive care (BSC).</p> <p>Regarding therefore this clinical standard from an ethical point of view, an evaluation of novel therapies within clinical trials requires a control against a 5-FU treatment rather than BSC. Nanoliposomal irinotecan (Nal-Iri) significantly improves overall and progression-free survival and response rate (RR) in combination with 5-FU compared to 5-FU alone in patients with metastatic pancreatic cancer after failure of gemcitabine treatment providing a rationale for potential efficacy in CCA as well (Chen LT et al. 2015).</p> <p><b>Research hypothesis:</b></p> <p>We hypothesize that the addition of nal-IRI to 5-FU improves progression-free survival (PFS) compared to 5-FU in patients with advanced, unresectable and metastatic cholangio- and gallbladder carcinoma after failure to respond to a gemcitabine treatment.</p>
Safety data	<ul style="list-style-type: none"> <li>• Treatment Emergent Adverse Events according to CTC 4.03</li> <li>• Frequency of abnormal laboratory parameters</li> </ul>
Sample size estimation	<p>Assumptions: The median PFS achieved with a combination of nal-IRI with 5-FU is estimated to be 3 months. The historical median PFS for 5-FU/FA is 1.5 months. The experimental therapy arm would be rated as insufficiently active, if the true median PFS is shorter than 3 months, as this corresponds to the efficacy of 5-FU alone. On the other hand, the experimental therapy would be</p>

	<p>considered to be a highly promising candidate for further development, if the true median PFS is 3 months or longer. Patient accrual is conducted for 24 month; treatment and follow-up are estimated to be 7 month on average per patient.</p> <p>With these assumptions a two-sided logrank test with an overall sample size of 99 subjects (49 in the control group and 50 in the experimental group) achieves a 90.3% power at a 5% significance level to detect a hazard ratio of HR=0.5 when the control group median survival time is 1.5 month. The study lasts for 31 month of which subject accrual (entry) occurs in the first 24 month. The proportion dropping out is 0.004 (equals 5% per year).</p> <p>In order to achieve balanced treatment arms it is proposed to recruit <b>N=100</b> patients into the study.</p> <p>For the final efficacy analysis a total of 96 observed events are required.</p>												
Study plan / time lines	<table> <tr> <td>First Patient In (FPI):</td> <td>Q4/2017</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 24 months</td> </tr> <tr> <td>Last Patient Last Visit (LPLV):</td> <td>after approx. 27 months</td> </tr> <tr> <td>End of follow-up period after LPLV:</td> <td>after approx. 31 months</td> </tr> <tr> <td>Study report:</td> <td>after approx. 42 months</td> </tr> <tr> <td>Publication:</td> <td>after approx. 45 months</td> </tr> </table>	First Patient In (FPI):	Q4/2017	Last Patient In (LPI):	after approx. 24 months	Last Patient Last Visit (LPLV):	after approx. 27 months	End of follow-up period after LPLV:	after approx. 31 months	Study report:	after approx. 42 months	Publication:	after approx. 45 months
First Patient In (FPI):	Q4/2017												
Last Patient In (LPI):	after approx. 24 months												
Last Patient Last Visit (LPLV):	after approx. 27 months												
End of follow-up period after LPLV:	after approx. 31 months												
Study report:	after approx. 42 months												
Publication:	after approx. 45 months												

Cholangiokarzinom (intra- und extrahepatisch), Gallenblasenkarzinom, Zweitlinie

**AIO-YMO/HEP-0316: 5-Fluorouracil (5-FU), folinic acid and irinotecan (FOLFIRI) versus 5-FU and folinic acid as second-line chemotherapy in patients with biliary tract cancer (IRIBIL): a randomized open-label phase 2 study**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer:	AIO-YMO/HEP-0316
Status:	in Vorbereitung
Rekrutierungszeitraum:	2017 – 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Oliver Waidmann
Kontaktadresse/ Kontaktperson:	Prof. Dr. Oliver Waidmann Universitätsklinikum Frankfurt Medizinische Klinik 1 Theodor-Stern-Kai 7 60590 Frankfurt am Main 0049-69-6301-5122 0049-69-6301-6580 E-Mail: <a href="mailto:oliver.waidmann@kgu.de">oliver.waidmann@kgu.de</a>
Die Synopse ist zu finden unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologists!	

Cholangiozelluläres Karzinom

**AIO-HEP-0112: Adjuvant chemotherapy with gemcitabine and cisplatin compared to standard of care (currently in stage 2 capecitabine) after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1). A randomized, multidisciplinary, multinational AIO/DGAV/DGVS phase III trial.**

## AIO-Studie

Studiennummer:	AIO-H EP-0112 - ACTICCA-1
Status:	in Rekrutierung
Rekrutierungszeitraum:	ab 2014
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Indication	Patients after curative intent resection of cholangiocarcinoma (intrahepatic, hilar or distal cholangiocarcinoma) or muscle invasive gallbladder cancer without evidence of metastatic disease.
Condition	Adjuvant treatment for cholangiocarcinoma (CCA) and muscle invasive gallbladder cancer
Study design	Randomized, controlled, two stage, multicenter, open labelled phase III trial
Principle Investigator	Henning Wege, Hamburg
Sponsor	Universitätsklinikum Hamburg-Eppendorf Funded by Deutsche Krebshilfe and medac GmbH (Germany) International funding by Cancer Research UK, KWF Kanker Bestrijding The Netherlands, AGITG Australia
Contact	Studienkoordination: Alexander Stein, Universitäres Cancer Center Hamburg E-Mail: <a href="mailto:a.stein@uke.de">a.stein@uke.de</a> E-Mail: <a href="mailto:acticca@uke.de">acticca@uke.de</a>
Endpoints	<u>Primary endpoints:</u> <ul style="list-style-type: none"> <li>• Disease free survival (DFS)</li> </ul> <u>Secondary endpoints:</u> <ul style="list-style-type: none"> <li>• Disease free survival rate at 24 months (DFSR@24)</li> <li>• Recurrence free survival</li> <li>• Overall survival (OS)</li> <li>• Safety and tolerability of adjuvant chemotherapy</li> <li>• Quality of life (QoL)</li> <li>• Function of biliodigestive anastomosis (in terms of surgical revision, requirement of PTCD)</li> <li>• Rate and severity of biliary tract infections</li> <li>• Patterns of disease recurrence</li> <li>• Locoregional control</li> </ul>
Number of patients/sites	781 patients to be randomized, 187 I in stage 1 and 594 in stage 2. 20 sites in Germany / 5 sites in the Netherlands / >20 sites in United Kingdom 8-10 sites in Australia / 2 sites in Denmark / 1 site in Austria
Start of recruitment	QII 2014 / Current status 05 APR 2018: 274 pts included/247 pts randomized
Study duration	Duration of recruitment (stage 2): 48 months. Expected total duration: 72 plus further 36 months follow up for overall survival

	(maximum of 5 years per individual patient).
Main selection criteria for treatment phase	<ol style="list-style-type: none"> <li>1. Histologically confirmed adenocarcinoma of biliary tract (intrahepatic, hilar or extrahepatic cholangiocarcinoma or muscle invasive gallbladder cancer) after radical surgical therapy with macroscopically complete resection (mixed tumor entities (HCC/CCA) are excluded)</li> <li>2. Macroscopically complete resection (R0/1) within 6(-16) weeks before start of chemotherapy</li> <li>3. No prior chemotherapy for CCA</li> <li>4. Written informed consent</li> <li>5. ECOG 0-1</li> <li>6. Age &gt;18 years</li> <li>7. Adequat haematologic function: ANC <math>\geq 1.5 \times 10^9/L</math>, platelets <math>\geq 100 \times 10^9/L</math>, haemoglobin <math>\geq 9 \text{ g/dl}</math> or <math>\geq 5.59 \text{ mmol/L}</math></li> <li>8. Adequate liver function as measured by serum transaminases (AST and ALT) <math>\leq 5 \times \text{ULN}</math> and conjugated (direct) bilirubin <math>\leq 3 \times \text{ULN}</math></li> <li>9. Adequate renal function, i.e. serum creatinine <math>\leq 1.5 \times \text{ULN}</math>, glomerular filtration rate <math>\geq 50 \text{ mL/min}</math></li> </ol>
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><b>enrolment phase</b></p> </div> <div style="width: 45%;"> <p><b>treatment phase</b></p> </div> </div>	
Treatment, dosage and administration	<p>All patients eligible for the treatment phase in stage 2 will be randomized to adjuvant chemotherapy with gemcitabine and cisplatin and observation or capecitabine and observation.</p> <p><b>Arm A: Gemcitabine/cisplatin and observation</b>          Therapy will be administered on days 1 and 8 every 3 weeks. Cisplatin (25 mg per square meter of body-surface area) and gemcitabine (1000 mg per square meter) (Valle, Wasan et al. 2010).</p> <p><b>Arm B: Capecitabine and observation</b>          Therapy will be administered from day 1 to 14 every 3 weeks, with capecitabine (1250 mg per square meter of body-surface area, twice daily).</p> <p><b>Observation</b>          Post-resection evaluation for tumor recurrence will be conducted following current clinical standards (CT or MRI every 3 months for two years after randomization followed by 6-monthly abdominal ultrasound for further 3 years and at the discretion of the investigator thereafter) until disease recurrence (radiological signs of recurrence or histological tumour detection by cytology or biopsy) in both groups.</p> <p><b>Duration of treatment</b>          Adjuvant treatment will be administered for 24 weeks (8 cycles of 3 weeks) postoperatively starting 6-16 weeks after surgery. In case of progressive disease (radiological signs of recurrence), unacceptable toxicity or withdrawal of consent, treatment will be terminated.</p>





## Interdisziplinäre Arbeitsgruppe Hodentumoren

### Hodentumoren, Seminom Stadium IIA/B

#### **Carboplatin chemotherapy and involved node radiotherapy in stage IIA/B seminoma (Protocol SAKK 01/10)**

#### **AIO-assozierte Studie**

Studiennummer/-Code:	SAKK 01/10 (in Kooperation mit der AIO)
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 – 2018
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2017

Art der Studie Study Type	Phase-II
Verantwortlicher Studienleiter nach AMG	Dr. Alexandros Papachristofilou, Basel, Schweiz
Kontaktadresse/ Kontaktperson:	Dr. Alexandros Papachristofilou Radiation Oncology University Hospital Basel Phone: +41 61 265 49 46 Fax: +41 61 265 54 69 E-Mail: apapachristofilou@uhbs.ch
Studienziele/ Objectives	<u>Primäres Studienziel:</u> Effektivität (3-Jahres progressionsfreies Überleben) <u>Sekundäre Studienziele:</u> akute und Langzeittoxizität
Zielparameter/ Objectives	Ansprechrate, TTP, OS, Lokalisation des Progresses, Methode der Progress-Diagnose, akute und langfristige Toxizität, Sekundärmalignome, Metabolisches Syndrom, Hypogonadismus
Patientenzahl Number of patients	Geplant: 115 Patienten Bereits eingeschlossen: 96 (davon 44 aus Deutschland)
Haupt- Einschlusskriterien / Key inclusion criteria	Histologisch bestätigtes reines klassisches Seminom, therapiert mit primärer inguinaler Orchiektomie innerhalb von 12 Wochen vor Studieneinschluss. Multi-slice Computertomographie (CT) von Thorax, Abdomen und Becken oder Fludeoxyglucose (FDG-) Positronen-Emissions-Tomographie (PET)-CT innerhalb von 4 Wochen vor Registrierung, die eine Erkrankung im Stadium IIA/B bestätigt. Normales AFP und keine gemische Histologie.
Therapieschema Scheme of therapy	Einmalige Gabe von Carboplatin AUC 7 an Tag 1, dann 3 Wochen später Radiatio mit 15 x 2 Gy (Stadium IIA) oder 18 x 2 Gy (Stadium IIB) small volume, involved node therapy.
Tumorevaluierung Criteria for evaluation	Verlaufskontrollen 3, 6, 9, 12, 15, 18, 21, 24, 30 und 36 Monate nach Registrierung
Rationale	Patienten im Stadium IIA/B erreichen mit 3 Zyklen PEB oder einer großvolumigen paraaortalen und ipsilateral pelvischen Bestrahlung ("dogleg field") gute Heilungschancen, aber auch relevante Toxizitäten und scheinen übertherapiert

Hodentumoren, refraktäre Erkrankungssituation**AIO-GC-0116/ass: Cabazitaxel bei Patienten mit refraktären oder mehrfach rezidierten Keimzelltumoren****AIO-assoziierte Studie**

Studennummer/-Code:	AIO-GC-0116/ass
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 – 2017
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2017

Art der Studie Study Type	Multizentrische Phase II-Studie
Verantwortlicher Studienleiter nach AMG	Deutschland: Prof. Dr. Carsten Bokemeyer (International: Prof. Dr. med. Jan Oldenburg; Akershus University Hospital, Norway)
Kontaktadresse/ Kontaktperson:	Prof. Dr. med. Carsten Bokemeyer Kontakt: Dr. med. Christoph Oing II. Medizinische Klinik & Poliklinik Universitätsklinikum Hamburg-Eppendorf Tel.: (+49) 040 7410 53831 Fax: (+49) 040 7410 55139
Studienziele/ Objectives	<u>Primärer Studienendpunkt:</u> Evaluation der Wirksamkeit (objektivierbares Ansprechen n. RECIST 1.1, Verlauf Tumormarker AFP und $\beta$ HCG) von Cabazitaxel als Monotherapie <u>Sekundäre Studienendpunkte:</u> Krankheitskontrollrate, PFS, OS, Sicherheitsprofil, Veränderung der Serumtumormarkerlevel
Zielparameter/ Objectives	ORR (RECIST v1.1), Krankheitskontrollrate (SD + PR + CR), Tumormarkerverlauf (AFP, $\beta$ HCG), PFS, OS, Toxizität n. CTC-Kriterien
Patientenzahl Number of patients	Geplant: 29, bislang rekrutiert: 9 (Norwegen, Dänemark, Italien)
Rekrutierungszeitraum von/bis / period of	07/2015 (Norwegen), Deutschland voraussichtlich November 2017 bis Dezember 2018
Weitere teilnehmende Zentren erwünscht?	Nein (Deutsche Studienzentren: Hamburg, Berlin, Düsseldorf, Tübingen)
Haupt-Einschlusskriterien / Key inclusion criteria	Männliches Geschlecht, Alter $\geq$ 18 Jahre, Histologisch bestätigter metastasierter Keimzelltumor testikulären oder extragonadalen (d.h. retroperitonealen oder mediastinalen) Ursprungs, Krankheitsprogression während Cisplatin-basierter Chemotherapie <i>oder</i> Krankheitsprogression <i>oder</i> Rezidiv nach Hochdosischemotherapie <i>oder</i> Krankheitsprogression <i>oder</i> Rezidiv nach mindestens 2 verschiedenen Platin-basierten Therapieregimen, ECOG-Performance Status: 0 – 2, Lebenserwartung $\geq$ 3 Monate, adäquate Funktion von Leber, Nieren und Knochenmark bei Basisevaluation
Therapieschema Scheme of therapy	Cabazitaxel 25mg/m <sup>2</sup> , Tag 1, Wdh. Tag 22 für insgesamt 6 Zyklen
Tumorevaluierung	Objektives Ansprechen (n. RECIST v1.1), Serumtumormarkerwerte vor

Criteria for evaluation	Therapiebeginn und vor jedem weiteren und nach dem letzten Therapiezyklus
Rationale	Metastasierte Keimzelltumoren, die nach zwei oder mehr Cisplatin-basierten Chemotherapien / nach Hochdosismethotherapie rezidivieren haben eine schlechte Prognose ohne kurative Behandlungsoption. Taxane haben zytotoxische Wirkung auf refraktäre Keimzelltumoren gezeigt. Cabazitaxel ist ein synthetisches Taxan, welches entwickelt wurde, um die Resistenz gegen Docetaxel und Paclitaxel zu überwinden. Darüberhinaus scheint die Resistenzentwicklung unter Cabazitaxel weniger wahrscheinlich verglichen mit anderen Taxanen.

### Hodentumoren, alle Stadien

**AIO-GC-0316/ass: MicroRNA miR-371a-3p – neuer Serum-Biomarker bei Keimzelltumoren: eine multizentrische prospektive klinische Studie der Interdisziplinären Arbeitsgruppe Hodentumore.**

<b>AIO-assozierte Studie</b>	
Studiennummer/-Code:	AIO-GC-0316/ass
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 – 2017
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	April 2017

Art der Studie	Prospektive multizentrische Validierungsstudie
Verantwortlicher Studienleiter nach AMG	Prof. Dr. med. Klaus-Peter Dieckmann
Kontaktadresse	Prof. Dr. med. Klaus-Peter Dieckmann Klinik für Urologie Albertinen-Krankenhaus Tel.: +49 (0) 40 5588 2253 Fax: +49 (0) 40 5588 2381 <a href="mailto:Klauspeter.dieckmann@albertinen.de">Klauspeter.dieckmann@albertinen.de</a>
Studienziele	<u>Primärer Endpunkt:</u> Serumkonzentrationsbestimmung der miR-371a-3p <u>Sekundärer Endpunkt:</u> Tumormarkerkinetik unter operativer oder systemischer Therapie; Vergleich zu Expressionslevel und Kinetik von AFP und $\beta$ HCG; Expressionslevel unterschiedlicher Erkrankungsstadien St. I vs. II/III/IV und nach IGCCCG-Risikogruppen
Zielparameter	Serum-miRNA-Level der miR-371a-3p
Patientenzahl	Geplant: ca. 400, bislang Proben von knapp über 300 Patienten asserviert
Rekrutierungszeitraum von/bis	01.07.2015 bis vorraussichtlich 30.06.2017
Weitere teilnehmende Zentren erwünscht?	Ja
Haupt-Einschlusskriterien	Männliches Geschlecht, Erstdiagnose oder Rezidiv eines Keimzelltumors

Therapieschema	Keine Beeinflussung der Therapieentscheidung der behandelnden Ärzte. Entnahme von Patientenserum vor Therapiebeginn, sowie einmalig postoperativ bzw. vor jedem weiteren Chemotherapiezyklus und einmalig nach Ende einer Chemotherapie.
Tumorevaluierung	Serum-MiRNA-Level vor, während und nach Therapie (OP, Chemotherapie)
Rationale	Die Bestimmung der Serumtumormarker ist essenziell für Diagnosestellung, Prognosebeurteilung, Therapiewahl und Beurteilung des Therapieansprechens. Die Sensitivität und Spezifität der bisher etablierten Hodentumormarker AFP, $\beta$ HCG und LDH sind limitiert. Ziel der aktuellen Studie ist die Validierung des deutlich sensitiveren und spezifischeren Tumormarkers miR-371a-3p an einem großen Patientenkollektiv, nachdem eine Pilotstudie positiv verlaufen war (Dieckmann et al., Eur Urol 2016).

Registerstudie: Hodentumoren, reines Seminom, alle Stadien

**AIO-GC-0716/ass: Internationales Register zu Tumormarkerkonstellationen beim Seminom ("Tumor markers in seminoma patients: An observational study correlating the marker constellation with patient characteristics and outcome of the Global Germ Cell Cancer Consortium")**

**AIO-assoziierte Studie**

Studiennummer/-Code:	AIO-GC-0716/ass
Status:	in Rekrutierung
Rekrutierungszeitraum	2016 – 2017
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	Oktober 2017

Art der Studie Study Type	Retrospektive Registerstudie
Verantwortlicher Studienleiter nach AMG	Prof. Dr. med. Carsten Bokemeyer
Kontaktadresse/ Kontaktperson:	Dr. med. Christoph Seidel II. Medizinische Klinik & Poliklinik Universitätsklinikum Hamburg- Eppendorf Tel.: (+49) 040 7410 0 Fax: (+49) 040 7410 55234
Studienziele/ Objectives	<u>Primärer Endpunkt:</u> Verteilung und Charakteristik der Tumormarkererhöhung <u>Sekundäre Endpunkte:</u> Zusammenhänge zwischen Tumormarkerverlauf und Patienten- und Krankheits-
Zielparameter/ Objectives	Tumorgröße, Metastasierungsmuster, Primärtumorlokalisation, Stadium, LDH-Verlauf, Therapieansprechen, Restvitalität, Rezidivrate, PFS, OS
Patientenzahl Number of patients	Geplant: ca. 250 Patienten
Rekrutierungszeitraum von/bis	Voraussichtlich 12/2016 bis 12/2017
Weitere teilnehmende	Ja

Zentren erwünscht?	
Haupt-Einschlusskriterien / Key inclusion criteria	Histologisch nachgewiesenes reines Seminom, männliches Geschlecht, Alter > 18 Jahre, alle Tumorstadien, keine AFP-Erhöhung.
Therapieschema Scheme of therapy	Retrospektive Datenerhebung anhand von CRFs, keine Vorgabe eines Therapieregimes
Tumorevaluierung Criteria for evaluation	Retrospektive Erfassung des Krankheitsverlaufs und Überlebens
Rationale	Mäßiggradige Erhöhungen des Tumormarkers $\beta$ -HCGs finden sich bei etwa 30% aller Patienten mit reinem Seminom. Bisher existieren keinerlei Daten dazu, wie die spezifischen Charakteristika dieser besonderen Subgruppe wirklich sind und welche therapeutischen und prognostischen Konsequenzen dadurch entstehen.

### Hodentumoren, Rezidivsituation

**AIO-GC-0416/ass: A Randomized phase III trial comparing conventional-dose chemotherapy using paclitaxel, ifosfamide, and cisplatin (TIP) with high dose chemotherapy using mobilizing paclitaxel followed by High-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumours**

<b>AIO-assozierte Studie</b>	
Studiennummer/-Code:	AIO-GC-0416/ass
Status:	Für Deutschland Studienstart in Q1 2018 geplant
Rekrutierungszeitraum	2016 – 2020
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	Oktober 2017

Art der Studie	Phase-III; international, multizentrisch
Verantwortlicher Studienleiter nach AMG	Sponsor USA: Alliance; Darren Feldman; New York Sponsor Europa: EORTC; Thomas Powles MD; London Für Deutschland: Prof. Dr. med. Anja Lorch, Düsseldorf
Kontaktadresse/ Kontaktperson:	Univ.-Prof. Dr. med. Anja Lorch FÄ Hämatologie und Onkologie Leitung Bereich kons. urolog. Onkologie Klinik für Urologie Universitätsklinikum Düsseldorf Tel.: 0211- 81 08776 Fax: 0211- 81 04640 anja.lorch@med.uni-duesseldorf.de
Studienziele/ Objectives	<u>Primäres Studienziel:</u> Overall survival <u>Sekundäres Studienziel:</u> Progression-Free Survival (PFS) Favorable Response Rate (CR + PR-neg markers); Toxicity Prospective Evaluation of the IPFSG Prognostic Model
Zielparameter/ Objectives	OS, PFS, Favorable Response Rate (CR + PR-neg markers); Toxicity Prospective Evaluation of the IPFSG Prognostic Model Biologic correlates

Patientenzahl Number of patients	Geplant Gesamtstudie: 420 Patienten, pro Arm jeweils 210 Patienten Aus Deutschland: geplanter Einschluß von etwa 70-75 Patienten Studie in den USA in 08/16 gestartet, Studienstart in Italien im Sommer 2017 erfolgt, Start in Deutschland für Q1 2018 geplant
Rekrutierungszeitraum von/bis period of	Initial 08/16 – 08/20 für alle Zentren weltweit, jedoch Verlängerung geplant, da verspätete Initiierungen an allen europäischen Zentren incl. Deutschland.
Weitere teilnehmende Zentren erwünscht?	Folgende Zentren in Deutschland sind derzeit in Vorbereitung zum Studienstart: Berlin Vivantes, Berlin Charite, UK Dresden, UK Düsseldorf, UK Essen, UK Hamburg-Eppendorf, Städtisches Klinikum Koblenz, UK Marburg, UK Nürnberg, UK Ulm, Rot-Kreuz Klinikum München
Haupt-Einschlusskriterien / Key inclusion criteria	Male gender Age $\geq$ 18 years for Germany ECOG Performance Status 0 to 2 GCT histology (Seminoma and Nonseminoma) Unequivocal progression of measurable disease following one line of cisplatin-based chemotherapy Unequivocal progression of non-measurable disease with consecutive elevated markers following one line of cisplatin-based chemotherapy A minimum of three and maximum of six cisplatin-based treatment cycles No more than one prior line of chemotherapy for GCT Patients with late relapses who have unresectable disease Completion of a full informed consent
Therapieschema Scheme of therapy	4 Zyklen konventionelle Chemotherapie TIP <b>versus</b> 3 Zyklen CE- Hochdosischemotherapie
Tumorevaluierung Criteria for evaluation	Marker und Bildgebung Baseline, unter Therapie und im Rahmen der Nachsorge, Lebensqualitätsbogen QLQ-C30
Rationale	<p>Etwa 5-10% aller Betroffenen und etwa 30% der Männer mit initial metastasiertem Keimzelltumor benötigen zu irgendeinem Zeitpunkt ihrer Erkrankung eine Rezidivchemotherapie. Eine der erfolgreichsten konventionell dosierten Rezidivschemata kombiniert Cisplatin und Ifosfamid mit Paclitaxel (TIP).</p> <p>Je nach Risikofaktoren zum Rezidivzeitpunkt können noch etwa 15-60% der Patienten geheilt werden. Dennoch sind diese Ergebnisse vor allem bei Patienten mit Risikofaktoren im Rezidiv wesentlich schlechter als nach primärer Chemotherapie. Derzeit sterben in Deutschland bei einer Inzidenz von ca. 4000 Männern pro Jahr etwa 150-160 Betroffene an ihrer Erkrankung - zumeist in einem jungen Alter von 20-40 Jahren.</p> <p>Durch die Einführung der Hochdosischemotherapie (HDCT) mit Reinfusion autologer hämatopoetischer Stammzellen Ende der 80-iger Jahre konnten die unbefriedigenden Ergebnisse der konventionellen Rezidivchemotherapie verbessert werden. Über zwei oder drei Zyklen sequentiell verabreichtes hochdosiertes Carboplatin und Etoposid (CE) stellt dabei das Grundgerüst einer HDCT dar.</p> <p>Das optimale Vorgehen bei 1. Rezidiv nach cisplatinhaltiger Primärtherapie steht weltweit weiter in der Diskussion. Von vielen Experten wird der Nutzen einer HDCT insbesondere im ersten Rezidiv heftig bestritten. Andere Experten glauben hingegen mit der vorhandenen Evidenz einen Überlebensvorteil durch den Einsatz einer HDCT nachweisen zu können.</p> <p>Unsere eigene Arbeitsgruppe hat zwischen 2007 und 2008 knapp 1600 Datensätze zur Rezidivtherapie an 38 Zentren in Europa, den USA und Kanada gesammelt und ausgewertet. In allen Analysen zeigte sich dabei eine Überlegenheit der HDCT gegenüber der konventionell dosierten Therapie sowohl in Bezug auf das progressionsfreie Überleben als auch auf das</p>

	<p>Gesamtüberleben. Allerdings wurden die Daten wegen des retrospektiven Ansatzes von kritischen Experten nicht als ausreichenden Beleg erachtet.</p> <p>Da auf Grund der zu erwarteten Patientenzahl kein Land bzw. keine Studiengruppe diese Daten prospektiv überprüfen kann, haben sich mehrere Studiengruppen in den USA und Europa geeinigt, auf der Grundlage der aktuellen Daten die Rolle der HDCT im Rahmen einer internationalen, prospektiven randomisierten multizentrischen Phase III Studie zu überprüfen.</p> <p>Im Verlauf mehrerer Jahre konnte ein gemeinsames internationales Studienprotokoll verabschiedet werden. In diesem Protokoll sollen vier Zyklen der weltweit am häufigsten eingesetzten konventionell-dosierten Therapie mit TIP im Studienarm A mit einer sequentiellen HDCT mit CE im Studienarm B verglichen werden.</p> <p>Die Studie wird in internationaler Zusammenarbeit als „Intergroup Trial“ durchgeführt.</p> <p>Die Deutsche Studiengruppe Hodentumoren stellt eine der weltweit aktivsten Gruppen im Bereich männlicher Keimzelltumoren speziell im Bereich der HDCT dar. Aufgrund der bisherigen Studienaktivitäten wird aus Deutschland der wichtigste Beitrag bezüglich der Rekrutierung in dem Studienvorhaben erwartet.</p> <p>Erfahrungen einer eigenen prospektiven randomisierten Studie zum Einsatz der HDCT in Deutschland zeigten, dass nur wenige Zentren die erforderliche Expertise vorhalten und die erforderliche hohe Rekrutierungsfrequenz aufweisen können. Daher soll das Studienvorhaben deutschlandweit nur an maximal zwölf Zentren durchgeführt werden, die geographisch möglichst über die verschiedenen Bundesländer verteilt sind. Die Studie wird durch die Deutsche Krebshilfe gefördert.</p> <p>Die Durchführung des Forschungsvorhabens in Deutschland wird in Kooperation mit einem Koordinierungszentrum für Klinische Studien (KKS) als CRO erfolgen.</p>
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Registerstudie: Hodentumoren, refraktäre Erkrankungssituation

**AIO-GC-0516/ass: Internationales Register für Patienten refraktären Keimzelltumoren (“Palliative Systemic Treatment of Advanced Germ Cell Tumors: Options and Outcomes: An International Registry Study of the Global Germ Cell Cancer Consortium G3”)**

<b>AIO-assozierte Studie</b>	
Studennummer/-Code:	AIO-GC-0516/ass
Status:	in Vorbereitung
Rekrutierungszeitraum	2017 – 2018
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2017

Art der Studie Study Type	Retrospektive Registerstudie
Verantwortlicher Studienleiter nach AMG	Prof. Dr. med. Carsten Bokemeyer
Kontaktadresse/ Kontaktperson:	Dr. med. Christoph Oing II. Medizinische Klinik & Poliklinik Universitätsklinikum Hamburg-Eppendorf Tel.: (+49) 040 7410 53831 Fax: (+49) 040 7410 55139

Studienziele/ Objectives	<u>Primärer Endpunkt:</u> PFS und OS unter palliativer Systemtherapie <u>Sekundäre Endpunkte:</u> Therapieansprechen, Tumormarkerverlauf, Organfunktionen, Todesursachen, Symptome, Vortherapien
Zielparameter/ Objectives	Vortherapien, Therapieansprechen (CR/PR/SD/PD), PFS, OS, Tumormarkerverlauf, Organfunktionen, Todesursachen, Symptomlast
Patientenzahl Number of patients	Geplant: ca. 250 Patienten
Rekrutierungszeitraum von/bis period of	12/2016 bis voraussichtlich 06/2018
Weitere teilnehmende Zentren erwünscht?	Ja
Haupt-Einschlusskriterien / Key inclusion criteria	Männliches Geschlecht; metastasierter Keimzelltumor; Cisplatin-refraktäre Erkrankung; Systemtherapie (Mono- und Kombinationschemotherapie) in palliativer Intention; Versagen von mindestens 2 Vortherapien (inkl. Hochdosischemotherapie)
Therapieschema Scheme of therapy	Retrospektive Datenerhebung anhand von CRFs, keine Vorgabe eines Therapieregimes
Tumorevaluierung Criteria for evaluation	Retrospektive Erfassung des radiologischen Ansprechens nach RECIST (CR/PR/SD/PD) sowie des Tumormarkerverlaufs (AFP, $\beta$ HCG) während palliativer Systemtherapie
Rationale	Das Überleben Cisplatin-refraktärer Patienten ist i.d.R. auf wenige Monate begrenzt. Nach Versagen einer Hochdosischemotherapie und des GOP-Regimes gibt es keine weitere Standardtherapieoption. Die verfügbaren Daten zu palliativen Systemtherapien ist unzureichend. Ziel der Arbeit ist es, die Praxis der palliativen Systemtherapie und ihre Wirksamkeit zu evaluieren.

### AIO-GC-0616/ass: Register für HIV-positive Keimzelltumorpatienten

#### AIO-assozierte Studie

Studiennummer/-Code:	AIO-GC-0616/ass
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 – 2017
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	Oktober 2017

Art der Studie Study Type	Retrospektive multizentrische Registerstudie
Verantwortlicher Studienleiter nach AMG	Prof. Dr. Marcus Hentrich
Kontaktadresse/ Kontaktperson:	Rotkreuzklinikum München III. Medizinische Abteilung Nymphenburger Straße 163 80634 München Tel. 089 1303 4372 Fax. 089 6210 4375



	Marcus.hentrich@swmbrk.de
Studienziele/ Objectives	<u>Primäre Ziele:</u> - Progressionsfreies Überleben (PFS) - Gesamtüberleben (OS) <u>Sekundäre Ziele:</u> - Remissionsraten - Art und Toxizität der onkologischen Therapie - Therapie und Verlauf der HIV-Infektion
Zielparameter/ Objectives	Ansprechrate, PFS, OS, Toxizität, Verlauf der CD4-Zellen und der HIV-RNA, Therapie der HIV-Infektion
Patientenzahl Number of patients	50
Haupt-Einschlusskriterien Key inclusion criteria	- Histologisch gesicherter Keimzelltumor (ED nach 1995) - HIV-Infektion
Therapieschema Scheme of therapy	Nicht festgelegt
Tumorevaluierung Criteria for evaluation	Lokalem Standard entsprechend
Rationale	HIV-infizierte Patienten mit Keimzelltumoren (KZT) weisen eine ungünstigere Prognose auf als Patienten ohne HIV-Infektion. In der Ära effektiver antiretroviraler Therapien hat sich dies möglicherweise geändert.

### Registerstudie

#### **Erfassung von Leydigzelltumoren und noch selteneren Sertolizelltumoren**

<b>AIO-assoziierte Studie</b>	
Kontaktadresse/ Kontaktperson:	Prof. Dr. med. Sabine Kliesch Chefärztin der Klinischen Andrologie Centrum für Reproduktionsmedizin und Andrologie WHO Kollaborationszentrum, EAA Ausbildungszentrum Universitätsklinikum Münster Domagkstraße 11 48149 Münster E-Mail: sabine.kliesch@ukmuenster.de Tel. 02 51/83-5 60 96, -5 60 97 Fax 02 51/83-5 60 93
Beschreibung	Leydigzelltumoren sind seltene Tumoren des Hodens, die in 90% der Fälle gutartig sind. Da nach wie vor keine Klarheit bzgl. des Vorgehens (radikale Orchiektomie oder lokale organerhaltende Tumorenukleation) und der Nachsorge (engmaschige Kontrollen wie bei den malignen Keimzelltumoren?) und des Risikos der malignen Entartung besteht, werden alle Kliniken und Zentren gebeten, Ihre Leydigzelltumoren zu melden (z.B. Arztbrief, OP-Bericht, Pathohistologischer Befund) und die follow-up Daten zur Verfügung zu stellen. Da auch die pathohistologische Beurteilung und die Genesefaktoren für die Entstehung dieser Stromatumoren nur auf sehr begrenztem Wissen basieren, ist der Zugang zum Gewebe ebenfalls erwünscht. Ähnliches gilt für die noch selteneren Sertolizelltumore.

## Arbeitsgruppe Kolon-/Rektum-/ Dünndarmkarzinom

### Metastasiertes kolorektales Karzinom

**AIO-KRK-0212: Randomized phase II study for evaluation of efficacy and safety of maintenance treatment with 5-FU/FA plus panitumumab vs. 5-FU/FA alone after prior induction treatment with mFOLFOX6 plus panitumumab and re-induction with mFOLFOX6 plus panitumumab in case of progression for first-line treatment of patients with metastatic colorectal cancer (PanaMa)**

#### AIO-Studie

Studiennummer/-Code:	AIO-KRK-0212 - PanaMa
Status:	Rekrutierung
Rekrutierungszeitraum	2014 - 2019
Weitere Zentren:	Evtl. möglich, bei Interesse bitte bei der AIO-Studien-gGmbH melden
Letzte Aktualisierung	April 2018

Study design	Phase II, randomized, multi-center, open-label, parallel-group	
National Coordinating investigator	PD Dr. med. Dominik Paul Modest	
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534435; Fax: +49 30 322932926	
Translational research committee	Prof. Dr. Stefan Kasper, PD Dr. Dominik Modest, Prof. Dr. Sebastian Stintzing, Dr. Tanja Trarbach.	
Quality of life committee	Dr. N. Prasnikar, Dr. T. Trarbach	
Status:	<ul style="list-style-type: none"> <li>• 88 Study Sites initiated</li> <li>• 267 Patients enrolled</li> <li>• 175 Patients randomized</li> <li>• Interested Sites might be considered</li> </ul>	
Duration of study	Duration of accrual	64 months
	Final Analysis of primary study endpoint with 218 events:	78 months after start of enrollment
	End of FU (observation period of at least 24 months after randomization for each patient):	89 months after start of enrollment
	End of study:	24 months after last randomization
Total number of centers	Approx. 95	
Study population	Patients with metastatic colorectal cancer (wild-type RAS) in palliative first-line therapy	

Primary objective	To assess the efficacy of panitumumab plus 5-FU/ FA as maintenance after an induction treatment of 12 weeks with mFOLFOX6 plus panitumumab in the first-line treatment of RAS wild-type metastatic colorectal cancer patients compared to 5-FU/ FA maintenance alone in terms of progression-free survival.
Secondary objectives	<p>To compare maintenance arms with respect to:</p> <ul style="list-style-type: none"> <li>• Time from randomization until failure of treatment strategy (death/ progression)</li> <li>• Progression-free survival of re-induction</li> <li>• Objective response after 12 weeks of induction chemotherapy</li> <li>• Objective best response during maintenance and re-induction</li> <li>• Overall survival measured from time of randomization and from time of registration</li> <li>• Safety</li> <li>• Health and skin related Quality of life</li> </ul>
Exploratory objectives	<ul style="list-style-type: none"> <li>• Translational research parameters as defined in the respective section</li> <li>• Central review of CT/MRI scans</li> <li>• Depth of response (during induction and maintenance therapy)</li> </ul>
Planned sample size	Approx. 380 patients will be enrolled to reach the planned number of 252 randomizations.
Inclusion criteria	<ul style="list-style-type: none"> <li>• Signed written informed consent</li> <li>• Male or female <math>\geq 18</math> years of age</li> <li>• Histologically proven metastatic colorectal cancer</li> <li>• Molecular testing showing RAS wild-type in colorectal carcinoma cells</li> <li>• Life expectancy <math>&gt; 12</math> weeks</li> <li>• At least one measurable lesion according to RECIST 1.1</li> <li>• Adequate bone marrow, liver, kidney, organ and metabolic function <ul style="list-style-type: none"> <li>- Bone marrow function <ul style="list-style-type: none"> <li>o leukocyte count <math>\geq 3.0 \times 10^9/L</math></li> <li>o ANC <math>\geq 1.5 \times 10^9/L</math></li> <li>o platelet count <math>\geq 100 \times 10^9/L</math></li> <li>o hemoglobin <math>\geq 9</math> g/dL or 5.59 mmol/L (may be transfused or treated with erythropoietin to maintain/ exceed this level)</li> </ul> </li> <li>- Hepatic function <ul style="list-style-type: none"> <li>o Total bilirubin <math>\leq 1.5 \times</math> UNL</li> <li>o ALT and AST <math>\leq 2.5 \times</math> UNL (or <math>\leq 5 \times</math> UNL in presence of liver metastases)</li> <li>o AP <math>\leq 5 \times</math> UNL</li> </ul> </li> <li>- Renal function <ul style="list-style-type: none"> <li>o Creatinine clearance <math>\geq 50</math> mL/ according to Cockcroft-Gault formula or serum creatinine <math>\leq 1.5 \times</math> UNL</li> </ul> </li> <li>- Metabolic function <ul style="list-style-type: none"> <li>o Magnesium <math>\geq</math> lower limit of normal</li> <li>o Calcium <math>\geq</math> lower limit of normal</li> </ul> </li> </ul> </li> <li>• ECOG performance status 0 - 1</li> <li>• Women of child-bearing potential must have a negative pregnancy test</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>• Previous treatment for colorectal cancer in the metastatic setting</li> <li>• Previous EGFR-targeting therapy</li> <li>• <math>&lt; 6</math> months after end of adjuvant therapy</li> <li>• Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids</li> <li>• Chronic inflammatory bowel disease</li> <li>• Peripheral neuropathy <math>\geq</math> NCI-CTCAE V 4.03 grade 2</li> <li>• Other previous malignancies with the exception of a history of previous curatively treated basal cell carcinoma of the skin or pre-invasive</li> </ul>

	<p>carcinoma of the cervix or other curatively treated malignant disease without recurrence after at least 5 years of follow-up</p> <ul style="list-style-type: none"> <li>• Significant disease that, in the investigator's opinion, would exclude the patient from the study</li> <li>• History of cardiac disease; defined as: <ul style="list-style-type: none"> <li>- Congestive heart failure &gt; New York Heart Association (NYHA) class 2</li> <li>- Active coronary artery disease (myocardial infarction more than 6 months prior to start of study treatment is allowed)</li> <li>- Cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)</li> <li>- Uncontrolled hypertension (defined as blood pressure <math>\geq</math> 160 mmHg systolic and/or <math>\geq</math> 90 mmHg diastolic on medication)</li> </ul> </li> <li>• Patients with interstitial lung disease, e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan</li> <li>• Known HIV, hepatitis B or C infection</li> <li>• Known hypersensitivity reaction to any of the study components</li> <li>• Radiotherapy, major surgery or any investigational drug 21 days before registration</li> <li>• Pregnancy or lactation or planning to be pregnant during treatment and within 6 months after the end of treatment</li> <li>• Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for at least an additional 6 months after the end of treatment</li> <li>• Known alcohol or drug abuse</li> <li>• Any condition that is unstable or could jeopardize the safety of the patient and his compliance in the study</li> </ul>
Treatment scheme	<p><u>Induction chemotherapy</u> 6 cycles mFOLFOX6 plus panitumumab for 12 weeks</p> <p>Panitumumab 6mg/kg BW</p> <p>mFOLFOX6: 85 mg/m<sup>2</sup> Oxaliplatin 2h d1 400 mg/m<sup>2</sup> folinic acid 2h d1 2400mg/m<sup>2</sup> 5-FU over 46 h d1 -2 Q2w</p> <p>In case of delayed RAS testing outcome and urgent treatment exigence, patients can start treatment with a "cycle 0" of any common FOLFOX regimen (no capecitabine!) without panitumumab upon investigator's choice. Once the RAS status has been obtained and is wild-type, patients can be enrolled and start with the regular induction therapy.</p> <p><u>Maintenance</u> Patient with CR, PR and SD after 12 weeks of induction treatment, will be randomized in a 1:1 ratio to receive either 5-FU/FA + panitumumab q2w (arm A) or 5-FU/FA alone q2w (arm B) until tumor progression. Patient with curative resection within 12 weeks of induction therapy do not qualify for randomization.</p> <p><u>Re-induction:</u> After tumor progression, a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression</p> <p><u>Concomitant therapy:</u> Prophylactic management program for panitumumab-related acute and late skin toxicities (see section 6.5.2, 6.5.3)</p>
Primary parameter	Progression-free survival during maintenance therapy defined as time from randomization until disease progression or death, whatever occurs first.

Secondary parameters	<ul style="list-style-type: none"> <li>• Time from randomization until failure (death/ progression) of treatment strategy</li> <li>• Progression-free survival of re-induction</li> <li>• Objective response after 12 weeks of induction chemotherapy</li> <li>• Objective best response during maintenance and re-induction</li> <li>• Overall survival measured from time of randomization</li> <li>• Safety</li> <li>• Health and skin related Quality of life</li> </ul>
Exploratory parameters	<p>Translational research analysis in tumor tissue, circulation tumor cells, circulating tumor DNA and blood cells. These investigations will include DNA, RNA, immunohistochemistry, FISH, Sequencing from tumor/or blood cells as well as evaluations of laboratory markers (tumor markers).</p> <p>Central review of CT/MRI scans for resectability, volumetry and further related parameters (i.e. depth of response etc.)</p>
Study procedures	<p>After the initial screening procedure, eligible patients will be registered for study participation.</p> <p>The patient receives chemotherapy consisting of 6 cycles mFOLFOX6 plus panitumumab every 2 weeks. Patients showing CR, PR or SD after induction therapy and qualifying for subsequent maintenance treatment and re-induction treatment with all potential drug components, will be randomized to receive a maintenance regimen of 5-FU/FA + panitumumab or 5-FU/FA alone until tumor progression.</p> <p>After tumor progression a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression.</p> <p>Tumor assessments will be performed 12 weeks after treatment start with induction therapy and every 8 weeks during maintenance therapy and re-induction.</p> <p>All patients will have an end of treatment visit 4 weeks (+ 7 days) after the last dose of the study agent. Thereafter, all patients will be followed up for survival every 3 months.</p>
Randomization procedure	<p>Permuted block randomization will be applied to guarantee balanced group numbers throughout enrollment period. To increase homogeneity between treatment arms, randomization will be stratified by</p> <ol style="list-style-type: none"> <li>1. Response to induction therapy at time of randomization (CR/PR vs. SD)</li> <li>2. Prior oxaliplatin-containing adjuvant therapy (yes vs. no)</li> <li>3. Planned starting dose of panitumumab for maintenance therapy, if patient will be assigned to arm A (full dosage vs. reduced dosage)</li> </ol> <p>Randomization will be performed in the subgroup of patients achieving CR, PR or SD 12 weeks after start of induction therapy qualifying for maintenance treatment and re-induction treatment with all potential drug components.</p>
Sample size calculation	<p>With a total number of 218 events (progressions or death, whichever occurs first), a logrank test for testing superiority of progression-free survival with a 10% one-sided significance level will have 80% power to reject the null-hypothesis if the true median progression-free survival times in patients treated with maintenance alone and maintenance plus panitumumab are 7.5 and 10 months, respectively. A total of approx. 380 patients eligible for induction therapy should be accrued for randomisation of 252 patients needed to reach the required number of events.</p>
Planned interim analysis	<p>No confirmatory interim analyses for efficacy with the aim to stop the trial prematurely are foreseen within this study protocol.</p>

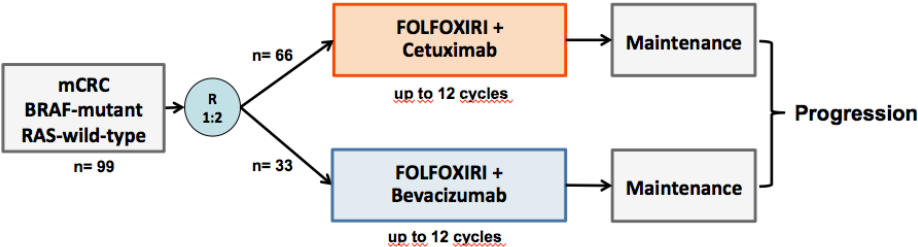
### AIO KRK-0116: Randomised study to investigate FOLFOXIRI plus Cetuximab vs. FOLFOXIRI plus bevacizumab as first-line treatment of BRAF-mutated metastatic colorectal cancer (FIRE-4.5)

#### AIO-Studie

Studiennummer/-Code:	AIO-KRK-0116 - FIRE-4.5
Status:	in Rekrutierung
Rekrutierungszeitraum	2016 - 2018
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Study Type	Randomisierte, multizentrische Phase-II Studie
Verantwortlicher Studienleiter nach AMG	Klinikum der Universität München Marchioninstraße 15, 81377 München Vertreten durch: Prof. Dr. med. Volker Heinemann
Objectives	<p><u>Primäres Studienziel:</u> Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 under treatment with FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab.</p> <p><u>Sekundäre Studienziele:</u></p> <ul style="list-style-type: none"> <li>• Progression-free survival (PFS) from randomisation</li> <li>• Overall survival (OS) from randomisation</li> <li>• Investigation of early tumour shrinkage (ETS) and depth of response (DpR)</li> <li>• Study of molecular biomarkers for prediction of sensitivity and secondary resistance of an anti-EGFR treatment with cetuximab (including tumour biopsies and liquid biopsies from blood samples)</li> <li>• Investigation of progressive analysis of tumour marker evolution (CEA and CA 19-9)</li> <li>• Recording of the safety and tolerance (NCI-CTCAE version 5.01 criteria) of the treatment</li> </ul>
Objectives	<ul style="list-style-type: none"> <li>- Objective response rate (ORR)</li> <li>- Progression-free Survival (PFS) and Overall Survival (OS)</li> <li>- Safety and Toxicity</li> </ul>
Number of patients	Geplant: 99 Patienten Bereits eingeschlossen: 27 (Apr. 2018)
Key inclusion criteria	<ul style="list-style-type: none"> <li>- Histologically confirmed, UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer, mCRC), primarily non-resectable or surgery refused by the patient</li> <li>- RAS wild-type tumour status (KRAS and NRAS exons 2, 3, 4) (proven in the primary tumour or metastasis)</li> <li>- BRAF-mutated (V600E) tumour (proven in primary or metastasis) <ul style="list-style-type: none"> <li>o Age <math>\geq 18</math> years</li> <li>o ECOG performance status 0-1</li> </ul> </li> <li>- Patient's written declaration of consent obtained</li> <li>- Presence of at least one measurable reference lesion according to the RECIST 1.1 – criteria (chest X-ray in two planes or chest CT and abdominal CT 4 weeks or less before randomisation)</li> <li>- Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of the tumour material.</li> <li>- Adequate haematopoietic function: <ul style="list-style-type: none"> <li>o Leukocytes <math>\geq 3.0 \times 10^9/L</math> with neutrophils <math>\geq 1.5 \times 10^9/L</math></li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ Thrombocytes <math>\geq 100 \times 10^9/L</math>,</li> <li>○ Haemoglobin <math>\geq 5.6</math> mmol/L (equivalent to 9 g/dL)</li> <li>- Adequate hepatic function: <ul style="list-style-type: none"> <li>○ Serum bilirubin <math>\leq 1.5</math> x upper limit of normal (ULN),</li> <li>○ ALAT and ASAT <math>\leq 2.5</math> x ULN (in the presence of hepatic metastases, ALAT and ASAT <math>\leq 5</math> x ULN)</li> </ul> </li> <li>- INR <math>&lt; 1.5</math> and aPTT <math>&lt; 1.5</math> x ULN (patients without anticoagulation). Therapeutic anticoagulation is allowed if INR and aPTT have remained stable within the therapeutic range for at least 2 weeks.</li> <li>- Adequate renal function: <ul style="list-style-type: none"> <li>○ Serum creatinine <math>\leq 1.5</math> x ULN or creatinine clearance (calculated according to Cockcroft and Gault) <math>\geq 50</math>ml/min.</li> </ul> </li> <li>- Adequate cardiac function: ECG and echocardiogram with a LVEF of <math>\geq 55\%</math></li> <li>- No previous chemotherapy for metastatic disease. One cycle (cycle 0) of either FOLFOX, FOLFIRI, or FOLFOXIRI is allowed prior to randomisation.</li> <li>- Time since last administration of any previous adjunctive chemotherapy <math>&gt;6</math> months</li> <li>- Any significant toxicities of previous treatments must have subsided to grade 0</li> </ul>
Key exclusion criteria	<ul style="list-style-type: none"> <li>- Grade III or IV heart failure (NYHA classification)</li> <li>- Myocardial infarction, unstable angina pectoris, balloon angioplasty (PTCA) with or without stenting within the past 12 months before randomisation</li> <li>- Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study</li> <li>- Additional cancer treatment (chemotherapy, radiation, immune therapy or hormone treatment) during the study treatment. Treatments that are conducted as part of an anthroposophic or homeopathic treatment approach, e.g. mistletoe therapy do not represent an exclusion criterion).</li> <li>- Previous chemotherapy for the colorectal cancer with the exception of adjunctive treatment, completed at least 6 months before entering the study.</li> <li>- Participation in a clinical study or experimental drug treatment within 30 days prior to study inclusion or within a period of 5 half-lives of the substances administered in a clinical study or during an experimental drug treatment prior to inclusion in the study, depending on which period is longest or simultaneous participation in another clinical study while taking part in the study</li> <li>- Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, cetuximab, irinotecan, bevacizumab, oxaliplatin, and chemically related substances and/or hypersensitivity to any of the excipients of any of the aforementioned substances</li> <li>- Known hypersensitivity to CHO (Chinese hamster ovary cells) - cellular products or other recombinant human or humanised antibodies</li> <li>- Patients with confirmed cerebral metastases. In case of clinical suspicion of brain metastases, a cranial CT or MRI must be performed to rule out brain metastases before study inclusion.</li> <li>- History of acute or subacute intestinal occlusion or chronic inflammatory bowel disease or chronic diarrhoea.</li> <li>- Symptomatic peritoneal carcinosis</li> <li>- Severe, non-healing wounds, ulcers or bone fractures</li> <li>- Patients with active infection (including confirmed HIV and/or HBV/HCV infection). In case of clinical suspicion of the presence of HIV or HBV/HCV infection, the latter should be ruled out before study inclusion.</li> <li>- Requirement for immunisation with live vaccine during the study treatment.</li> <li>- Uncontrolled hypertension</li> <li>- Marked proteinuria (nephrotic syndrome)</li> <li>- Arterial thromboemboli or severe haemorrhage within 6 months prior to randomisation (with the exception of tumour bleeding before tumour resection surgery)</li> <li>- Haemorrhagic diathesis or tendency towards thrombosis</li> </ul>

	<ul style="list-style-type: none"> <li>- Known DPD deficiency (specific screening not required)</li> <li>- Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required)</li> <li>- History of a second malignoma during the 5 years before inclusion in the study or during participation in the study, with the exception of a basalioma, spinalioma or cervical carcinoma in situ, if these were treated curatively.</li> <li>- Known history of alcohol or drug abuse</li> <li>- A significant concomitant disease which, especially chronic hepatic or renal disease, chronic inflammatory or autoimmune diseases, in the investigating physician's opinion, rules out the patient's participation in the study</li> <li>- Absent or restricted legal capacity</li> </ul>
Scheme of therapy	<p><b>FOLFOXIRI plus bevacizumab up to 12 cycles</b> one cycle (cycle duration 14 days) consists of:</p> <ul style="list-style-type: none"> <li>• Irinotecan 150 mg/m<sup>2</sup> iv, 30 - 90 min. day 1</li> <li>• Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min. day 1</li> <li>• Oxaliplatin 85mg/m<sup>2</sup> day 1</li> <li>• 5-FU 3000 mg/m<sup>2</sup> iv over 48 h days 1-2</li> <li>• Bevacizumab 5 mg/kg BW iv over 30 to 90* min day 1</li> </ul> <p><b>FOLFOXIRI plus cetuximab up to 12 cycles</b> one cycle (cycle duration 14 days) consists of:</p> <ul style="list-style-type: none"> <li>• Irinotecan 150 mg/m<sup>2</sup> iv, 30 - 90 min. day 1</li> <li>• Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min. day 1</li> <li>• Oxaliplatin 85mg/m<sup>2</sup> day 1</li> <li>• 5-FU 3000 mg/m<sup>2</sup> iv over 48 h days 1-2</li> <li>• Cetuximab initially 400 mg/m<sup>2</sup> with infusion rate of ≤5 mg/min., subsequently 250 mg/m<sup>2</sup> iv with infusion rate of ≤10 mg/min.days 1+8</li> </ul> <p><b>Study design</b></p>  <p><b>Primary Objective:</b> Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 during treatment with FOLFOXIRI plus bevacizumab versus FOLFOXIRI plus cetuximab.</p>
Criteria for evaluation	After treatment week 8, 16, 24 and every 12 treatment weeks thereafter tumor response evaluation according to RECIST 1.1
Rationale	<p>The question of the right treatment for BRAF-mutated colorectal cancer is currently the subject of scientific discussion. No clinical data are available to date for treatment with FOLFOXIRI plus bevacizumab. A retrospective analysis of 10 patients with BRAF-mutated tumours was able to show that it is possible to achieve a response (ORR) in 90% (9 patients), a median PFS of 12.8 months and a median OS of 23.8 months [Masi G et al Lancet Oncol 2010]. A validation study based on 15 patients was able to confirm the efficacy in BRAF-mutated patients of FOLFOXIRI plus bevacizumab, which resulted in a tumour response of 60%, a median PFS of 9.1 months and a median OS of 24.1 months [Loupakis F. et al Eur J Cancer 2014]. Furthermore, retrospective data from the TRIBE study are available, which suggest greater efficacy of FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab in 28 patients with BRAF-mutated tumours [Cremolini C et al Lancet Oncol 2015]. In this case, it was possible to demonstrate response rates of 56% versus 42%,</p>



	<p>median PFS times of 7.5 months versus 5.5 months and median OS times of 19.0 months versus 10.7 months, respectively [Cremolini C et al Lancet Oncol 2015]. However, none of the differences reached the significance level, owing to the small number of cases. Given the study design, it is not possible to make any statement concerning the additional benefit of bevacizumab in combination with FOLFOXIRI.</p> <p>A pooled retrospective assessment of the TRIP and MCBETH studies is available for colorectal tumour patients treated with FOLFOXIRI plus anti-EGFR antibodies [Salvatore L et al <i>Annals of Oncology</i> (2014) 25 (suppl_4)]. Only RAS/BRAF wild-type patients were assessed in this case. The response rates were around 82% versus 71 in comparison of anti-EGFR plus FOLFOXIRI with FOLFOXIRI plus Bevacizumab. PFS and OS data were not presented.</p>
Statistik	<p>This is a randomised, phase II trial, intended to study the efficacy of the two regimens - FOLFOXIRI plus cetuximab or FOLFOXIRI plus bevacizumab - as part of first-line treatment with reference to the endpoint of tumor response (ORR according to RECIST 1.1) in patients suffering from BRAF-mutant colorectal cancer.</p> <p>The efficacy of FOLFOXIRI plus cetuximab will be assessed as promising if:</p> <ul style="list-style-type: none"> <li>• The null hypothesis (ORR in the FOLFOXIRI plus cetuximab arm <math>\leq</math> 55%) can be rejected at a significance level of 0.1 and</li> <li>• Response (ORR) in the FOLFOXIRI plus cetuximab arm is greater than in the FOLFOXIRI plus bevacizumab arm.</li> </ul> <p>Hence, the hypotheses to be tested are:</p> <ul style="list-style-type: none"> <li>• H0: ORR (arm B) <math>\leq</math> 55%</li> <li>• H1: ORR (arm B) <math>\geq</math> 70%</li> </ul> <p>Since an ORR of <math>\geq</math>70% is expected in the FOLFOXIRI plus cetuximab arm, 53 patients are required in the FOLFOXIRI plus cetuximab arm in order to reject the null hypothesis with a power of 80% at a significance level of 0.1 (two-stage design according to Fleming with 20 patients in the first stage and 53 patients in the second stage).</p> <p>The null hypothesis would be rejected if at least 17 out of the first 20 patients (85%) or at least 33 patients (62.5%) in the second stage (total evaluable n=53) show a tumour response according to RECIST 1.1 (partial (PR) or complete response (CR)) and, at the same time, response (ORR) in the FOLFOXIRI plus cetuximab arm is numerically greater than in the FOLFOXIRI plus bevacizumab arm. If less than 12 patients of the first 20 patients show tumor response according to RECIST 1.1 the study would be terminated due to "futility".</p> <p>27 further patients are used as a control arm with the standard recommended therapy of FOLFOXIRI and bevacizumab according to Loupakis et al. (TRIBE study) to investigate efficacy and safety of both study arms.</p>

### AIO-KRK-0216: Avelumab and cetuximab in combination with FOLFOX in patients with previously untreated metastatic colorectal cancer – The phase II AVETUX-CRC trial

#### AIO-Studie

Studiennummer/-Code:	AIO-KRK-0216 - AVETUX
Status:	in Rekrutierung
Rekrutierungszeitraum	12 months
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Study Type	Phase II
Coordinating Investigator	Alexander Stein University Medical Center Hamburg-Eppendorf Department of Internal Medicine II (Oncology Center) Hubertus Wald Tumorzentrum Martinistr. 52, 20246 Hamburg
Contact	a.stein@uke.de
Endpoints	<p><u>Primary endpoint:</u></p> <ul style="list-style-type: none"> <li>Progression Free Survival Rate after 12 months of treatment (PFSR@12) (acc. to RECIST v1.1)</li> </ul> <p><u>Secondary endpoints:</u></p> <ul style="list-style-type: none"> <li>Response Rate (RR) according to RECIST v1.1 and modified RECIST</li> <li>Progression Free Survival (PFS) according to RECIST v1.1 and mRECIST</li> <li>Overall survival (OS)</li> <li>Safety and tolerability</li> <li>Translational research (correlation of clonal dynamics (RAS/EGFR subclones) with immune response signature to determine control of mutant subclones by the combination of anti-EGFR with anti-PD-L1, and PD-L1 (and MSI) status with efficacy)</li> </ul>
Primary Objective	The primary clinical objective is to determine the efficacy of a standard 1st line regimen (FOLFOX and cetuximab) in patients with RAS/BRAF wildtype, MSI or MSS MCRC with avelumab in terms of progression free survival rate after 12 months (acc. to RECIST v1.1).
Number of patients/sites	Planned: 43 patients in 11 sites Actual: 30 patients (09.04.2018)
Key inclusion criteria	<ol style="list-style-type: none"> <li>Patients with histologically confirmed, previously untreated RAS and BRAF wildtype, MSI or MSS metastatic colorectal cancer (primary tumor may be present)</li> <li>Patients with at least one measurable lesion acc. to RECIST v1.1</li> <li>ECOG Performance status <math>\leq</math> 1</li> <li>Adequate haematologic, liver and renal function</li> <li>At least 6 months after completion of adjuvant chemotherapy.</li> </ol>
Key exclusion criteria	<ol style="list-style-type: none"> <li>Significant acute or chronic infections including, among others: <ol style="list-style-type: none"> <li>Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)</li> <li>Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive)</li> </ol> </li> <li>Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent (Subjects with diabetes type I, vitiligo,</li> </ol>

	<p>psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible)</p> <ol style="list-style-type: none"> <li>3. Concomitant treatment with corticosteroids or other immunosuppressants, besides treatment of brain metastases as mentioned in criteria 2 or: <ol style="list-style-type: none"> <li>a. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses <math>\leq 10</math> mg or 10 mg equivalent prednisone per day</li> <li>b. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable</li> </ol> </li> <li>4. All other significant diseases (for example, inflammatory bowel disease, uncontrolled asthma, colitis and pneumonitis), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment</li> </ol>
Scheme of therapy	<p>All eligible patients will receive cetuximab and mFOLFOX6 combined avelumab from the second cycle onwards.</p> <p><b>Cetuximab</b> at a dose of 250 mg/m<sup>2</sup> iv over 60 to 90 min (day 1 and 8) (first dose 400mg/m<sup>2</sup>)</p> <p><b>mFOLFOX6</b> (administration according to local standard)</p> <p>Oxaliplatin at a dose of 85 mg/m<sup>2</sup> iv 5-FU 400 mg/m<sup>2</sup> iv bolus (day 1) LV at a dose of 400 mg/m<sup>2</sup> iv 5-FU at a dose of 2400 mg/m<sup>2</sup> iv</p> <p><b>Avelumab</b> at a dose of 10mg/kg iv over 60 to 90 min (day 1 from cycle 2 onwards)</p> <p><b>Duration of treatment</b> Treatment with avelumab, cetuximab and FOLFOX will be administered until progression (according to RECIST v1.1), intolerable toxicity, withdrawal of consent or secondary resection. Administration of avelumab will be limited to a maximum of 18 months.</p>
Criteria for evaluation	RECIST v1.1
Rationale	<p>Inhibition of the PD-1/L1 axis has shown to improve survival as single agent in a variety of tumor types (e.g. melanoma and lung cancer) (Robert, Long et al. 2014, Borghaei, Paz-Ares et al. 2015). The efficacy of single agent PD-1/L1 inhibition in patients with highly advanced and treatment refractory MCRC seems to be limited to those with hypermutated tumors characterized by mismatch repair deficiency (Le, Uram et al. 2015).</p> <p>Recent data show the beneficial impact on systemic control of the combination of checkpointinhibition and local ablative strategies (e.g. radiotherapy or radiofrequency ablation), likely triggered by the locoregional immune activation due to the antigen release (Sharabi, Lim et al. 2015, Twyman-Saint Victor, Rech et al. 2015, Shi, Chen et al. 2016). However, first line chemotherapy in combination with EGFR inhibitors (FOLFOX with cetuximab) for patients with RAS wildtype MCRC result in objective response rates (&gt;30% tumor shrinkage in largest diameter) of about 60%, thus substantial antigen release will likely occur triggering immune control (Venook, Niedzwiecki et al. 2014, Bokemeyer, Kohne et al. 2015). Selecting upfront patients with BRAF wildtype will further increase efficacy. Chemotherapy itself has immune sensitizing properties, in particular 5FU and oxaliplatin, which may impact on the efficacy of PD-1/L1 inhibition (Duffy and Greten 2014). Furthermore, the induction of immunogenic cell death has been recently shown for cetuximab (Pozzi, Cuomo et al. 2016).</p>

### AIO-KRK-0117: Aflibercept and 5-FU vs. FOLFOX as 1st line treatment option for elderly or frail elderly patients with metastatic colorectal cancer

#### AIO-Studie

Studiennummer/-Code:	AIO-KRK-0117
Status:	in Vorbereitung, Einschluss des 1. Pat. wird in Q2 2018 erwartet
Rekrutierungszeitraum:	2018 – 2020
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung:	April 2018

Phase	Randomized phase II
Coordinating Investigators	Prof. Dr. Ralf-Dieter Hofheinz Tagestherapiezentrum am ITM & III. Med. Klinik Universitätsmedizin Mannheim Theodor-Kutzer-Ufer 1-3 68167 Mannheim, Germany Phone: +49 - 621 – 3832855 Fax: +49 - 621 – 3832488
Study design	This is a controlled, open-label, randomized phase- II trial (1:1 randomisation) investigating 5-FU + aflibercept and 5-FU + oxaliplatin in elderly and frail elderly patients with mCRC scheduled to receive first line treatment.
Duration of study	4,5 years
Indication	Metastatic colorectal cancer
Country Total number of sites	Germany 35 sites
Primary objective	To assess the rates of progression-free survival at six months calculated from the start of treatment in elderly / frail elderly patients with metastatic colorectal cancer undergoing a 1 <sup>st</sup> line treatment.
Secondary objectives	To compare the treatment arms with respect to: <b>Safety</b> <ul style="list-style-type: none"> <li>- Dose intensities of study medication</li> <li>- Type, incidence and severity of AEs and SAEs</li> <li>- Laboratory parameters</li> </ul> <b>Efficacy</b> <ul style="list-style-type: none"> <li>- Response rate assessed by the local investigators</li> <li>- Overall and progression-free survival</li> </ul> <b>Patient reported outcomes</b> <ul style="list-style-type: none"> <li>- Quality of life</li> <li>- Geriatric assessment</li> <li>- Overall treatment utility</li> </ul>
Primary endpoint	Rate of patients free of progression at the time point of 6 month calculated from the start of treatment. Response assessment will be done in a standardized manner using CT scan.
Secondary endpoints	<b>Safety</b> <ul style="list-style-type: none"> <li>• Dose intensities of study medication</li> <li>• Type, incidence and severity of AEs, SAEs (CTCAE version 4.03)</li> <li>• Dose reduction or discontinuation of study drug due to adverse events</li> <li>• Rate of treatment discontinuation due to toxicity</li> <li>• Type, incidence and severity of laboratory abnormalities</li> </ul>

	<p><b>Efficacy</b></p> <ul style="list-style-type: none"> <li>• Response rates (response will be assessed by the local investigator using RECIST criteria v. 1.1; CT scans are conducted at 3 and 6 months and every three months thereafter)</li> <li>• Overall and progression-free survival (OS)</li> </ul> <p><b>Patient reported outcomes</b></p> <ul style="list-style-type: none"> <li>• Quality of life using EQ5D</li> <li>• Geriatric assessment using G8, ADL and IADL</li> <li>• Overall treatment utility (as defined in FOCUS2 trial)</li> </ul>
Planned sample size	176 evaluable patients total (88 per arm). Assuming a 10% drop out rate a total of 196 patients will be recruited.
Target population	Elderly or frail elderly patients with metastatic colorectal cancer scheduled to undergo palliative 1 <sup>st</sup> line chemotherapy
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. To enter this trial the oncologist has to confirm, that the patient was in his or her opinion not a candidate for standard full-dose combination therapy. Moreover, the oncologist has to state the reason for entering the trial (Advanced age alone versus both age and frailty). As an operational definition for frailty the G8 screening tool will be used upon inclusion of the patient in a standardized manner. Briefly, G8 is an established screening tool that includes seven items from the Mini Nutritional Assessment (MNA) and an age-related item (&lt;80, 80 to 85, or 85 years). The total score can range from 0 to 17. The result on the G8 is considered abnormal if the score is <math>\leq 14</math>, indicating a geriatric risk profile.</li> <li>2. Patients have to have histologically confirmed mCRC with unidimensionally measurable inoperable advanced or metastatic disease</li> <li>3. ECOG performance status of 2 or better.</li> <li>4. Life expectancy of 3 months or longer at enrolment</li> <li>5. Patients &gt;70 years with no upper age limit</li> <li>6. Previous adjuvant chemotherapy is allowed if completed more than 6 months before randomisation</li> <li>7. Previous rectal (chemo)radiotherapy is allowed if completed more than 6 months before randomisation</li> <li>8. Hematological status: <ul style="list-style-type: none"> <li>• Neutrophils (ANC) <math>\geq 1.5 \times 10^9/L</math></li> <li>• Platelets <math>\geq 100 \times 10^9/L</math></li> <li>• Hemoglobin <math>\geq 9</math> g/dL</li> </ul> </li> <li>9. Adequate renal function: <ul style="list-style-type: none"> <li>• Serum creatinine level <math>\leq 1.5</math> x upper limit normal (ULN)</li> </ul> </li> <li>10. Adequate liver function: <ul style="list-style-type: none"> <li>• Serum bilirubin <math>\leq 1.5</math> x upper limit normal (ULN)</li> <li>• Alkaline phosphatase <math>&lt; 5</math> x ULN</li> <li>• AST and ALT <math>&lt; 3</math> x ULN (unless liver metastases are present then <math>&lt; 5</math> x ULN in that case)</li> </ul> </li> <li>11. Proteinuria <math>&lt; 2+</math> (dipstick urinalysis) or <math>\leq 1</math> g/24hour</li> <li>12. Signed and dated informed consent, and willing and able to comply with protocol requirements</li> <li>13. Regular follow-up feasible</li> <li>14. Male patients with a partner of childbearing potential must agree to use effective contraception (Pearl Index <math>&lt; 1</math>) during the course of the trial and at least 3 months after last administration of the study drug.</li> </ol>
Exclusion Criteria	<ol style="list-style-type: none"> <li>1. Prior systemic chemotherapy for mCRC</li> <li>2. Other concomitant or previous malignancy, except: <ul style="list-style-type: none"> <li>• Adequately treated in-situ carcinoma of the uterine cervix</li> <li>• Basal or squamous cell carcinoma of the skin</li> <li>• Cancer in complete remission for <math>&gt; 5</math> years</li> </ul> </li> <li>3. Any other serious and uncontrolled non-malignant disease, major surgery or</li> </ol>

	<p>traumatic injury within the last 28 Days</p> <ol style="list-style-type: none"> <li>4. History or evidence upon physical examination of CNS metastasis unless adequately treated (irradiation and no seizure with appropriate treatment)</li> <li>5. Uncontrolled hypercalcemia</li> <li>6. Pre-existing peripheral neuropathy (NCI grade <math>\geq 2</math>)</li> <li>7. Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy),</li> <li>8. Treatment with any other investigational medicinal product within 28 days prior to study entry.</li> <li>9. Significant cardiovascular disease: <ul style="list-style-type: none"> <li>• Cardiovascular accident or myocardial infarction or unstable angina <math>\leq 6</math> months before start of study treatment</li> <li>• Severe cardiac arrhythmia</li> <li>• New York Heart Association grade <math>\geq 2</math> congestive heart failure</li> <li>• Uncontrolled hypertension (defined as systolic blood pressure <math>&gt;150</math> mmHg and/or diastolic blood pressure <math>&gt;100</math> mmHg), or history of hypertensive crisis, or hypertensive encephalopathy.</li> <li>• History of stroke or transient ischemic attack <math>\leq 6</math> months before start of study treatment</li> <li>• Coronary/peripheral artery bypass graft <math>\leq 6</math> months before start of study treatment.</li> <li>• Deep vein thrombosis or thromboembolic events <math>\leq 1</math> month before start of study treatment</li> </ul> </li> <li>10. Patients with known allergy to any excipient to study drugs,</li> <li>11. Any of the following within 3 months prior to randomization: Grade 3-4 gastrointestinal bleeding/hemorrhage, treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event.</li> <li>12. Bowel obstruction.</li> <li>13. Treatment with CYP3A4 inducers unless discontinued <math>&gt; 7</math> days prior to randomization</li> <li>14. Known dihydropyrimidine dehydrogenase (DPD) deficiency</li> <li>15. Involvement in the planning and/or conduct of the study (applies to both Sanofi staff and/or staff of sponsor and study site)</li> <li>16. Patient who might be dependent on the sponsor, site or the investigator</li> <li>17. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</li> <li>18. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</li> </ol>
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Treatment schedule after randomization	<p><b>Arm A (mFOLFOX7):</b> Patients in the 5-FU / oxaliplatin arm receive modified (m) FOLFOX 7: Levofolinate 320 mg/m<sup>2</sup> and oxaliplatin 68 mg/m<sup>2</sup> by concurrent 2-h intravenous infusion, 5-fluorouracil 1920 mg/m<sup>2</sup> 46-h intravenous infusion. This regimen represents the 80% dosage reduced mFOLFOX 7. The 80% dose reduction was shown to be a tolerable regimen in frail elderly patients in the FOCUS 2 study.</p> <p><b>Arm B (Aflibercept + mL5FU2):</b> Patients in the 5-FU / aflibercept arm receive aflibercept 4mg/kg as 1-h infusion followed by levofolinate 320 mg/m<sup>2</sup> by 2-h intravenous infusion, 5-fluorouracil 1920 mg/m<sup>2</sup> 46-h intravenous infusion (mLV5FU2). The decision to use reduced doses of 5-FU and levofolinate was made to have comparable doses to the reduced FOLFOX 7.</p>
Scientific rationale	<p>The current trial seeks to evaluate a new treatment option for elderly / frail elderly patients with mCRC including 5-FU – better tolerated than capecitabine in the FOCUS2 study – in conjunction with aflibercept, a broad active anti-angiogenic drug within a randomized phase-II setting. Patients will be randomized using a 1:1 randomization between 5-FU / aflibercept and 5-FU / oxaliplatin using the oxaliplatin-based regimen established in FOCUS2 trial. Main goal is to estimate the 6-months PFS rate with 5-FU / Aflibercept and the safety of this regimen. The decision to use a randomized phase-II design using the “FOCUS2- FOLFOX” is based on two assumptions; (i) Bias can be better controlled by using a randomized phase-II design (ii) A clear standard regimen in frail elderly cannot be defined, but FOLFOX was superior to 5-FU alone in FOCUS2 and the patient population included in the FOCUS2 study represents the patient population scheduled to be included in the current trial.</p> <p>Provided the randomized phase-II study shows adequate efficacy of 5-FU / aflibercept and a tolerable safety profile, the study will be carried on to the phase-III part of the trial. Description of the terms and conditions to expand the current trial are not part of this protocol. Briefly, a potential phase-III study should aim at showing non-inferiority of 5-FU / aflibercept regarding 6-months PFS rate as primary endpoint. This would allow to include all patients from the phase-II part in the phase-III study in order to save time and patients.</p>
Randomization and stratification procedures	<p>After the initial screening procedure, eligible patients will be randomized in a ratio of 1:1 to receive either mFOLFOX7 or Aflibercept + mL5FU2. Permuted block randomization will be applied. Stratification factors: G8 score ≤14 versus 15-17 &amp; ECOG 0/1 versus 2</p>
Statistical considerations and sample size calculation	<p><b>Sample Size Estimation:</b> The aim of the randomized phase-II trial is to gain a precise estimation of 6 months progression free-survival (PFS) rate of 5FU-Aflibercept for planning of a following phase III study in elderly and frail elderly patients with mCRC scheduled to receive first line treatment. Sample size calculation was done using R version 2.15.2 (R Core Team (2014). <a href="http://www.R-project.org/">http://www.R-project.org/</a>). Assumptions:</p> <ul style="list-style-type: none"> <li>• Uniform recruitment of patients during randomized phase II-part</li> <li>• PFS exponential distribution <math>PFS(t)=exp(rt)</math></li> <li>• Median <math>PFS_{5FU-Aflibercept}=6</math> months equivalent to a mean <math>PFS_{5FU-Aflibercept}=8.7</math> months</li> </ul> <p>In summary, with 88 evaluable patients in the 5-FU / aflibercept arm and an accrual of 24 months the lower limit of the 95% confidence limit for the 6 months PFS is 42.4%. Randomization of a total 176 patients will be stratified by G8 score and ECOG and will be performed on a 1:1-basis. Assuming a 10% drop out rate a total of 196 patients need to be recruited. Stratification factors: G8 score ≤14 versus 15-17 &amp; ECOG 0/1 versus 2</p>
	<p><b>Safety</b> The dose intensities of study medication will be calculated over the whole study duration and will be summarized descriptively by summary statistics. AEs, will be summarized by presenting the number and percentages of patients having any AE and having an AE in each NCI-CTC category. Summaries will also</p>

	<p>be presented for AEs by severity and relationship to study medication. Tables will be broken down by study arm.</p> <p>All deaths and serious adverse events will be listed and briefly described.</p> <p>Laboratory evaluations will be analyzed by summary statistics per parameter, visit and treatment group.</p> <p><b>Others</b> Vital signs will be analyzed using summary statistics broken down per treatment group and visit. Physical examination as well as ECOG will be analyzed by calculating frequencies and percentages broken down per treatment group and visit.</p>
Number of patients, and location	Total number of patients: 196 Location of sites: Germany
Anzahl eingeschl. Pat.	0 (Studie in Vorbereitung)
Weitere Zentren:	ja

**AIO-KRK-0316/ass: A Phase IIb study with run in safety phase of Ramucirumab in combination with TAS102 vs. TAS102 monotherapy in chemotherapy refractory metastatic colorectal cancer patients [RAMTAS]**

**AIO-assoziierte Studie**

Studiennummer/-Code:	AIO-KRK-0316/ass   RAMATAS
Status:	eingereicht
Rekrutierungszeitraum	2018 - 2019
Weitere Zentren:	es sind noch Plätze frei
Letzte Aktualisierung	April 2018

Condition	metastatic colorectal cancer (mCRC)
Principal Investigator	Prof Dr. med. Stefan Kasper University Hospital Essen, West German Cancer Center Hufelandstr. 55, 45147 Essen, Germany Tel.: +49 201 723 3449 Fax.: +49 201 723 5549 Email: stefan.kasper@uk-essen.de
Study group	Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft e.V.
CRO	Institut für Klinisch-Onkologische Forschung Krankenhaus Nordwest, Steinbacher Hohl 2-26 60488 Frankfurt am Main, Germany
Objectives	<p>Primary objective: To determine the efficacy of Ramucirumab in combination with TAS102 vs. TAS102 monotherapy in patients with refractory mCRC. Primary endpoint will be overall survival (OS) according to Kaplan-Meier.</p> <p>Secondary objectives: Overall Response Rate (ORR) (complete remission and partial remission) Disease control rate (DCR) (complete remission, partial remission and stable disease) Progression Free Survival (PFS) OS rate at 6 and 12 months</p>



	<p>Efficacy (ORR, PFS, OS) in patients who develop neutropenia <math>\geq</math> grade 2 (ANC<math>\leq</math>1500/<math>\mu</math>l) in cycle 1</p> <p>Toxicity/safety</p> <p>Quality of life (QoL)</p> <p>Translational research program</p>
Study type	An interventional, prospective, randomized (1:1), controlled, open label, multicenter phase IIb study with run in safety phase
Rational	<p>Patients with mCRC who have progressed on/after Fluoropyrimidins, Oxaliplatin, Irinotecan, anti-angiogenic and anti-EGFR therapies have limited therapeutic options with a dismal prognosis and a median overall survival below 6 months (1,2). Recently TAS102, an oral agent that combines trifluridine and tipiracil hydrochloride significantly improved overall survival in patients with refractory mCRC (1). In addition the anti-angiogenic drugs Bevacizumab, Aflibercept, Regorafenib and Ramucirumab are effective beyond progression on prior anti-angiogenic therapies (2-5). The combination of TAS102 and the anti-VEGFR2 antibody Ramucirumab is the next logical step to improve efficacy and prevent resistance in mCRC.</p>
Key inclusion criteria	<p>Metastatic and inoperable, colorectal cancer who have progressed on/after or did not tolerate:</p> <p>Fluoropyrimidins, Oxaliplatin, Irinotecan, anti-angiogenic therapies (Bevacizumab, Aflibercept, Regorafenib or Ramucirumab) and when indicated anti-EGFR antibodies (Cetuximab or Panitumumab)</p> <p>signed informed consent before start of specific protocol procedure</p> <p>age<math>&gt;</math>18 years</p> <p>histologically or cytologically documented diagnosis of adenocarcinoma of the colon or rectum</p> <p>presence of at least one measurable site of disease following RECIST 1.1 criteria</p> <p>ECOG performance 0-1</p> <p>known RAS mutational status</p> <p>life expectancy of at least 3 months</p> <p>adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening</p> <p>absolute neutrophil count (ANC)<math>\geq</math>1500/<math>\mu</math>l</p> <p>platelet count <math>\geq</math>100,000/<math>\mu</math>l</p> <p>total bilirubin <math>&lt;</math>1.5xULN</p> <p>ALT and AST <math>&lt;</math>3xULN, <math>&lt;</math>5xULN if liver metastasis present</p> <p>PT-INR/PTT<math>&lt;</math>1.5xULN, patients therapeutically anticoagulated with LMWH, heparin or NOACs (dabigatran, rivaroxaban, abixaban) are allowed to participate, patients anticoagulated with phenprocoumon or warfarin should be switched to LMWH, heparin or NOACs</p> <p>creatinine clearance <math>\geq</math>30ml/min and serum creatinine <math>\leq</math>2.0xULN</p> <p>confirmed menopause or negative pregnancy test within 7 days of the start of treatment and willingness to use highly effective methods of contraception</p> <p>willingness and able to comply with the protocol for the duration of the study</p>
Key exclusion criteria	<p>prior therapy with TAS102</p> <p>investigational drug therapy within 4 weeks of study entry</p> <p>major surgery within 4 weeks of starting therapy within this study</p> <p>symptomatic brain metastasis</p> <p>clinically significant cardiovascular disease (NYHA<math>&gt;</math>II°, LV-EF<math>&lt;</math>45%, myocardial infarction within 6 months prior study entry)</p> <p>active clinically serious infections (<math>&gt;</math>grade 2 NCI-CTC version 4.0)</p> <p>history of uncontrolled HIV infection or chronic hepatitis B or C</p> <p>patients with evidence of bleeding diathesis</p> <p>arterial thromboembolic events <math>&lt;</math>6 months prior study entry</p> <p>patients with second primary cancer within 5 years, except adequately treated basal skin cancer or carcinoma in-situ of the cervix or bladder, or low/intermediate risk prostate cancer (Gleason score <math>\leq</math> 7) with normal PSA levels</p> <p>any condition that could jeopardize the safety of the patient and their compliance of the study</p>

	breast-feeding patients substance abuse, medical, psychological or social conditions that may interfere with the participation in the study
Sample Size	144 patients (randomization 1:1) Strata: previous anti-angiogenic therapy $\geq$ or $<$ 12 months in total
Interventions	Run in phase with safety analyses after 20 and 40 patients: Arm A: Ramucirumab 8 mg/kg d1+15, q4w TAS102 35mg/m <sup>2</sup> BID d1-5, 8-12, q4w Arm B TAS102 35mg/m <sup>2</sup> BID d1-5, 8-12, q4w
Sample Size and Statistical Analyses	According to results of the RECURSE trial the median OS upon TAS102 treatment will be 7.1 months with a 6 and 12 months survival probability of 58% and 27%, respectively (1). An expected improvement in OS, corresponding to an increased rate after 6 months from 58% to 70% could be detected with a power of 80% and a significance level of 10% with a logrank test (one-sided), if 72 patients per treatment group (144 in total) are included in the study. This calculation assumes an exponential shape of the survival curves, an accrual time of 12 months and a total observation time, i.e. maximum follow-up duration, of 24 months.
Time schedule	Start of trial/First patient in (FPI): Q II/2018 Last patient in (LPI) Q I/2019 LPLV (last patient last visit) date QI/2020 Recruitment period (months): 12 months Minimum follow-up-period: 12 months
Participating centers	30 in total

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2: Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303-12.

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**AIO-KRK-0114: Randomisierte Studie zur Wirksamkeit einer Cetuximab-Reexposition bei Patienten mit metastasiertem kolorektalem Karzinom (RAS Wildtyp) welche auf eine Erstlinien-Behandlung mit FOLFIRI plus Cetuximab ein Ansprechen zeigten (FIRE-4)**

**AIO-Studie**

Studiennummer/-Code:	AIO-KRK-0114 - FIRE-4
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 - 2020
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Art der Studie	Randomisierte, multizentrische Phase-III Studie		
Verantwortlicher Studienleiter nach AMG	Klinikum der Universität München Marchioninistraße 15 81377 München Vertreten durch: Prof. Dr. med. Volker Heinemann		
Kontaktadresse/ Kontaktperson:	<table border="0"> <tr> <td>Prof. Dr. V. Heinemann Medizinische Klinik III Sekt. Matthias Wolff Klinikum Großhadern LMU München Marchioninstr. 15 81377 München Tel: 089 4400 -72208 Fax: 089 4400 -75256</td> <td>Dr. B. Deuß ClinAssess GmbH Abteilung Projektmanagement Birkenbergstr. 82 51379 Leverkusen Tel.: +49 (0) 2171 / 36 336 0 Fax: +49 (0) 2171 / 36 336 55</td> </tr> </table>	Prof. Dr. V. Heinemann Medizinische Klinik III Sekt. Matthias Wolff Klinikum Großhadern LMU München Marchioninstr. 15 81377 München Tel: 089 4400 -72208 Fax: 089 4400 -75256	Dr. B. Deuß ClinAssess GmbH Abteilung Projektmanagement Birkenbergstr. 82 51379 Leverkusen Tel.: +49 (0) 2171 / 36 336 0 Fax: +49 (0) 2171 / 36 336 55
Prof. Dr. V. Heinemann Medizinische Klinik III Sekt. Matthias Wolff Klinikum Großhadern LMU München Marchioninstr. 15 81377 München Tel: 089 4400 -72208 Fax: 089 4400 -75256	Dr. B. Deuß ClinAssess GmbH Abteilung Projektmanagement Birkenbergstr. 82 51379 Leverkusen Tel.: +49 (0) 2171 / 36 336 0 Fax: +49 (0) 2171 / 36 336 55		
Studienziele	<p><u>Primäres Studienziel:</u> Prospektive Untersuchung des Gesamtüberlebens ab Beginn der Drittlinientherapie (OS3) unter einer Cetuximab-Reexposition gegenüber einer anti-EGFR freien Therapie bei Patienten, welche auf eine Erstlinientherapie mit Cetuximab und FOLFIRI mit CR, PR oder SD &gt;6 Monate angesprochen haben</p> <p><u>Sekundäre Studienziele:</u></p> <ul style="list-style-type: none"> <li>• Ansprechrate ORR</li> <li>• Progressions-freie Zeit PFS</li> <li>• Gesamtüberleben (OS1) ab Beginn der Erstlinientherapie</li> <li>• Early tumor shrinkage und der Remissionstiefe</li> <li>• Untersuchung von molekularen Biomarkern zur Prädiktion von Sensitivität und sekundärer Resistenz einer anti-EGFR Therapie mit Cetuximab</li> <li>• Prospektive Validierung eines Biomarker Scores</li> <li>• Prospektive Analyse des Tumormarkerverlaufs (CEA und CA 19-9)</li> <li>• Erfassung der Sicherheit und Verträglichkeit</li> </ul>		
Zielparameter	<ul style="list-style-type: none"> <li>- Gesamtüberleben in der Drittlinientherapie (OS3)</li> <li>- Progressionsfreies Überleben im Rahmen der Erstlinientherapie (PFS1)</li> </ul>		
Patientenzahl	Geplant: 550 Patienten Bereits eingeschlossen: 289 Patienten (Stand: April 2018)		
Haupt-Einschlusskriterien	<p>Haupteinschlusskriterien:</p> <ul style="list-style-type: none"> <li>• Adenokarzinom des Kolons oder Rektums im UICC Stadium IV, primär nicht resektabel</li> <li>• RAS - Wildtyp-Status (KRAS und NRAS Exone 2-4) des Tumors (nachgewiesen in Primärtumor oder Metastase)</li> </ul>		

	<ul style="list-style-type: none"> <li>• Alter <math>\geq 18</math></li> <li>• ECOG 0-1</li> <li>• Vorliegen mindestens einer messbaren Referenzläsion entsprechend der RECIST 1.1 –Kriterien (CT Thorax und Abdomen 4 Wochen oder weniger vor Randomisation)</li> <li>• Adäquate Knochenmarksfunktion:       <ul style="list-style-type: none"> <li>- Leukozyten <math>\geq 3,0 \times 10^9/L</math> mit Neutrophilen <math>\geq 1,5 \times 10^9/L</math></li> <li>- Thrombozyten <math>\geq 100 \times 10^9/L</math>,</li> <li>- Hämoglobin <math>\geq 5,6 \text{ mmol/L}</math> (entspr. 9 g/dL)</li> </ul> </li> <li>• Adäquate Leberfunktion:       <ul style="list-style-type: none"> <li>- Serumbilirubin <math>\leq 1,5 \times</math> obere Normwertgrenze,</li> <li>- ALAT und ASAT <math>\leq 2,5 \times</math> obere Normwertgrenze (bei Vorliegen von Lebermetastasen ALAT und ASAT <math>\leq 5 \times</math> obere Normwertgrenze)</li> </ul> </li> <li>• INR <math>&lt; 1,5</math> und aPTT <math>&lt; 1,5 \times</math> obere Normwertgrenze (Patienten ohne Antikoagulation).</li> <li>• Adäquate Nierenfunktion:       <ul style="list-style-type: none"> <li>- Serumkreatinin <math>\leq 1,5 \times</math> obere Normwertgrenze oder Kreatinin Clearance (berechnet nach Cockcroft und Gault) <math>\geq 50 \text{ ml/min}</math></li> </ul> </li> <li>• adäquate Herzfunktion: EKG und Echokardiogram mit einer LVEF von <math>\geq 55\%</math></li> </ul> <p><b>Einschlusskriterium nur für Eingang 1:</b></p> <ul style="list-style-type: none"> <li>• Zeit zur letzten Gabe einer vorangegangenen adjuvanten Chemotherapie <math>&gt; 6</math> Monate</li> </ul> <p><b>Zusätzliche Einschlusskriterien nur für Eingang 2:</b></p> <ul style="list-style-type: none"> <li>• Stattgehabte Erstlinientherapie mit FOLFIRI und Cetuximab;</li> <li>• Stattgehabte Zweitlinientherapie <u>ohne</u> FOLFIRI, Irinotecan oder eine gegen EGFR gerichtete Substanz</li> <li>• Letzte Gabe einer gegen den EGFR gerichteten Substanz <math>\geq 4</math> Monate vor Randomisation 2</li> <li>• Nachweis eines RAS-Wildtyp Tumors innerhalb von 4 Wochen vor Randomisation</li> <li>• CT Untersuchungen mit dem Nachweis von PR oder CR oder SD <math>\geq 6</math> Monate nach RECIST Version 1.1 Kriterien als bestes Ansprechen im Rahmen der Erstlinientherapie mit FOLFIRI und Cetuximab</li> </ul>
Haupt-Ausschlusskriterien	<p><b>Hauptausschlusskriterien</b></p> <ul style="list-style-type: none"> <li>• Nachweis einer RAS-Mutation oder fehlende Untersuchung auf RAS-Mutation</li> <li>• Primär resektable Metastasen und Patient wünscht Resektion</li> <li>• Herzinsuffizienz Grad III oder IV (NYHA-Klassifikation)</li> <li>• Myokardinfarkt, instabile Angina pectoris, Ballonangioplastie (PTCA) mit oder ohne Stenting innerhalb der letzten 6 Monate vor Studieneinschluss</li> <li>• Medizinische oder psychologische Beeinträchtigungen, die mit eingeschränkter Einwilligungsfähigkeit einhergehen oder die Durchführung der Studie nicht erlauben</li> <li>• Zusätzliche Krebstherapie (Chemotherapie, Bestrahlung, Immuntherapie oder Hormonbehandlung) während der Studientherapie in der Erstlinien- und Drittlinientherapie (Therapien welche im Rahmen eines anthroposophischen oder Homöopathischen Heilansatzes durchgeführt werden z.B. Misteltherapie stellen kein Ausschlusskriterium dar)</li> <li>• Teilnahme an einer klinischen Studie oder experimentelle medikamentöse Behandlung innerhalb von 30 Tagen vor Aufnahme oder während der Studienteilnahme</li> <li>• Bekannte Hypersensitivität oder allergische Reaktion gegen eine der folgenden Substanzen: 5-Fluorouracil, Cetuximab, Oxaliplatin, Irinotecan, Bevacizumab und chemisch verwandte Substanzen</li> <li>• Bekannte oder klinisch vermutete Hirnmetastasen</li> <li>• Akuter oder subakuter Darmverschluss oder chronisch-entzündliche Darmerkrankung in der Anamnese oder chronische Diarrhoe</li> <li>• Arterielle Thromboembolien oder schwere Blutungen innerhalb von 6 Monaten vor Aufnahme in die Studie (Ausnahme Tumorblutung vor der Tumoresektionsoperation)</li> </ul>

	<ul style="list-style-type: none"> <li>• Bekannter DPD-Mangel (spezielles Screening nicht erforderlich)</li> <li>• Bekannter Glukuronidierungsdefekt (Gilbert-Meulengracht-Syndrom) (spezielles Screening nicht erforderlich)</li> <li>• Zweitmalignom in der Anamnese während der letzten 5 Jahre vor Studieneinschluss oder während der Studienteilnahme, mit Ausnahme eines Basalioms, Spinalioms oder eines in-situ-Karzinoms der Cervix uteri, soweit diese kurativ behandelt wurden.</li> <li>• Fehlende oder eingeschränkte juristische Geschäftsfähigkeit</li> </ul>
<p>Therapieschema</p>	<p><b>FOLFIRI plus Cetuximab</b>  ein Zyklus (Zykluslänge 14 Tage) besteht aus:</p> <ul style="list-style-type: none"> <li>• Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min Tag 1</li> <li>• Folinsäure (racemisch) 400 mg/m<sup>2</sup> iv, 120 min Tag 1</li> <li>• 5-FU 400 mg/m<sup>2</sup> Bolus Tag 1</li> <li>• 5-FU 2400 mg/m<sup>2</sup> iv über 46 h Tag 1-2</li> <li>• Cetuximab initial 400 mg/m<sup>2</sup> als 120 min Infusion, danach jeweils 250 mg/m<sup>2</sup> iv als 60 min Infusion Tag 1 + 8</li> </ul> <p><b>FUFA plus Bevacizumab</b>  Ein Zyklus (Zykluslänge 21 Tage) besteht aus:</p> <ul style="list-style-type: none"> <li>• Folinsäure (racemisch) 400 mg/m<sup>2</sup> iv, 120 min Tag 1</li> <li>• 5-FU 400 mg/m<sup>2</sup> Bolus Tag 1</li> <li>• 5-FU 2400 mg/m<sup>2</sup> iv über 46 h Tag 1-2</li> <li>• Bevacizumab 7,5 mg/kg KG iv</li> </ul> <p><b>Capecitabine plus Bevacizumab</b>  Ein Zyklus (Zykluslänge 21 Tage) besteht aus:</p> <ul style="list-style-type: none"> <li>• Capecitabin 1250 mg/m<sup>2</sup> 2 x tgl p.o. Tag 1-14</li> <li>• Bevacizumab 7,5 mg/kg KG i.v</li> </ul> <p><b>Irinotecan plus Cetuximab (2. Teil)</b>  Ein Zyklus (Zykluslänge 42 Tage) besteht aus:</p> <ul style="list-style-type: none"> <li>• Irinotecan 125 mg/m<sup>2</sup> iv, 60 - 90 min wöchentlich (D1, D8, D15, D22) d.h. über 4 Wochen gefolgt von einer 14 tägigen Pause</li> <li>• Cetuximab initial 400 mg/m<sup>2</sup> als 120 min Infusion, danach jeweils 250 mg/m<sup>2</sup> iv als 60 min Infusion wöchentlich (D1, D8, D15, D22, D29, D36)</li> </ul> <p><b>Windowtherapie:</b>  Nach Maßgabe des Prüfarztes z.B. XELOX/FOLFOX plus Bevacizumab</p> <p><b>Studiendesign:</b></p>
<p>Tumorevaluierung</p>	<ul style="list-style-type: none"> <li>• Ansprechen nach RECIST 1.1 (nach 8, 16 und 24 Wochen, danach alle 12 Behandlungswochen)</li> <li>• Untersuchung des Primärtumors (erweiterte Mutations- und Expressionsanalysen)</li> <li>• Liquid Biopsies (Baseline und zum jeweiligen Progress)</li> <li>• Pharmakogenomische Untersuchungen an einer Vollblutprobe</li> </ul>
<p>Rationale</p>	<p>Die Frage der richtigen Sequenz der palliativen Therapiemöglichkeiten stellt sich zunehmend. So konnte die retrospektive Untersuchung von Santini und Kollegen zeigen, dass Patienten, welche auf eine Erstlinientherapie mit</p>

	<p>Cetuximab eine Tumorreduktion nach RECIST oder eine Krankheitsstabilisierung über &gt; 6 Monate erreichten, auf eine Reexposition mit Cetuximab nach einer anti-EGFR freien Zweitlinientherapie eine hohe Ansprechrate von 54% und eine erstaunlich gutes Gesamtüberleben im Rahmen der Drittlinie von 6,6 Monaten zeigten (Santini et al Ann Oncol 2012). Diese Daten weisen darauf hin, dass es bei initial Cetuximab-sensitiven Patienten, die nach Resistenzentwicklung eine Cetuximab-freie „Window“ Therapie erhielten, sinnvoll sein kann, eine Reexposition mit einem Cetuximab-basierten Regime durchzuführen.</p>
Statistik	<p>Für das primäre Studieziel (OS3 ) werden folgende Annahmen gemacht: Um mit einer HR von 0,67 einen Unterschied bzgl. OS3 mit einer Power von 80% und einem einseitigen alpha von 2,5% nachzuweisen werden 196 Ereignisse benötigt. Bei 196 benötigten Ereignissen und einer angenommenen Dropout-Rate von 15% sind damit 230 Patienten (115 Patienten pro Therapiearm) erforderlich.</p>

Kolonkarzinom, frühe Stadien**AIO-KRK-0317: RANDOMIZED TRIAL OF FOLFOX ALONE OR COMBINED WITH ATEZOLIZUMAB AS ADJUVANT THERAPY OF PATIENTS WITH STAGE III COLON CANCER WITH DEFICIENT DNA MISMATCH REPAIR OR MICROSATELLITE INSTABILITY (ATOMIC)****AIO-Studie**

Studiennummer/-Code:	AIO-KRK-0317 - ATOMIC-Trial
Status:	in Vorbereitung, geplanter Studienstart (FPI) Q3 2018
Rekrutierungszeitraum:	geplant 2018 – 2020
Weitere Zentren:	weitere Zentren auf Anfrage
Letzte Aktualisierung	April 2018

PI International	Frank Sinicrope, Rochester, MN, USA
PI Deutschland	Prof. Dr. Anke Reinacher-Schick, Katholisches Klinikum Bochum, St. Josef-Hospital Universitätsklinikum der Ruhr-Universität, Abteilung für Hämatologie, Onkologie und Palliativmedizin, Gudrunstraße 56, 44791 Bochum, ☎ +49 – 234 509-3591, onkologie@klinikum-bochum.de

**Eligibility Criteria**

Histologically proven stage III colon adenocarcinoma  
 Presence of MSI-H or deficient (d) MMR  
 Completely resected tumors  
 Entire tumor in colon  
 No evidence of residual involved lymph node disease or metastatic disease  
 Patients known to have Lynch Syndrome are eligible  
 No other planned concurrent investigational agents or other tumor directed therapy  
 No active autoimmune disease, including colitis, panhypopituitarism, adrenal insufficiency

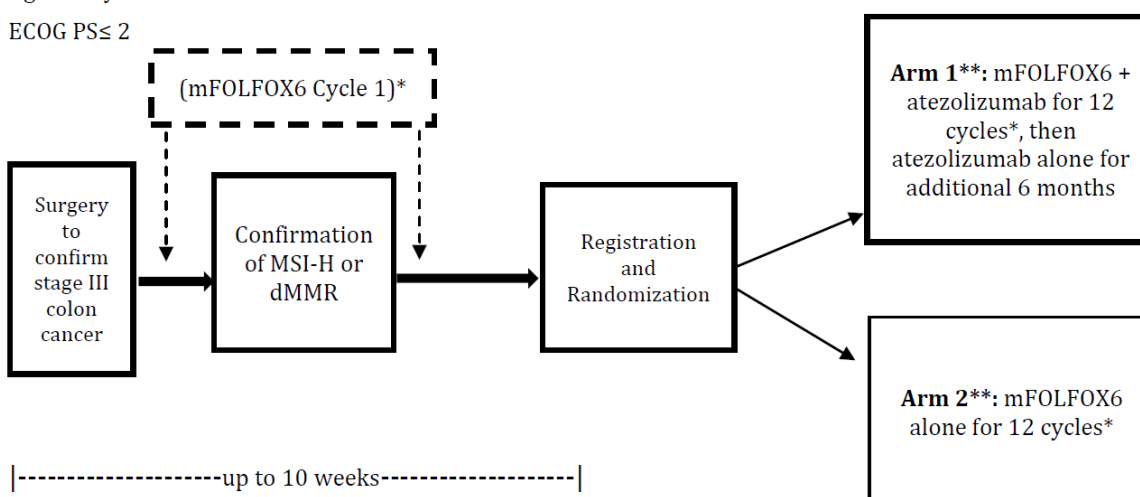
No known active hepatitis B or C infection

No active pulmonary disease with hypoxia  
 No grade  $\geq 2$  peripheral motor or sensory neuropathy  
 Non pregnant, non-nursing  
 Age  $\geq 18$  years  
 ECOG PS  $\leq 2$

**Required Initial Laboratory Values**

Absolute neutrophil count (ANC)  $\geq 1500/\text{mm}^3$   
 Platelet Count  $\geq 100,000/\text{mm}^3$   
 AST/ALT  $\leq 2.5$  ULN  
 Bilirubin  $\leq 1.5$  ULN\*\*  
 Creatinine  $\leq 1.5$  ULN  
 or  
 Calc. Creatinine Clear  $\geq 45$  mL/min  
 TSH WNL\*\*\*

\* Platelets  $\geq 75,000$  for patients who received Cycle 1 mFOLFOX6 prior to registration  
 \*\* Except in the case of Gilbert disease  
 \*\*\* Supplementation is acceptable to achieve a TSH WNL



- \* 1 Cycle = 14 days. One cycle of mFOLFOX6 is allowed prior to registration. If Cycle 1 started prior to registration, then the first post-registration cycle will be mFOLFOX6 Cycle 2. For patients who started Cycle 1 prior to registration and who are randomized to Arm 1, atezolizumab will start with Cycle 2.
- \*\* The standard of care for the time window between end of mFOLFOX6 Cycle 1 and start of mFOLFOX6 Cycle 2 is 14 days; however, up to 28 days is allowed between end of Cycle 1 and start of Cycle 2, if delays are made due to toxicity.

**Patients will be followed for recurrence and survival every 6 months for five years after registration.** Subsequently follow patients for survival every 6 months for three additional years.

### AIO-KRK-0217: Circulating tumor DNA based decision for adjuvant treatment in colon cancer stage II evaluation (CIRCULATE)

#### AIO-Studie

Studiennummer/-Code:	AIO-KRK-0217 - CIRCULATE
Status:	in Vorbereitung Förderantrag beim BMG wurde im April 2017 gestellt. Finanzierung nahezu geklärt
Rekrutierungszeitraum:	Studienstart voraussichtlich 2019
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

APPLICANT/ COORDINATING INVESTIGATOR	PD Dr. med. Gunnar Folprecht University Hospital Carl Gustav Carus University Cancer Center / Medical Department I Fetscherstr. 74, 01307 Dresden, Germany
CONDITION	Colon cancer UICC stage II without microsatellite instability
OBJECTIVE(S)	The study evaluates the value of postoperative circulating tumor DNA (ctDNA) as selection criterion in patients with colon cancer UICC stage II. <u>Primary:</u> <ul style="list-style-type: none"> <li>- To determine the disease free survival (DFS) in patients (pts) with stage II colon cancer who are positive for ctDNA after the resection of the primary with vs. without chemotherapy</li> </ul> <u>Secondary:</u> <ul style="list-style-type: none"> <li>- To determine the overall survival (OS) in pts with stage II colon cancer who are positive for ctDNA after the resection of the primary with vs. without chemotherapy</li> <li>- To determine the DFS and OS in pts with stage II colon cancer without adjuvant chemotherapy who are positive vs. who are negative for ctDNA after the resection of the primary</li> </ul>
INTERVENTION(S)	Patients with resected colon cancer stage II and III treated at approx. 180 colon cancer centers are enrolled in the AIO COLOPREDICT screening platform and screened for micro satellite instability (MSI) - and for this project for frequent tumour mutations (i.e. TP53, KRAS, APC...) in the formaline fixed paraffin embedded (FFPE) primary tumor material. For patients with colon cancer stage II, the patient specific mutation will be analysed in postoperative plasma samples by ultra-deep sequencing to determine the presence of the patient specific mutation (i.e. TP53, KRAS, APC...). Patients who are positive for postoperative ctDNA and microsatellite stable (MSS) are randomized (2:1) to adjuvant chemotherapy or to follow up. All patients negative for postoperative ctDNA are not randomized but followed up. <u>Experimental intervention:</u> Chemotherapy (oxaliplatin / fluoropyrimidine, in pts who are positive for postoperative ctDNA; elderly pts: fluoropyrimidine) <u>Control intervention:</u> Follow up (no chemotherapy) <u>Duration of intervention per patient:</u> 6 months ( <u>chemotherapy cohort</u> ) <u>Follow-up per patient:</u> 5 years
KEY INCLUSION AND EXCLUSION CRITERIA	<u>Key inclusion criteria:</u> <ul style="list-style-type: none"> <li>- Histologically proven colon cancer stage II, microsatellite stable</li> <li>- Resection of the primary 3 – 8 weeks before randomization</li> <li>- Age &gt; 18 years</li> </ul> <u>Key exclusion criteria:</u> <ul style="list-style-type: none"> <li>- Clinical high risk situation, if it is regarded as certain indication for adjuvant therapy by the treating physician and the patient</li> <li>- Contraindication to chemotherapy (inadequate bone marrow, hepatic, renal function)</li> <li>- Comorbidity influencing the prognosis of the patients (i.e. secondary</li> </ul>



	<p>cancer)</p> <ul style="list-style-type: none"> <li>- Participation at another interventional study for postoperative therapy</li> </ul>
OUTCOME(S)	<p><u>Primary efficacy endpoint:</u></p> <ul style="list-style-type: none"> <li>- DFS of patients with positive postoperative ctDNA at study enrolment by treatment arm</li> </ul> <p><u>Key secondary endpoint(s):</u></p> <ul style="list-style-type: none"> <li>- OS of pts with positive postoperative ctDNA by treatment arm</li> <li>- DFS and OS of untreated pts by postoperative ctDNA</li> </ul> <p><u>Assessment of safety:</u></p> <ul style="list-style-type: none"> <li>- Toxicity</li> </ul>
STUDY TYPE	Investigator initiated, prospective, controlled, randomized, confirmatory study
STATISTICAL ANALYSIS	<p><u>Efficacy:</u></p> <ul style="list-style-type: none"> <li>- DFS in pts positive for postoperative ctDNA by treatment arm</li> </ul> <p><u>Description of the primary efficacy analysis and population:</u></p> <ul style="list-style-type: none"> <li>- Stratified log rank test for DFS in all randomized pts positive for postoperative ctDNA treated with or without chemotherapy</li> </ul> <p><u>Safety:</u></p> <p>Descriptive safety data for both arms will be reported in detail for per protocol treated pts by treatment arm. Further, numbers of grade 3-5 events and rates of pts with grade 3-5 events will be compared according to system organ classes following the intent to treat principle</p> <p><u>Secondary endpoint(s):</u></p> <ul style="list-style-type: none"> <li>- Overall survival by treatment arm</li> <li>- DFS and OS of untreated pts by presence/absence of postoperative ctDNA</li> </ul>
SAMPLE SIZE	<p><u>To be assessed for eligibility:</u> n = 2150 (screened for ctDNA, MSI)</p> <p><u>To be allocated to trial:</u> n = 189 (randomized pts)</p> <p><u>To be analysed:</u> n = 183</p>
TRIAL DURATION	<p><u>Time for preparation of the trial (months):</u> 9</p> <p><u>Recruitment period (months):</u> 36</p> <p><u>First patient in to last patient out (months):</u> 60</p> <p><u>Time for data clearance and analysis (months):</u> 8 (primary analysis)</p> <p><u>Duration of the entire trial (months):</u> 77 (including preparation); plus 3 years long term follow-up for overall survival</p>

Lebermetastasen**AIO-KRK-0314/ass: Panitumumab nach Resektion von Lebermetastasen des kolorektalen Karzinoms bei Patienten mit RAS-Wildtyp (PARLIM-Trial)****AIO-assoziierte Studie**

Studiennummer/-Code:	AIO-KRK-0314/ass - PARLIM
Status:	in Rekrutierung
Rekrutierungszeitraum	2014 – ca. 2020
Weitere Zentren:	Leider keine weiteren Zentren mehr möglich
Letzte Aktualisierung	März 2018

Studienleitung	Prof. Dr. med. Volker Heinemann, Ludwig-Maximilians-Univ. München
Studienkoordination	PD Dr. med. Dominik P. Modest Medizinische Klinik III, Klinikum Großhadern Ludwig-Maximilians-Univ. München, Marchioninstr. 15 81377 München, Dominik.Modest@med.uni-muenchen.de
Primäres Zielkriterium	Die Studie hat das Ziel, die Wirksamkeit der postoperativen Therapie mit FOLFOX plus Panitumumab gefolgt von einer 3-monatigen Erhaltungstherapie mit Panitumumab bei Patienten mit RAS-Wildtyp zu untersuchen und mit den historischen Daten für die Standard-FOLFOX-Chemotherapie, die anhand der randomisierten Kontrollgruppe ohne den Antikörper verifiziert wird, zu vergleichen.
Sekundäre Zielkriterien	Die Studie hat das Ziel, die Verträglichkeit der Panitumumab-basierten Therapie in einem postoperativen Setting zu untersuchen. Zusätzlich sollen Prädiktoren für die Behandlungswirksamkeit durch die Auswertung der molekularen Pathologie der Erkrankung identifiziert werden.
Primärer Endpunkt	Progressionsfreies Überleben (PFS) 2 Jahre nach der Randomisierung
Sekundäre Endpunkte	<ul style="list-style-type: none"> <li>• Verträglichkeit und Nebenwirkungen</li> <li>• Gesamtüberleben</li> </ul>
Explorative Endpunkte	<ul style="list-style-type: none"> <li>• Translationale Forschung</li> <li>• Biomarkerprogramm</li> </ul>
Studientyp und Studiendesign	Randomisierte, open-label, multizentrische Phase II Studie, in mehreren Ländern durchgeführte Studie (Deutschland und Österreich)
Patientenanzahl	111 geplante Patienten Rekrutierungsstand: 94 rand. Pat. (Stand: (März 2018))
Geschätzte Anzahl der Zentren	bis zu 70 Zentren in Deutschland und Österreich (davon bis zu 15 Zentren)
Stratifizierung	<ol style="list-style-type: none"> <li>1. FONG-Score 0-2 verglichen mit 3-5</li> <li>2. R0 versus R1</li> <li>3. Vorbehandlung mit einem gegen EGFR gerichteten Wirkstoff</li> </ol>
Einschlusskriterien	<ol style="list-style-type: none"> <li>1. Patient hat seine schriftliche Einverständniserklärung gegeben.</li> <li>2. R0/1-Resektion von Lebermetastasen, die mindestens vier Wochen aber nicht länger als 8 Wochen zurückliegt (die Einreichung des Befundes des Pathologen ist für die Randomisierung zwingend erforderlich, um eine R2 Resektion auszuschließen)</li> <li>3. Histologisch bestätigte Diagnose eines metastierten Kolorektalkarzinoms mit Beschränkung auf die Leber</li> <li>4. RAS- Wildtyp des Tumors, getestet in:</li> </ol>

	<ul style="list-style-type: none"> <li>• <i>KRAS</i> exon 2 (codons 12/13)</li> <li>• <i>KRAS</i> exon 3 (codons 59/61)</li> <li>• <i>KRAS</i> exon 4 (codons 117/146)</li> <li>• <i>NRAS</i> exon 2 (codons 12/13)</li> <li>• <i>NRAS</i> exon 3 (codons 59/61)</li> <li>• <i>NRAS</i> exon 4 (codons 117/146)</li> </ul> <p>5. Alter <math>\geq</math> 18 Jahre</p> <p>6. ECOG Performance-Status 0-1</p> <p>7. Frauen im gebärfähigen Alter müssen geeignete Verhütungsmethoden anwenden</p> <p>8. Ausschluss einer Schwangerschaft</p> <p>9. Relevante Toxizitäten vorheriger Behandlungen müssen abgeklungen sein</p> <p>10. Magnesium <math>\geq</math> untere Normwertgrenze; Kalzium <math>\geq</math> untere Normwertgrenze</p> <p>11. Durch EKG und Echokardiogramm bestätigte normale kardiale Funktion (LVEF <math>\geq</math> 55%)</p> <ul style="list-style-type: none"> <li>• Keine symptomatische kongestive Herzinsuffizienz</li> <li>• Keine instabile Angina pectoris</li> <li>• Keine kardialen Arrhythmien</li> </ul> <p>12. Adäquate Organfunktion wie in Tabelle 1 definiert:</p> <p>Table 1: Adäquate Leber- und Nierenfunktionswerte</p> <table border="1" data-bbox="555 878 1228 1272"> <thead> <tr> <th>SYSTEM</th> <th>LABORWERTE</th> </tr> </thead> <tbody> <tr> <td colspan="2">Hämatologisch</td> </tr> <tr> <td>Neutrophile</td> <td><math>\geq</math>1,5 G/L</td> </tr> <tr> <td>Leukozyten</td> <td><math>&gt;</math>3,0 G/L</td> </tr> <tr> <td>Hämoglobin</td> <td><math>\geq</math>9 g/dL</td> </tr> <tr> <td>Thrombozyten</td> <td><math>\geq</math>100 G/L</td> </tr> <tr> <td colspan="2">Hepatisch</td> </tr> <tr> <td>Albumin</td> <td><math>\geq</math>2,5 g/dL</td> </tr> <tr> <td>Serumbilirubin</td> <td><math>\leq</math>2 mg/dL</td> </tr> <tr> <td>AST und ALT</td> <td><math>\leq</math>3 <math>\times</math> ULN</td> </tr> <tr> <td colspan="2">Renal</td> </tr> <tr> <td>Serumkreatinin</td> <td><math>\leq</math>1,5 mg/dL</td> </tr> </tbody> </table>	SYSTEM	LABORWERTE	Hämatologisch		Neutrophile	$\geq$ 1,5 G/L	Leukozyten	$>$ 3,0 G/L	Hämoglobin	$\geq$ 9 g/dL	Thrombozyten	$\geq$ 100 G/L	Hepatisch		Albumin	$\geq$ 2,5 g/dL	Serumbilirubin	$\leq$ 2 mg/dL	AST und ALT	$\leq$ 3 $\times$ ULN	Renal		Serumkreatinin	$\leq$ 1,5 mg/dL
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Ausschlusskriterien	<p>Ein Teilnehmer ist nicht geeignet für den Studieneinschluss, falls eines der folgenden Kriterien zutrifft:</p> <ol style="list-style-type: none"> <li>1. Bekannte Manifestation von Metastasen</li> <li>2. Progression während der präoperativen Behandlung</li> <li>3. RAS-Mutation des Tumors</li> <li>4. Kontraindikation gegen eine Behandlung mit 5-Fluorouracil/ Folinsäure oder Oxaliplatin</li> <li>5. Bekannte Unverträglichkeit von Panitumumab</li> <li>6. Bekannter DPD-Mangel</li> <li>7. Polyneuropathie <math>&gt;</math> Grad 1 (NCI-CTCv4), welche die Anwendung von Oxaliplatin ausschließt</li> <li>8. Nachweis von Aszites oder Zirrhose</li> <li>9. Patient ist schwanger oder stillt oder plant innerhalb von 6 Monaten nach Ende der Behandlung schwanger zu werden</li> <li>10. Teilnehmer (männlich oder weiblich) ist nicht willens während oder bis zu 6 Monate nach der Behandlung (männlich oder weiblich) eine hochwirksame Verhütungsmethode (gemäß Standard der Einrichtung) zu verwenden</li> <li>11. Operation, offene Biopsie oder signifikante traumatische Verletzung innerhalb von 28 Tagen vor Studieneinschluss oder geplante Operation im Verlauf der Studie. Kleinere chirurgische Eingriffe wie die Implantation von intravenösen Portsystemen (7 Tage vor Studieneinschluss) oder von zentralen Venenkathedern (2 Tage vor Studieneinschluss) sind davon ausgenommen.</li> <li>12. Klinisch signifikante kardiovaskuläre Erkrankung (einschließlich Myokardinfarkt, instabile Angina pectoris, symptomatische kongestive Herzinsuffizienz, schwerwiegende unkontrollierte kardiale Arrhythmien)</li> </ol>																								

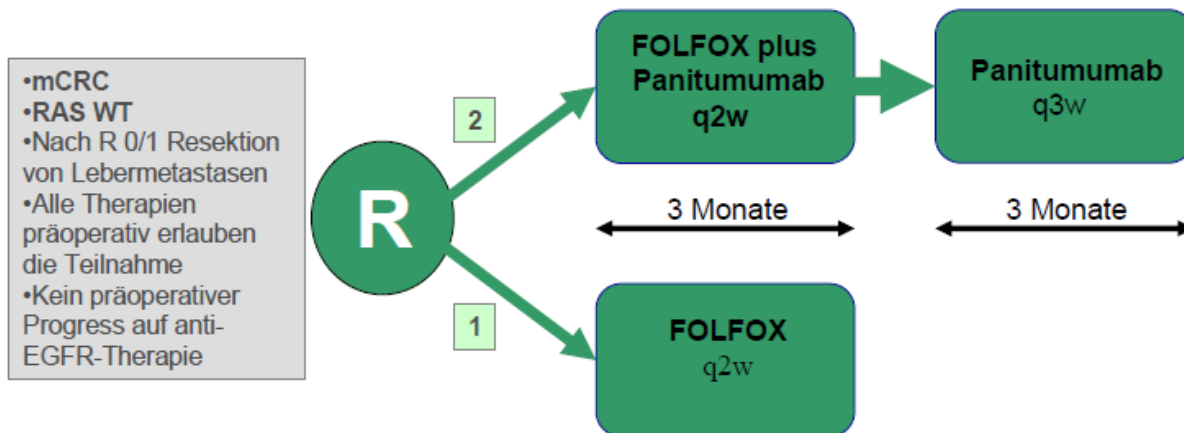
	<p>≤1 Jahr von Einschluss/Randomisierung</p> <ol style="list-style-type: none"> <li>13. Anamnese einer interstitiellen Lungenerkrankung z.B. Pneumonitis oder pulmonale Fibrose oder Nachweis einer interstitiellen Lungenerkrankung in der Baseline-Thorax-Aufnahme</li> <li>14. Gleichzeitige Erkrankung oder Zustand, durch welchen der Teilnehmer nicht geeignet ist für die Studienteilnahme oder welcher sich auf die Sicherheit des Teilnehmers auswirkt.</li> <li>15. Psychologische, familiäre, soziologische oder geographische Bedingungen, die eine Einhaltung des Protokolls nicht erlauben.</li> <li>16. Gleichzeitige Krebstherapie (Chemotherapie, Bestrahlung, biologische Therapie, Immuntherapie oder hormonale Therapie) während der Studie.</li> <li>17. Gleichzeitige Behandlung mit einem Prüfpräparat, Teilnahme an einer anderen klinischen Studie oder jegliche ausdrücklich verbotene Medikation während der Studie.</li> <li>18. Bekannte sofortige oder verzögerte Überempfindlichkeitsreaktion oder Idiosynkrasie auf chemisch verwandte Arzneimittel zu 5-Fluorouracil, Folsäure, Oxaliplatin oder Panitumumab.</li> <li>19. Andere aktive Malignität</li> <li>20. Bekannter Alkoholabusus oder Drogensucht</li> <li>21. Unfähigkeit die Einwilligungserklärung zu erteilen</li> </ol>
Behandlungsschema	<p>mFOLFOX6  Folinsäure 400 mg/m<sup>2</sup>, 2-h-Infusion, d1  5-FU 400 mg/m<sup>2</sup> Bolus i.v., d1  5-FU 2400 mg/m<sup>2</sup> 46-h-Infusion, d1-2  Oxaliplatin 85 mg/m<sup>2</sup> 2-h-Infusion d1  Wiederholung des Zyklus nach 2 Wochen</p> <p>Panitumumab initial 3 Monate (+ mFOLFOX6)  6 mg/kg KG alle 2 Wochen</p> <p>Panitumumab-Erhaltungstherapie Phase (3 Monate)  9mg/kg KG alle 3 Wochen</p> <p>Dauer der postoperativen Chemotherapie  FOLFOX wird für 3 Monate gegeben.  Panitumumab wird gleichzeitig mit der FOLFOX-Chemotherapie (3 Monate) und als zusätzliche Einzelmedikament-Erhaltungstherapie für weitere 3 Monate im experimentellen Arm verabreicht.</p> <p>Die Behandlung innerhalb der Studie wird bei Diagnose des Wiederauftretens beendet</p>
Deeskalation der Chemotherapie	<p>Bei Patienten, die während der Therapie eine Unverträglichkeit von Oxaliplatin aufgrund von allergischen Reaktionen oder Polyneuropathie entwickeln, kann FOLFOX zu 5-Fluorouracil/Folsäure deeskaliert werden.</p>
Baseline-Untersuchungen	<p>Innerhalb von 2 Wochen vor erster Verabreichung der Studienmedikation</p> <ul style="list-style-type: none"> <li>• Einverständniserklärung</li> <li>• RAS-Status</li> <li>• Anamnese (einschließlich Tumorstatus, vorherige Tumortherapien, vorherige/begleitende Erkrankungen, Begleitmedikation)</li> <li>• Körperliche Untersuchung</li> <li>• Versand der Blutproben (10ml PAXGene) und Gewebeproben der resezierten Lebermetastasen an das Labor des Leiters der klinischen Prüfung</li> <li>• Gewicht</li> <li>• Größe</li> <li>• Urinuntersuchung mittels Streifentest</li> <li>• Vitalzeichen (einschließlich Blutdruck und Puls)</li> <li>• ECOG-Performance-Status</li> <li>• Großes Blutbild (einschließlich Differentialblutbild)</li> <li>• Serumchemie (einschließlich Kreatinin, Harnstoff, Harnsäure, berechnete Kreatinin-Clearance (MDRD), Elektrolyte (Natrium, Kalium, Kalzium,</li> </ul>

	<p>Magnesium), AST, ALT, gamma-GT, LDH, CRP, AP, Gesamtbilirubin, Gesamteiweiß, Albumin), INR falls der Patient orale Antikoagulantien einnimmt</p> <ul style="list-style-type: none"> <li>• Tumormarker (CEA, CA 19-9)</li> <li>• Schwangerschaftstest (bei gebärfähige Frauen)</li> <li>• EKG</li> <li>• Echokardiographie</li> <li>• CT Thorax/Abdomen (zum Ausschluss von Metastasen, innerhalb von 6 Wochen vor der ersten Gabe von Studienmedikation durchzuführen)</li> </ul>
Untersuchungen während der FOLFOX-Chemotherapie (beide Arme)	<p>An Tag 1 jedes FOLFOX-Zyklus (beide Arme)</p> <ul style="list-style-type: none"> <li>• Anamnese (Symptome, Toxizitäten, Begleitmedikation)</li> <li>• Körperliche Untersuchung</li> <li>• Gewicht</li> <li>• Urinuntersuchung mittels Streifentest (nur in monatlichen Intervallen)</li> <li>• Vitalzeichen (einschließlich Blutdruck und Puls)</li> <li>• ECOG-Performance-Status</li> <li>• Großes Blutbild (einschließlich Differentialblutbild)</li> <li>• Serumchemie (einschließlich Kreatinin, Harnstoff, Harnsäure, berechnete Kreatinin-Clearance (MDRD), Elektrolyte (Natrium, Kalium, Kalzium, Magnesium), AST, ALT, gamma-GT, LDH, CRP, AP, Gesamtbilirubin, Gesamteiweiß, Albumin), INR falls der Patient orale Antikoagulantien einnimmt</li> <li>• Tumormarker (CEA, CA 19-9)</li> </ul>
Untersuchungen während Panitumumab-Erhaltung (experimenteller Arm)	<p>An Tag 1 jedes 3-wöchigen Behandlungszyklus</p> <ul style="list-style-type: none"> <li>• Anamnese (Symptome, Toxizitäten, Begleitmedikation)</li> <li>• CT Thorax/Abdomen (nur Zyklus 1 Tag 1 der Erhaltungstherapie)</li> <li>• Gewicht</li> <li>• Körperliche Untersuchung</li> <li>• ECOG-Performance-Status</li> <li>• Tumormarker (CEA, CA 19-9)</li> <li>• Großes Blutbild (einschließlich Differentialblutbild)</li> <li>• Serumchemie (einschließlich Kreatinin, Harnstoff, Harnsäure, berechnete Kreatinin-Clearance (MDRD), Elektrolyte (Natrium, Kalium, Kalzium, Magnesium), AST, ALT, gamma-GT, LDH, CRP, AP, Gesamtbilirubin, Gesamteiweiß, Albumin), INR falls der Patient orale Antikoagulantien einnimmt</li> </ul>
Untersuchungen <u>zum</u> Ende der Studienbehandlung	<ul style="list-style-type: none"> <li>• Die Behandlung endet nach 6 Monaten für den experimentellen Arm und nach 3 Monaten für den Kontrollarm</li> <li>• Anamnese (Symptome, Toxizitäten, Begleitmedikation)</li> <li>• Körperliche Untersuchung</li> <li>• Gewicht</li> <li>• Vitalzeichen (einschließlich Blutdruck und Puls)</li> <li>• ECOG-Performance-Status</li> <li>• Großes Blutbild (einschließlich Differentialblutbild)</li> <li>• Serumchemie (einschließlich Kreatinin, Harnstoff, Harnsäure, berechnete Kreatinin-Clearance (MDRD), Elektrolyte (Natrium, Kalium, Kalzium, Magnesium), AST, ALT, gamma-GT, LDH, CRP, AP, Gesamtbilirubin, Gesamteiweiß, Albumin), INR falls der Patient orale Antikoagulantien einnimmt</li> <li>• Tumormarker (CEA, CA 19-9)</li> <li>• EKG</li> <li>• Echokardiographie</li> <li>• CT Thorax/Abdomen</li> </ul>
Follow-Up Untersuchungen für mindestens 36 Monate <u>nach</u> Randomisierung	<p>Alle 3 Monate für mindestens 36 Monate nach Randomisierung</p> <ul style="list-style-type: none"> <li>• Serumchemie (einschließlich Kreatinin, Elektrolyte (Natrium, Kalium, Kalzium), AST, ALT, gamma-GT, LDH, CRP, AP, Gesamtbilirubin, Gesamteiweiß, Albumin)</li> <li>• Großes Blutbild</li> <li>• Tumormarker (CEA und CA19-9)</li> </ul>

	<ul style="list-style-type: none"> <li>• CT Thorax/Abdomen alle 3 Monate bis 2 Jahre nach Randomisierung, danach alle 6 Monate bis zu 36 Monate nach Randomisierung</li> <li>• Informationen zum Überleben</li> <li>• Anhaltende Toxizitäten (nur beim ersten Follow up)</li> </ul>
Rekrutierungszeitraum	5-6 Jahre
Bereitstellung der Medikation	Panitumumab wird als Studienmedikation bereitgestellt. Alle anderen verwendeten Chemotherapeutika werden innerhalb der Studie gemäß Fachinformation verwendet und deshalb von den teilnehmenden Zentren beschafft.
Fallzahl und Begründung	<p>2:1 Randomisierung von Patienten mit RAS-Wildtyp Ziel: einen Nachweis für eine Verbesserung des 2-Jahres-PFS um 15% zu erhalten.</p> <p>Es werden 67 Patienten mit RAS-Wildtyp, die für den Progressionsstatus nach 2 Jahren auswertbar sind, in der experimentellen Behandlungsgruppe benötigt. Gemäß der 2:1 Randomisierung werden dem Vergleichsarm 34 Patienten zugeteilt. Unter Annahme einer Drop-out-Rate von 10% muss eine Gesamtzahl von 111 (101 + 10) Patienten randomisiert werden.</p> <p>Die Fallzahl ist durch die folgenden Annahmen begründet:</p> <p>Mitry und Kollegen haben eine gepoolte Analyse von zwei randomisierten Studien, welche die Wirkung eines Mayo-Regimes, das für 6 Monate nach der R0-Resektion von Lebermetastasen appliziert wurde, durchgeführt (Mitry et al. 2008). Abgesehen von der adjuvanten Behandlung durften die Patienten keine vorherige Chemotherapie erhalten haben. Das 2-Jahres-PFS wurde knapp über 53% berechnet.</p> <p>Die EORTC-Studie hat die perioperative Behandlung mit FOLFOX4 untersucht und nur Patienten mit resektablen Lebermetastasen eingeschlossen. In dieser Studie wurde das progressionsfreie Überleben nach 2 Jahren auf ungefähr 55% geschätzt. (Nordlinger et al., Lancet 2008; 371: 1007-16).</p> <p>In einer großen Kohorte von Patienten mit Lebermetastasen eines kolorektalen Karzinoms, die sich einer Leberteilektomie unterzogen haben wurde beschrieben, dass der Resektionsstatus R0 versus R1 eine untergeordnete Rolle für das krankheitsfreie-, progressionsfreie- und Gesamtüberleben spielt (de Haas 2008). Bei 436 Patienten dieser Kohortenstudie war die 5-Jahres-progressionsfreie und -krankheitsfreie Überlebensrate etwas besser für die R0-Resektionen (vergleichen mit den R1-Resektionen), beide Gruppen zeigten jedoch keinen signifikanten Unterschied. Anders als der präoperative CEA-Level (siehe auch FONG Score) und große Hepatektomie, war die R1-Resektion kein unabhängiger Prädiktor für das Gesamtüberleben.</p> <p>Die vorgeschlagene Studie untersucht Patienten, die sich einer primären oder sekundären R0/1-Resektion unterzogen haben. Als Konsequenz werden primär und sekundär R0- und R1-resizierte Patienten in die Studie eingeschlossen.</p> <p>Aus diesen Gründen nehmen wir an, dass die alleinige Chemotherapie ein 2-Jahres-PFS von <math>\leq 50\%</math> in unserer Zielpopulation verursacht.</p> <p>Eine 2-Jahres PFS-Rate <math>\leq 50\%</math> im experimentellen Arm würde deshalb als Misserfolg der Studie bewertet werden. Eine Verbesserung um 15 Prozentpunkte auf 65% unter Panitumumab plus FOLFOX würde als sehr vielversprechend und von großer klinischer Bedeutung bewertet werden. Die Studie sollte mit einer Power von 80% die experimentelle Kombination als "aussichtsreich" bezeichnen, wenn der wahre Anteil der Patienten mit einem progressionsfreiem Überleben nach zwei Jahren 65% oder mehr beträgt und zur gleichen Zeit den Typ I-Fehler von falsch-positiver Annahme, dass die neue Kombination wirksam ist (<math>&gt;65\%</math>), obwohl die wahre Rate erfolglos ist (<math>&lt;50\%</math>), unter 5% halten.</p>
Studiendauer	<p>Vergleichsarm:</p> <p>FOLFOX: 3 Monate (6 Zyklen)</p> <p>Experimenteller Arm:</p> <p>FOLFOX: 3 Monate (6 Zyklen)</p>

	<p>Panitumumab: 6 Monate</p> <p>Follow-up-Zeitraum: Der minimale Follow-up-Zeitraum wird 36 Monate nach Randomisierung betragen, um eine adäquate Beurteilung des progressionsfreien Überlebens zu ermöglichen</p>
Rationale	<p>Bis zu 50% der Patienten mit Kolorektalkarzinom (CRC) entwickeln im Verlauf der Erkrankung Lebermetastasen. Bei 30-40% der Patienten ist die Metastasierung auf die Leber beschränkt. Bei diesen Patienten kann die R0/1-Resektion der Metastasen zu einer bedeutenden Verbesserung des Gesamtüberlebens beitragen.</p> <p>Die primäre Resektion der Lebermetastasen ist bei 15-20% der Patienten möglich (Scheele 2005, Petrelli 2005). Aktuelle Studien zeigen an, dass eine perioperative Chemotherapie das Überleben nach der Resektion von Lebermetastasen verbessern kann (Portier 2007, Nordlinger 2007). Dennoch wurde nachgewiesen, dass 70-80% der Patienten ein Rezidiv nach Resektion der Lebermetastasen erleiden. Die Stratifizierung für das Rezidivrisiko kann anhand des FONG-Scores durchgeführt werden (Fong 1999).</p> <p>Diese Studie untersucht die Wirksamkeit der postoperativen Chemotherapie kombiniert mit einer gegen EGFR gerichteten Behandlung unter Verwendung von Panitumumab.</p> <p>Die Mehrheit der Patienten stellt sich nach einer chemotherapeutischen Vorbehandlung mit verschiedenen, nicht zwangsläufig standardisierten Schemata, dem Chirurgen vor. Die postoperative Behandlung nach der Resektion der Lebermetastasen ist ebenfalls kein klar definierter Behandlungsstandard in Deutschland.</p> <p>Basierend auf der Studie von Nordlinger et al. wurde ein auf Oxaliplatin-basierendes Schema für die postoperative Behandlung ausgewählt (Nordlinger 2008). Aus Gründen der Praktikabilität wurde mFOLFOX6 als Chemotherapie-Backbone für die zusätzliche Behandlung ausgewählt (Allegra 2010).</p> <p>Außerdem gibt es Belege, dass die Kombination von FOLFOX mit Panitumumab mit einer erhöhten Antitumoraktivität verbunden ist (Douillard et al. ESMO 2009). Deshalb wird im experimentellen Arm die Kombination von FOLFOX plus Panitumumab untersucht. Da beim Kolorektalkarzinom monoklonale Antikörper, die gegen EGFR gerichtet sind, bei Patienten mit einer RAS-Mutation nicht aktiv sind, wird der experimentelle Arm einschließlich Panitumumab nur bei Patienten mit RAS-Wildtyp zur Anwendung kommen (Amado 2008; Oliner 2013).</p> <p>Die geplante Studie hat das Ziel, die Wirksamkeit der postoperativen Therapie mit FOLFOX plus Panitumumab gefolgt von einer 3-monatigen Erhaltungstherapie mit Panitumumab bei Patienten mit RAS-Wildtyp zu untersuchen und mit den historischen Daten für die Standard-FOLFOX-Chemotherapie, die anhand der randomisierten Kontrollgruppe ohne den Antikörper verifiziert wird, zu vergleichen. (Abbildung 1: Studiendesign).</p> <p>Die Studie erlaubt eine präoperative Behandlung mit Schemata wie zum Beispiel FOLFIRI, XELIRI, FOLFOX oder XELOX +/-Bevacizumab oder +/-Cetuximab, aber auch Patienten ohne chemotherapeutische Vorbehandlung sind für die Studie qualifiziert. Es sind jedoch nur Patienten geeignet, die während der präoperativen Behandlung keinen Progress erlitten haben.</p> <p>Nach der Operation wird ein behandlungsfreier Zeitraum von mindestens 4 Wochen, aber nicht länger als 8 Wochen gestattet.</p> <p>Patienten mit RAS-Wildtyp (50% von allen Patienten) werden dann in einem Verhältnis von 2:1 in den experimentellen Arm mit FOLFOX + Panitumumab oder in den Vergleichsarm mit alleinigem FOLFOX randomisiert. Die Kombinationsbehandlung wird über einen Zeitraum von 3 Monaten durchgeführt, nach welchem Patienten im experimentellen Arm eine Erhaltungstherapie mit Panitumumab für weitere 3 Monate erhalten. Im Vergleichsarm wird die Behandlung jedoch nach 3 Monaten beendet</p>

(Abbildung 1).

**Figure 1: Studien Design**

### Cetuximab/FOLFIRI with or without oxaliplatin and FOLFOXIRI with or without bevacizumab in neoadjuvant treatment of non-resectable colorectal liver metastases (CELIM 2)

#### AIO-assoziierte Studie

Studiennummer/-Code:	CELIM 2
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 - 2018 (voraussichtlich länger)
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Study type	Open, randomized, multicenter
Sponsor	Technical University Dresden 01062 Dresden, Germany PD Dr. Folprecht (LKP) Mail: gunnar.folprecht@uniklinikum-dresden.de
Objective	The aim of this study is to investigate the following schedules for efficacy with regard to response to neoadjuvant treatment of patients with non-resectable liver metastases: <ul style="list-style-type: none"> <li>• Cetuximab/FOLFOXIRI and cetuximab/FOLFIRI in patients with ras wild type tumours and</li> <li>• Bevacizumab/FOLFOXIRI and FOLFOXIRI in patients with ras mutant tumours.</li> </ul>
Primary endpoint	Rate of patients with partial or complete response according to modified RECIST criteria
Secondary endpoint	Rate of patients who had a R0 resection of all lesions and are disease free for at least 6 months
Other endpoints	<ul style="list-style-type: none"> <li>• R0 resection rate</li> <li>• Rate of liver resection with macroscopically tumour free margins and/or RFA Progression free survival</li> </ul>



	<ul style="list-style-type: none"> <li>• Disease free survival after resection</li> <li>• Overall survival</li> <li>• Toxicity (safety population)</li> <li>• Pathological response in resected tumour tissue</li> <li>• Evaluation of molecular predictive markers for response and toxicity</li> </ul>
Study design	<p>Patients with liver metastases from colorectal and without known extrahepatic metastases will be screened for this study including ras status (b-raf status according to local standard).</p> <p>Patients receive chemotherapy according to the allocation and are re-evaluated for resectability every 8 weeks for a maximum of 6 months. Resectable patients will be resected and receive an adjuvant treatment to complete 12 cycles. In certain circumstances, a second resection is allowed within the study.</p> <p>Patients with <b>ras wild-type</b> tumours will be randomized to receive:</p> <ul style="list-style-type: none"> <li>• Cetuximab/FOLFIRI or</li> <li>• Cetuximab/FOLFOXIRI</li> </ul> <p>Patients with <b>ras mutations</b> will be randomized to receive:</p> <ul style="list-style-type: none"> <li>• FOLFOXIRI or</li> <li>• FOLFOXIRI/bevacizumab</li> </ul>
Key inclusion criteria	<ul style="list-style-type: none"> <li>• Non-resectable, histologically confirmed, synchronous or metachronous colorectal liver metastases.</li> <li>• WHO PS <math>\leq</math> 1</li> <li>• Written informed consent</li> <li>• Adequate bone marrow function, liver function (see full protocol)</li> <li>• Age <math>\geq</math> 18 years</li> </ul>
Key exclusion criteria	<ul style="list-style-type: none"> <li>• Any evidence of extrahepatic metastases, distant lymph node metastases and primary tumour recurrence</li> <li>• Prior systemic antitumour therapy with anti- EGFR-, antiangiogenetic drugs or with chemotherapy (except adjuvant chemotherapy with an interval of <math>\geq</math> 6 months or in combination with radiation as radio sensitizer)</li> <li>• Renal insufficiency, inflammatory bowel disease, relevant hypertension, proteinuria, neuropathy, concurrent systemic immune therapy, chemotherapy, hormone or immune suppressive treatment, peptic ulcera or esophagitis / gastritis, arteriothrombotic events, deep vein thrombosis</li> <li>• History of other malignancies</li> <li>• Hypertension with an arterial blood pressure <math>&gt;</math> 150/90 mmHg</li> <li>• Known proteinuria <math>&gt;</math> 1 g/day (to be tested if proteinuria more than 1+ in the urinary dipstick analysis)</li> </ul> <p>For further in- and exclusion criteria, see full protocol</p>
Sample size	256 patients to be randomized (138 randomized ras/b-raf wild type patients, 118 randomized ras mutant)
Recruitment	Jan 2013 – Dec 2018, 86 patients recruited (APR 2018)
Scheme of therapy	<p><b>Cetuximab/FOLFIRI:</b> Cetuximab 400 mg/m<sup>2</sup> (first dose, 2 h), then 250 mg/m<sup>2</sup> (1 h) weekly Irinotecan 180 mg/m<sup>2</sup>, d-I Folinic acid 400 mg/m<sup>2</sup> (2 h), 5-FU 400 mg/m<sup>2</sup> (Bolus), 5-FU 2400 mg/m<sup>2</sup> (46 h) every 2 weeks</p> <p><b>Cetuximab/FOLFOXIRI:</b> Cetuximab 400 mg/m<sup>2</sup> (first dose, 2 h), then 250 mg/m<sup>2</sup> (1 h) weekly Irinotecan 125 mg/m<sup>2</sup>, Oxaliplatin 85 mg/m<sup>2</sup> (2 h), d-I Folinic acid 400 mg/m<sup>2</sup> (2 h), 5-FU 3200 mg/m<sup>2</sup> (46 h) every 2 weeks</p>

	<p><b>FOLFOXIRI:</b> Irinotecan 165 mg/m<sup>2</sup>, Oxaliplatin 85 mg/m<sup>2</sup> (2 h), d-l Folinic acid 400 mg/m<sup>2</sup> (2 h), 5-FU 3200 mg/m<sup>2</sup> (46 h) every 2 weeks</p> <p><b>Bevacizumab/FOLFOXIRI:</b> Bevacizumab 5 mg/kg (90 – 30 min i.v.), Irinotecan 165 mg/m<sup>2</sup>, Oxaliplatin 85 mg/m<sup>2</sup> (2 h), d-l Folinic acid 400 mg/m<sup>2</sup> (2 h), 5-FU 3200 mg/m<sup>2</sup> (46 h) every 2 weeks</p>
Criteria for evaluation	response (RECIST 1.1 criteria) and resections
Rationale	<p>The aim of this study is to investigate the following schedules for efficacy with regard to response rate in neoadjuvant treatment of patients with non-resectable liver metastases:</p> <ul style="list-style-type: none"> <li>- Cetuximab/FOLFOXIRI and cetuximab/FOLFIRI in patients with ras wild type tumours and</li> <li>- Bevacizumab/FOLFOXIRI and FOLFOXIRI in patients with ras mutant tumours.</li> </ul>

### AIO-KRK-0115/ass: Complete Excision of colorectal Liver Metastases in patients with unfavorable prognostic factors or medical treatment alone (CELIM-3-Trial)

#### AIO-assoziierte Studie

Studiennummer/-Code:	AIO-KRK-0115/ass - CELIM-3
Status:	in Vorbereitung – Förderantrag beim BMBF wurde gestellt
Rekrutierungszeitraum	48 Monate – Studienstart noch offen
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

COORDINATING INVESTaGATOR	PD Dr. Gunnar Folprecht, University Cancer Center Prof. Dr. Jürgen Weitz, Dpt. of Surgery University Hospital Carl Gustav Carus Fetscherstr. 74, 01307 Dresden Gunnar.Folprecht@uniklinikum-dresden.de Tel.: +49 351 458 4794
TITLE OF STUDY	*Complete *Excision of colorectal *Liver *Metastases in patients with unfavorable prognostic factors or medical treatment alone (CELIM3)
CONDITION	Metastatic colorectal cancer, liver metastases
OBJECTIVE(S)	To determine the effect of metastasectomy in colorectal cancer patients with unfavorable prognostic factors with uncertain benefit from resection with regard to overall survival and quality of life
INTERVENTION(S)	<p><u>Experimental intervention / index test:</u> Resection of all metastases (with or without ablation), systemic therapy in case of progression according to local standard</p> <p><u>Control intervention / reference test:</u> No resection / ablation unless changes in medical findings, systemic therapy according to local standard</p> <p><u>Follow-up per patient:</u></p> <ul style="list-style-type: none"> <li>- Resections to be completed within 6 months</li> <li>- Chemotherapy will be performed according to local standard (not as pharmaceutical trial)</li> </ul>

	<p><u>Duration of intervention per patient:</u> 6 years or until end of study whatever occurs first</p> <p><u>Experimental and / or control off label or on label in Germany:</u> Not applicable (chemotherapy follows local standard, resection not off-label)</p>
KEY INCLUSION AND EXCLUSION CRITERIA	<p><u>Key inclusion criteria:</u> The patients are included if they:</p> <ol style="list-style-type: none"> <li>1. Have technically resectable metastases of colorectal cancer (multistep approaches, ablation, portal vein embolization allowed) AND</li> <li>2. Are treated at least 4 months with chemotherapy (at least doublet combination plus antibody or triplet combination) with known response to this treatment (in patients with contra-indications, doublet combination as minimum requirement) AND</li> <li>3. Have unfavourable prognosis defined as: <ol style="list-style-type: none"> <li>a. more than 10 metastases OR</li> <li>b. disease free survival after the last resection shorter than 6 months and more than 3 metastases OR</li> <li>c. Basingstoke score 20 or more OR</li> <li>d. Basingstoke score 15 or more in patients with <ol style="list-style-type: none"> <li>i. Age <math>\geq</math> 70 and ECOG <math>&gt;</math> 0 or significant co-morbidity (Charlson Co-Morbidity index <math>&gt;</math> 2)</li> <li>ii. disease free survival after the last resection shorter than 6 months</li> <li>iii. More than three operations planned</li> </ol> </li> </ol> </li> <li>4. Are discussed in the multidisciplinary tumour board confirming criteria 1-3</li> <li>5. Have a WHO performance status 0-1</li> <li>6. Are generally operable</li> <li>7. Have a signed informed consent</li> </ol> <p><u>Key exclusion criteria:</u> Patients are excluded if they:</p> <ol style="list-style-type: none"> <li>1. Are younger than 18 years, pregnant, breast-feeding or have a severe psychiatric disease</li> <li>2. Are legally dependent or cannot understand the informed consent</li> <li>3. Have brain metastases</li> </ol>
OUTCOME(S)	<p><u>Primary efficacy endpoint:</u> 1. Overall survival in the intention-to-treat (ITT) population (primary endpoint)</p> <p><u>Key secondary endpoint(s):</u></p> <ol style="list-style-type: none"> <li>1. Quality of life</li> <li>2. Overall survival in patients as per protocol analysis</li> <li>3. Safety of resection</li> <li>4. Rate of resection and pathological outcome (margins)</li> <li>5. Disease free survival in resected patients</li> <li>6. Duration / protocols of subsequent chemotherapies</li> </ol> <p><u>Assessment of safety:</u> 90 day mortality</p>
STUDY TYPE	Randomized, controlled, open, interventional, confirmatory trial

STATISTICAL ANALYSIS	<p><u>Description of the primary efficacy / test accuracy analysis and population:</u>  The primary endpoint is overall survival. The null hypothesis to be tested is that the hazard ratio of the treatment effect is equal or greater than 1. The tests will be done at a global one-sided type one error of 2.5%.  The primary efficacy analysis will be performed according to the intent to treat. A Cox regression model will be fitted for the estimation of the treatment effect. Stratification factors used for randomization will be entered into the model. This ITT analysis will allow for an unbiased assessment of the overall efficacy of metastasectomy in this specific patient population. A complementary analysis will be performed in the per protocol population in order to correct for cross-over effects. Additional exploratory analyses will be performed in order to test for risk factors and to check for interactions of the treatment effect. One interim efficacy analysis has been planned which will be triggered by the observation of 131 events. The final efficacy analysis will be triggered by the observation of 219 events.</p> <p><u>Safety:</u>  Descriptive analysis of mortality in both arms, perioperative morbidity. Chemotherapy toxicity (QoL).  Data will be supervised by a Data Safety Monitoring Board.</p> <p><u>Secondary endpoints:</u>  Descriptive analysis (DFS), multivariate analysis</p>
SAMPLE SIZE	<p>Assuming a median survival time of 28.6 months in the chemotherapy arm and of 42 months in the liver resection arm, proportional hazards, constant accrual over 4 years plus 2 years of follow-up and a 2% drop-out rate, the sample size was calculated for a one-sided alpha of 2.5%, and a power of 80%. Accounting for one interim analysis a total of 366 patients are expected to yield the necessary number of events (N=219) in order to test for superiority of the experimental arm.</p> <p>To be assessed for eligibility (n = 650)  To be allocated to trial (n = 366)  <u>To be analysed (n = 366)</u></p>
TRIAL DURATION	<p>First patient in to last patient out (months): 12  <u>Duration of the entire trial (months): 60</u>  <u>Recruitment period (months): 48</u></p>
PARTICIPATING CENTERS	<p><u>To be involved (n): 80</u></p>

### Rektumkarzinom

#### **AIO-KRK-0214: mFOLFOX6 vs. mFOLFOX6 + aflibercept as neoadjuvant treatment in MRI-defined T3-rectal cancer: a randomized phase-II-trial**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-KRK-0214
Status:	in Rekrutierung
Rekrutierungszeitraum	Juli 2017 – Q 3 2020
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	09. April 2018
Study design	Randomized, open labeled, parallel group, multicenter phase II study with two arms. Patients with locally advanced rectal or rectosigmoid cancer staged cT3 CRM-negative with MRI will receive 6 cycles of neoadjuvant treatment with

	mFOLFOX6 (Arm A) vs. mFOLFOX6 + aflibercept (Arm B) followed by surgery.
Coordinating Investigator	Prof. Dr. Ralf-Dieter Hofheinz Tagestherapiezentrum am ITM & III. Med. Klinik Universitätsmedizin Mannheim Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany Phone: +49 - 621 - 38 32 855, Fax: +49 - 621 - 38 32 488
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin, Germany Phone: +49-30-8145 344 31, Fax: +49-30-3229 329 26
Anticipated start date	Q1/2017
Duration of study	5 years
Indication	Locally advanced cT3 rectal cancer
Countries Total number of sites	Germany, Austria 40 sites
Recruited patients	9 in 27 Sites
Primary objective	To investigate the <b>pathological tumor response</b> based on central pathologic review of the mFOLFOX6/aflibercept combination as compared to mFOLFOX6 alone in patients with locally advanced rectal cancer staged cT3 CRM-negative with MRI.
Secondary objectives	To compare the treatment Arms with respect to:  <b>Safety</b> - Dose intensities of study medication - Type, incidence and severity of AEs and SAEs - Laboratory parameters  <b>Efficacy</b> - Survival, disease-free survival, relapse-free survival - Downstaging and downsizing using a standardized regression grading (Dworak regression grading)  <b>Surgical morbidity and mortality</b> - Perioperative in-hospital morbidity and mortality within 28 days after surgery  <b>Others</b> - Vital signs, Physical examination, WHO/ECOG  The following secondary objectives will be considered beyond the clinical study report: <b>Quality assurance of MRI (central read)</b> - Comparison of the local read of: <ul style="list-style-type: none"> <li>• T, N, M Staging</li> <li>• High localization</li> <li>• Distance to circumferential resection margin (CRM)</li> </ul>
Planned sample size	209 patients total (70 Arm A, 139 Arm B)
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. Age <math>\geq</math> 18 years</li> <li>2. Signed and dated informed consent, and willing and able to comply with protocol requirements</li> <li>3. WHO/ECOG Performance Status (PS) 0-1</li> <li>4. Diagnosis of rectal adenocarcinoma</li> <li>5. Candidate for sphincter-sparing surgical resection prior to neoadjuvant therapy according to the primary surgeon, i.e. no patient will be included for whom surgeon indicates need for abdomino-perineal resection (APR) at baseline.</li> <li>6. Clinical staging is based on the combination of the following</li> </ol>

	<p>assessments:</p> <ul style="list-style-type: none"> <li>• Physical examination by the primary surgeon</li> <li>• CT scan of the chest/abdomen</li> <li>• Pelvic MRI</li> <li>• Rigid rectoscopy / endoscopic ultrasound (ERUS)</li> <li>• Both examinations (MRI + ERUS) are mandatory</li> </ul> <p>7. The tumor has to fulfill the following criteria:</p> <ul style="list-style-type: none"> <li>• No symptomatic bowel obstruction</li> <li>• Locally advanced rectal and rectosigmoid cancer, i.e. lower border of tumor &gt; 5 cm and &lt; 16 cm from anal verge as determined by rigid rectoscopy</li> <li>• MRI criteria:       <ol style="list-style-type: none"> <li>a. Lower border of tumor below a line defined by promontorium and symphysis, regardless of the criterion “&lt; 16 cm from anal verge as determined by rigid rectoscopy”.</li> <li>b. No evidence that tumor is adjacent to (defined as within 2 mm of) the mesorectal fascia on MRI (i.e. CRM &gt; 2 mm)</li> <li>c. Only T3-tumors are included, i.e infiltration into perirectal fat &lt; 10 mm provided CRM &gt; 2 mm</li> <li>d. <b>Note:</b> MRI criteria are used for the definition of T3 tumor (i.e. exclusion of T2 and T4 situation).</li> </ol> </li> </ul> <p>8. Hematological status:</p> <ul style="list-style-type: none"> <li>• Neutrophils (ANC) <math>\geq 2 \times 10^9/L</math></li> <li>• Platelets <math>\geq 100 \times 10^9/L</math></li> <li>• Hemoglobin <math>\geq 9</math> g/dL (previous transfusion of packed blood cells allowed)</li> </ul> <p>9. Adequate renal function:</p> <ul style="list-style-type: none"> <li>• Serum creatinine level <math>\leq 1.5</math> x upper normal limit (ULN) or <math>\leq 1.5</math> mg/dl</li> <li>• Creatinine clearance <math>\geq 30</math> ml/min</li> </ul> <p>10. Adequate liver function:</p> <ul style="list-style-type: none"> <li>• Serum bilirubin <math>\leq 1.5</math> x upper normal limit (ULN)</li> <li>• Alkaline phosphatase &lt; 3 x ULN</li> <li>• AST and ALT &lt; 3 x ULN</li> </ul> <p>11. Proteinuria &lt; 2+ (dipstick urinalysis) or <math>\leq 1</math> g/24hour or <math>\leq 500</math> mg/dl</p> <p>12. Regular follow-up feasible</p> <p>13. For female patients of childbearing potential, negative serum pregnancy test within 1 week (7 Days) prior of starting study treatment</p> <p>14. Female patients of childbearing potential (i.e. did not undergo surgical sterilization – hysterectomy, bilateral tubal ligation, or bilateral oophorectomy - and is not post-menopausal for at least 24 consecutive months) must commit to using highly effective and appropriate methods of contraception until at least 6 months after the end of study treatment such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), vasectomized partner, bilateral tubal occlusion, sexual abstinence. If an oral contraception is used, a barrier method of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge) has to be applied additionally.</p> <p>15. Fertile male patients with a partner of childbearing potential must commit to using highly effective and appropriate methods of contraception (details see above) until at least 9 months after the end of study treatment.</p>
Exclusion Criteria	<ol style="list-style-type: none"> <li>1. Distant metastases (CT scans of thorax and abdomen are mandatory)</li> <li>2. cT2 and cT4 tumors (defined by MRI criteria)</li> <li>3. Exclusion of potentially compromised CRM as defined by MRI criteria (i.e. &gt; 2 mm distance from CRM)</li> <li>4. Prior antineoplastic therapy for rectal cancer</li> <li>5. History or evidence upon physical examination of CNS metastasis</li> <li>6. Uncontrolled hypercalcemia</li> </ol>

	<ol style="list-style-type: none"> <li>7. Pre-existing permanent neuropathy (NCI-CTCAE grade <math>\geq 2</math>)</li> <li>8. Uncontrolled hypertension (defined as systolic blood pressure <math>&gt;150</math> mmHg and/or diastolic blood pressure <math>&gt;100</math> mmHg), or history of hypertensive crisis, or hypertensive encephalopathy</li> <li>9. Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy, radiotherapy)</li> <li>10. Treatment with any other investigational medicinal product within 28 Days prior to study entry</li> <li>11. Known dihydropyrimidine dehydrogenase (DPD) deficiency</li> <li>12. Treatment with CYP3A4 inducers unless discontinued <math>&gt; 7</math> Days prior to randomization</li> <li>13. Any of the following in 3 months prior to inclusion: <ul style="list-style-type: none"> <li>• Grade 3-4 gastrointestinal bleeding (unless due to resected tumor)</li> <li>• Treatment resistant peptic ulcer disease</li> <li>• Erosive esophagitis or gastritis</li> <li>• Infectious or inflammatory bowel disease</li> <li>• Diverticulitis</li> </ul> </li> <li>14. Any active infection within 2 weeks prior to study inclusion</li> <li>15. Vaccination with a live, attenuated vaccine within 4 weeks prior to the first administration of the study medication</li> <li>16. Other concomitant or previous malignancy, except: <ul style="list-style-type: none"> <li>• Adequately treated in-situ carcinoma of the uterine cervix</li> <li>• Basal or squamous cell carcinoma of the skin</li> <li>• Cancer in complete remission for <math>&gt; 5</math> years</li> </ul> </li> <li>17. Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 Days</li> <li>18. Pregnant or breastfeeding women</li> <li>19. Patients with known allergy to any excipient to study drugs</li> <li>20. History of myocardial infarction and/or stroke within 6 months prior to randomization, NYHA class III and IV congestive heart failure</li> <li>21. Severe renal insufficiency (creatinine clearance <math>&lt; 30</math>ml/min)</li> <li>22. Bowel obstruction</li> <li>23. Contra-indication to the assessment by MRI</li> <li>24. Involvement in the planning and/or conduct of the study (applies to both Sanofi staff and/or staff of sponsor and study site)</li> <li>25. Patient who might be dependent on the sponsor, site or the investigator</li> <li>26. Patients who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</li> <li>27. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</li> </ol>
Investigational Product	Aflibercept (Zaltrap®) 4 mg/kg BW i.v.
Treatment schedule after randomization	<p><b>Arm A:</b> Oxaliplatin 85 mg/m<sup>2</sup>, Leucovorin 350 mg/m<sup>2</sup> i.v. as 2 h infusion on Day 1, 5-FU 400 mg/m<sup>2</sup> i.v. as bolus on Day 1 and 2400 mg/m<sup>2</sup> as 46 h infusion q2w</p> <p><b>Arm B:</b> Oxaliplatin 85 mg/m<sup>2</sup>, Leucovorin 350 mg/m<sup>2</sup> i.v. as 2 h infusion on Day 1, 5-FU 400 mg/m<sup>2</sup> i.v. as bolus on Day 1 and 2400 mg/m<sup>2</sup> as 46 h infusion q2w, Aflibercept 4 mg/kg BW i.v. on Day 1 q2w</p>
Primary endpoint	Pathologic complete response (pCR) rate, defined by the number of patients with a pCR finding divided by the number of patients in the analysis set. The pCR will be assessed at the end of the treatment in a standardized manner independently by a central pathology.

Secondary endpoints	<p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• Dose intensities of study medication</li> <li>• Type, incidence and severity of AEs, SAEs and AESIs</li> <li>• Dose reduction or discontinuation of study drug due to adverse events</li> <li>• Rate of treatment discontinuation due to toxicity</li> <li>• Type, incidence and severity of laboratory abnormalities</li> </ul> <p><b>Efficacy</b></p> <ul style="list-style-type: none"> <li>• Rate of R0-wide, R0-narrow (according to CRM definitions in S3-guideline Version 1.1 August 2014), R1 and locoregional R2 resection</li> <li>• Disease-free survival (DFS) rate</li> <li>• Relapse-free survival (RFS) in resected patients</li> <li>• Overall survival (OS)</li> <li>• Downstaging and downsizing using a standardized regression grading (Dworak regression grading)</li> </ul> <p><b>Surgical morbidity and mortality</b></p> <ul style="list-style-type: none"> <li>• Type, incidence and severity of perioperativ medical events</li> <li>• Mortality within 28 days after surgery</li> </ul> <p><b>Others</b></p> <ul style="list-style-type: none"> <li>• Vital signs</li> <li>• Physical examination</li> <li>• WHO/ECOG</li> </ul>
Randomization procedure	After the initial screening procedure, eligible patients will be randomized in a ratio of 1:2 to receive either mFOLFOX6 or Afibercept+mFOLFOX6. Permuted block randomization will be applied.
Scientific rationale	Patients with locally advanced rectal cancer are generally recommended to receive preoperative radiotherapy or radiochemotherapy. The advantage of combined-modality therapy in rectal cancer is that it has reduced local pelvic recurrence – a dreaded and morbid event – to rates of about 10%. There is good quality evidence that preoperative radiotherapy reduces local recurrence but there is little if any impact on overall survival. One strategy to reduce the distant recurrence rate, and thereby increase the cure rate, would be to introduce systemic treatment earlier to prevent dissemination of micrometastases. The present trial is designed to compare two neoadjuvant chemotherapy regimens in patients with non-metastatic T3 CRM-negative rectal cancers using quality-controlled MRI of the pelvis as a main inclusion criterion. This strategy is believed to reduce acute and long-term toxicity caused by preoperative radiotherapy and to administer effective systemic chemotherapy early in the course of disease as neoadjuvant chemotherapy.
Interim analysis	No interim analysis is planned for this study.
Statistical considerations and sample size calculation	<p><b>Sample Size Estimation:</b> The calculation of the sample size is based on a Fisher's exact test. It is assumed that the proportion for pCR in Arm A (mFOLFOX6) is 10%. The sample size is calculated such that a difference of absolute 17% (therefore pCR in Arm B 27%) could be detected with a type I error rate of 5% and a power of 80%. Based on these assumptions and using a randomization ratio of 1:2, the resulting total sample size is given by 198 patients (Arm A: 66 pts; Arm B: 132 pts.). Accounting for a dropout rate of 5%, the study is planned to recruit a total pf 209 patients (Arm A: 70; Arm B: 139).</p> <p><b>Statistical Considerations:</b> An observed cases approach will be applied, and missing data will not be imputed.</p>
Statistical analysis	STABIL – Statistische und Biometrische Lösungen Pistorstr. 7, 66482 Zweibrücken, Germany



Study plan	FPI:	Q1/2017
	LPI:	Q1/2020
	Duration of treatment:	up to 5.5 months
	Follow-up:	3 years
	Follow-up for LPI:	12 months after EOT visit
	LPO:	Q3/2021
	Study report:	Q3/2022

**AIO-KRK-0113/ass: Randomised trial comparing completeness of adjuvant chemotherapy after early vs. late diverting stoma closure in low anterior resection for rectal cancer (COCSTOM)**

**AIO-assozierte Studie**

Studiennummer/-Code:	AIO-KRK-0113/ass - COCSTOM
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 – 2018
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	März 2018

Coordinating Investigator	Prof. Dr. P. Kienle
Indication	Rectal cancer UICC II-III, low anterior resection, stoma closure, adjuvant chemotherapy
Objectives	To investigate Completeness of adjuvant Chemotherapy (CoC) and quality of life (QoL), morbidity and disease free survival after early vs. late diverting stoma closure
Trial design	Randomised, controlled, two parallel group, multicentre trial
Eligibility criteria	<p><u>Key inclusion criteria:</u></p> <ol style="list-style-type: none"> <li>1. Temporary diverting stoma (independent from the stoma type)</li> <li>2. Elective curative low anterior resection (LAR) with total mesorectal excision (TME) after neoadjuvant therapy (long-course chemoradiation or short-term radiotherapy – 5x5 Gy) for UICC II-III rectal cancer</li> <li>3. No anastomotic leakage after LAR</li> <li>4. Indication for adjuvant chemotherapy</li> <li>5. Written informed consent</li> <li>6. Age <math>\geq 18</math> years</li> <li>7. Patients able to cooperate (ability of subject to understand character and individual consequences of the clinical trial)</li> </ol> <p><u>Key exclusion criteria:</u></p> <ol style="list-style-type: none"> <li>1. ASA &gt;3</li> <li>2. Inflammatory bowel disease</li> <li>3. Contraindication to adjuvant chemotherapy after rectal cancer resection</li> <li>4. Immunocompromised patients</li> <li>5. Participation in another intervention-trial with interference of intervention and outcome of this study</li> </ol>
Sample size	<p>To be assessed for eligibility: n = 400</p> <p>To be allocated to trial: n = 257</p> <p>To be analyzed: n = 214</p>

Interventions	<p><u>Experimental intervention:</u> Early stoma closure (EC) 8-10 days after tumour resection followed by adjuvant chemotherapy.</p> <p><u>Control intervention:</u> Late stoma closure (LC) 4 weeks after completion of adjuvant chemotherapy, 25 weeks after randomisation.</p> <p>In both arms, adjuvant chemotherapy starts within 4 (earliest) to 12 weeks (latest) after randomisation.</p>
Primary endpoint	CoC defined as the percentage of randomised patients which complete all planned cycles of adjuvant chemotherapy (4 cycles for 5-FU or 5 cycles for Capecitabine, or 5 cycles XELOX, or 8 cycles de Gramont schedule, or 8 cycles FOLFOX6).
Secondary endpoint(s)	<ol style="list-style-type: none"> <li>1. QoL (EORTC QLQ-C30, CR 29)</li> <li>2. Stoma-related complications</li> <li>3. Individual CoC rate calculated for each patient</li> <li>4. Percentage of patients stopping adjuvant therapy or undergoing dose modifications or delay</li> <li>5. Disease-free survival (DFS)</li> <li>6. Local and distant recurrence-free survival</li> <li>7. Cumulative days of hospitalisation and number of readmissions</li> <li>8. Rate of symptomatic anastomotic leaks after stoma closure</li> <li>9. Mortality</li> <li>10. Post-operative complications (Clavien-Dindo-classification Grade 3, 4)</li> <li>11. Toxicity of adjuvant chemotherapy (NCI-CTC criteria)</li> </ol>
Statistical analysis	<p><u>General:</u> Confirmatory analysis for primary outcome, descriptive analysis of secondary outcomes</p> <p><u>Description of the primary efficacy test and population:</u> The analysis is based on the intention-to-treat (ITT) population using the ITT principles (dropouts and missing data will be counted as failures). For the analysis of the primary endpoint, the Mantel-Haenszel stratified test will be used. Corresponding 95% confidence interval (CI) will be calculated for the CoC rates in both groups and for the rate difference and odds ratio. There will be stratification by centre.</p> <p><u>Safety:</u> Calculation and descriptive comparison of the rates of adverse events (AEs) and serious adverse events (SAEs) based on all patients receiving at least one protocol-specified procedure.</p> <p><u>Secondary endpoints:</u> Exploratory analysis of QoL, individual CoC rate, percentage of patients stopping adjuvant therapy or undergoing dose modification or delay, DFS, local and distant recurrence-free survival, length of hospitalisation, number of readmissions, number of stoma-related complications and re-operations, rate of symptomatic anastomotic leakages, mortality, toxicity of adjuvant chemotherapy (NCI-CTC criteria)</p>
Trial duration	<p><u>First patient in to last patient out (months):</u> December 2013 – April 2020 (77 months)</p> <p><u>Duration of the entire trial (months):</u> July 2013 – December 2020 (90 months)</p> <p><u>Recruitment period (months):</u> December 2013 – April 2018 (53 months)</p> <p><u>Number of patients:</u> 240 (12.03.2018) (in 40 Sites)</p>
Financing of the trial	German Research Foundation

Registerstudien**AIO-KRK-0413/ass: COLOPREDICT PLUS 2.0 - Register - Retro- und prospektive Erfassung der Rolle von MSI und KRAS für die Prognose beim Kolonkarzinom im Stadium I, II + III****AIO-assoziierte Studie**

Studiennummer/-Code:	AIO-KRK-0413/ass - COLOPREDICT PLUS 2.0
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 – 2022
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Verantwortlicher Studienleiter nach AMG	Prof. Dr. med. Andrea Tannapfel (molekulare Diagnostik/ Gewebebank) Institut für Pathologie der Ruhr-Universität Bochum Zentrale Gewebebank Bürkle-de-la-Camp-Platz 1, 44789 Bochum Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809 E-Mail: Andrea.tannapfel@rub.de
Projektkoordination	Prof. Dr. med. Anke Reinacher-Schick (Leitung klinische Registerdaten) Abteilung für Hämatologie, Onkologie und Palliativmedizin St. Josef-Hospital Bochum Klinikum der Ruhr-Universität Tel.: 0234-509-3591, Fax:-Nr.: 0234-509-3592 E-Mail: onkologie@klinikum-bochum.de
Kontaktadresse/ Kontaktperson:	Institut für Pathologie der Ruhr-Universität Bochum Bürkle-de-la-Camp-Platz 1, 44789 Bochum Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809 Ansprechpartner: Frau Westphal (0234-302-4924, stephanie.westphal@pathologie-bochum.de) Frau Remmel (0234-509-2368, anna.remmel@rub.de)
Studienziele	<u>Primäres Studienziel:</u> Im Rahmen des Colopredict Plus Registers sollen retrospektiv und prospektiv Patienten mit Kolonkarzinomen im Stadium I, II und III erfasst und in Bezug auf ihre Versorgung über 5 Jahre dokumentiert und analysiert werden. Primäres Studienziel ist die Bestimmung der Rolle einer Mikrosatelliteninstabilität (MSI) in Kombination mit einer KRAS-Mutation bei der Prognose von Kolonkarzinomen im Stadium II ohne klinische Risikofaktoren. Hierzu sollen in Tumorgewebeproben der rekrutierten Patienten MSI und KRAS bestimmt werden und parallel klinische und histopathologische Daten der Patienten dokumentiert werden. Primärer Zielparameter ist das Rückfall-freie Überleben nach 5 Jahren (kombinierter Endpunkt aus Rezidiv und Tod jeglicher Ursache).  <u>Sekundäre Studienziele:</u> <ul style="list-style-type: none"> <li>• Rolle von MSI und KRAS auf die Prognose von Patienten mit Kolonkarzinomen im Stadium II mit Risikofaktoren</li> <li>• Prognose von Patienten im Stadium III A, B und C (UICC 7. Auflage) unter Standardchemotherapie</li> </ul> <u>Explorativ:</u> <ul style="list-style-type: none"> <li>• Identifizierung einer molekularen Prognose-Signatur für Patienten im Stadium II, die die aktuelle Behandlungs- und Versorgungsrealität in Deutschland widerspiegelt mit Fokus auf die Darmkrebszentren der DKG. Eingesetzt werden sollen Transkriptom-, miRNA- und Methylierungs-</li> </ul>

	<p>Profilinguntersuchungen</p> <ul style="list-style-type: none"> <li>Identifizierung von Patienten für mögliche Therapiestudien über bestimmte genetische oder andere molekulare Tumoreigenschaften (fakultativ)</li> </ul>
<p>Geplante Patientenzahl</p>	<p>Zur Planung des Umfangs des Registers wird von einer 5-Jahres rezidivfreien Überlebenszeit von 90% mit MSI/KRAS WT im Vergleich zu 75% mit MSS/KRAS MT bei Patienten im Stadium II ohne Risikofaktoren ausgegangen. Dieser Unterschied wird als klinisch minimal relevant bezeichnet, so dass –falls dieser Unterschied tatsächlich vorhanden ist- ein log-rank-Test auf dem zweiseitigen 5% Signifikanzniveau mit einer Sicherheit von 80% statistische Signifikanz liefern soll. Nimmt man zusätzlich exponential-verteilte rezidivfreie Überlebenszeiten und eine jährliche Dropout-Rate von 10% an, so werden ca. 115 Patienten pro Gruppe benötigt.</p> <p>Zur Sicherstellung dieser gruppenspezifischen Fallzahlen muss berücksichtigt werden, dass nur etwa 10% der Stadium-II-Patienten ohne RF Patienten mit MSI/KRAS WT sein werden. Demzufolge müssen ca. 1150 Patienten im Stadium II ohne Risikofaktoren in das Register aufgenommen werden. Nimmt man weiter an, dass etwa 75% der Registerpatienten im Stadium II keine RF haben, müssen etwa 1550 Patienten im Stadium II aufgenommen werden. Wird zusätzlich berücksichtigt, dass ca. 50% der in das Register aufzunehmenden Patienten im Stadium III sein werden, müssen insgesamt etwa 3100 Patienten in das Register aufgenommen werden. Um im Rahmen der Studie detailliertere Subgruppenanalysen zu den molekularen Markern durchführen zu können, wird die Studie auf 8000 Patienten erweitert.</p>
<p>Anzahl eingeschlossene Patienten</p>	<p>2418</p>
<p>Flow-Chart</p>	<p>The flow chart starts with a box labeled 'n=8000 Kolonkarzinom Stadium I, II und III'. It branches into four stages: Stadium I, Stadium II ohne RF, Stadium II mit RF, and Stadium III. Each stage is linked to specific prognostic markers (MSI/MSS, KRAS WT/MT) and then to an adjuvant therapy (Adj. Therapie). For Stadium II ohne RF, a comparison is shown: MSI/KRAS WT (5 Jhr. RFS: 9%) vs. MSS/KRAS MT (5 Jhr. RFS: 23%). A legend at the bottom states: 'Retrospektiv: Primärer Endpunkt: MSI/KRAS WT vs. MSS/KRAS MT' and 'Explorativ: Identifikation einer Prognosesignatur (Versorgungsrealität)'.</p>
<p>Anzahl teilnehmende Zentren</p>	<p>Die Registerstudie soll vor allem, aber nicht ausschließlich innerhalb der Darmkrebszentren der DKG durchgeführt werden. 10 Stadium I/II/III Patienten pro Zentrum pro Jahr, 200 Zentren sollten rekrutiert werden. 4 Jahre Rekrutierungszeit.</p>
<p>Start des prospektiven Registers Amendment 3</p>	<p>September 2013 Mai 2018</p>
<p>Haupt-Einschlusskriterien</p>	<p>Patienten, die sich in den Behandlungskontext des teilnehmenden Zentrums begeben haben und die folgende Kriterien erfüllen:</p> <ul style="list-style-type: none"> <li>männliche und weibliche Patienten mit der Diagnose eines</li> </ul>

	<p>Kolonkarzinoms im Stadium I, II oder III</p> <ul style="list-style-type: none"> <li>• Bereitschaft der mit dem Studienzentrum kooperierenden Pathologie, Gewebeproben gemäß der Protokollanforderungen für die wissenschaftlichen Analysen zur Verfügung zu stellen</li> <li>• Alter <math>\geq</math> 18 Jahre und in Besitz der Fähigkeit, die Anforderungen des Registers und die Aufklärung dazu zu verstehen, zu hinterfragen und zu bemessen</li> <li>• gemäß ICH-GCP unterschriebene Einwilligungserklärung zur Teilnahme an dem Register</li> <li>• unterschriebene Schweigepflichtsentbindung der behandelnden Ärzte für die Zwecke der Studierhebungen</li> </ul>
Haupt-Ausschlusskriterien /	<p>Patienten, die</p> <ul style="list-style-type: none"> <li>• die Einschlusskriterien nicht erfüllen</li> <li>• ihr Einverständnis zur Studienteilnahme zurückziehen</li> </ul>
Therapie	<p>Die mögliche adjuvante Therapie der Patienten ist von dieser Registerstudie unabhängig und wird vom behandelnden Arzt nach Aufklärung des Patienten gemäß der S3-Leitlinie zur Behandlung des kolorektalen Karzinoms festgelegt. Die Entscheidung über eine mögliche adjuvante Therapie wird dokumentiert.</p>
Zielparameter	<p>Primär:</p> <ul style="list-style-type: none"> <li>• 5-Jahres Rückfall-freies Überleben von MSI/KRAS WT Patienten versus MSS/KRAS MT Patienten im Stadium II ohne RF</li> </ul> <p>Sekundär:</p> <ul style="list-style-type: none"> <li>• 5-Jahres Rückfall-freies Überleben von MSI/KRAS WT Patienten versus MSS/KRAS MT Patienten im Stadium II mit RF</li> <li>• OS, DFS im Stadium II</li> <li>• RFS, DFS und OS im Stadium III</li> <li>• Identifizierung einer Prognosesignatur für Patienten im Stadium II ohne RF</li> <li>• Identifizierung von Patienten für mögliche Therapiestudien über bestimmte genetische oder andere molekulare Tumoreigenschaften (fakultativ)</li> </ul> <p>Ausblick: Etablierung einer PEF- Strategie (Partizipative Entscheidungsfindung)</p>
Statistik	<p>Alle im Register dokumentierten Daten zur Beschreibung des Patientenkollektivs in Bezug auf Krankheitscharakteristiken, Demographie sowie Therapie werden mittels statistischer Standardverfahren deskriptiv ausgewertet. Die rückfallfreie Überlebenszeit und das Gesamtüberleben werden mittels Kaplan-Meier Methoden ausgewertet. Schätzungen für die zugehörigen 5-Jahres-Raten und die assoziierten 95% Konfidenzintervalle werden daraus abgeleitet. Zur statistischen Analyse der Primärfragestellung wird ein log-rank Test auf dem 5% Signifikanzniveau durchgeführt. Zusätzlich werden multivariable Cox Proportional Hazards Modelle gerechnet. Für die explorative Beurteilung anderer prognostischer Faktoren/molekularer Marker werden explorative Subgruppenanalysen durchgeführt.</p>

## Arbeitsgruppe Kopf-Hals-Tumoren

### AIO-KHT-0115: A randomized phase II study comparing pembrolizumab with methotrexate in elderly, frail or cisplatin-ineligible patients with head and neck cancers (ELDORANDO)

#### AIO-Studie

Studiennummer/-Code: AIO-KHT-0115 - ELDORANDO

Status: Rekrutierung

Rekrutierungszeitraum: 2018 – 2020

Weitere Zentren: aktuell nicht erforderlich

Letzte Aktualisierung: April 2018

National Coordinating Investigator	Prof. Dr. med. Viktor Grünwald Medical School Hannover (MHH), Dept. of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Carl-Neuberg-Str. 1, 30625 Hannover Tel: +49-511/532-9196 or -4077, Fax: +49-511/532-8077 E-Mail: Gruenwald.viktor@mh-hannover.de
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431; Fax: +49 30 322932926
Study design	The study is designed as an open-label, randomized, prospective, multicenter, phase II study of pembrolizumab or methotrexate in elderly, frail or cisplatin-ineligible patients with squamous carcinoma of the head and neck (HNSCC)
Indication	Squamous carcinoma of the head and neck (SCCHN)
Proposed countries / Total number of sites	Germany Number of sites total: 10
Primary objective	To assess antitumor activity of pembrolizumab in SCCHN.
Secondary objectives	To assess quality of life (QoL), predictive biomarkers, and efficacy of pembrolizumab in SCCHN.
Exploratory objectives	To assess: <ul style="list-style-type: none"> <li>• predictive value of PD-L1 expression</li> <li>• exploration of molecular-genetic pro-inflammatory markers in archival tumor specimen</li> </ul>
Planned sample size	A total of 100 patients will be randomized, 50 per treatment arm, Recruiting.
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Cooperation and willingness to complete all aspects of the study including participation in the translational research</li> <li>2. Signed and dated written informed consent must be given prior to study inclusion</li> <li>3. Histological or cytological confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC) not amenable to local therapies</li> <li>4. Progressive disease at study entry</li> <li>5. At least 1 measurable lesion according to RECIST 1.1</li> <li>6. No previous systemic treatment for metastatic disease</li> <li>7. Not eligible for cisplatin-based chemotherapy, defined as: <ul style="list-style-type: none"> <li>- ECOG 2 and/or</li> <li>- calculated CrCl &lt;60 mL/min (measured by MDRD)</li> </ul> </li> <li>8. Age ≥18 years</li> <li>9. ECOG performance status 0 - 2</li> <li>10. Brain metastases require completion of local therapy with discontinuation of steroids prior to start of treatment</li> <li>11. If of childbearing potential, willingness to use effective contraceptive</li> </ol>

	<p>method (double barrier method) for the duration of the study and 2 months after last dose</p> <p>12. Adequate bone marrow function, liver and renal function:</p> <ol style="list-style-type: none"> <li>Absolute neutrophil count <math>\geq 1.5 \times 10^9/L</math></li> <li>Thrombocytes <math>\geq 100 \times 10^9/L</math></li> <li>Hemoglobin <math>\geq 9 \text{ g/dL}</math></li> <li>INR <math>\leq 1.5</math> and PPT <math>\leq 1.5 \times</math> upper limit during the last 7 days before therapy</li> <li>Bilirubin <math>&lt; 1.5 \times</math> lower limit and</li> <li>AST (GOT) and ALT (GPT) <math>&lt; 3 \times</math> lower limit (5 x lower limit in case of liver metastases)</li> </ol> <p>13. Tumor block must be available at study inclusion for central pathology testing</p>
Exclusion criteria	<ol style="list-style-type: none"> <li>Live expectancy less than 3 months</li> <li>Nasopharynx carcinoma</li> <li>Anticancer treatment during the last 30 days prior to start of treatment, including systemic therapy, radiotherapy or major surgery</li> <li>Participation in a clinical trial within the last 30 days prior to study treatment</li> <li>History of allogeneic tissue/solid organ transplant</li> <li>History of pneumonitis that has required oral or i.v. steroids</li> <li>Evidence of interstitial lung disease</li> <li>Minor surgery <math>\leq 24</math> hours prior first dose of study treatment</li> <li>Symptomatic acute cardiovascular or cerebrovascular disease</li> <li>Known active HBV, HCV or HIV infection</li> <li>Has any other active infection requiring systemic therapy.</li> <li>Patients with active tuberculosis</li> <li>Prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)</li> <li>A diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.</li> <li>Patient has had a prior monoclonal antibody, which does significantly interfere with the immune system or which does have a systemic therapeutic effect on the tumor within 4 weeks prior to randomization</li> <li>Patient has not recovered (i.e., <math>\leq</math> Grade 1 or at baseline) from adverse events any toxicities due to agents administered more than 4 weeks earlier. [Subjects with <math>\leq</math> Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.]</li> <li>Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study</li> <li>Has received a live vaccine within 30 days prior to the first dose of trial treatment.</li> <li>Has known hypersensitivity to methotrexate or pembrolizumab or any of constituent of the products.</li> <li>Other active malignancy requiring treatment</li> <li>Lactating or pregnant women, women of child-bearing potential who do not agree to the usage of highly effective contraception methods (allowed methods of contraception, meaning methods with a rate of failure of less than 1% per year are implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner). Women of childbearing potential must have a negative pregnancy test (serum <math>\beta</math>-hCG) at Screening.</li> <li>Any psychiatric illness that would affect the patient's ability to understand</li> </ol>

	<p>the demands of the clinical trial</p> <p>23. Patient has already been recruited in this trial (does not include screening failures)</p> <p>24. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>25. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p>
Randomization criteria	<p>Randomization will be performed 1:1</p> <p>Strata:</p> <ul style="list-style-type: none"> <li>• ECOG performance status (PS 0-1 vs. 2)</li> <li>• HN-CCI index (&lt;2 vs. ≥2)</li> </ul>
Investigational drug	Pembrolizumab at fixed dose
Treatment phase	<p>Arm A: Pembrolizumab 200 mg q3w i.v. until disease progression or non-tolerable toxicity (maximum 2 years)</p> <p>Arm B: Methotrexate (MTX) 40 mg/m<sup>2</sup> weekly i.v. until disease progression or non-tolerable toxicity (maximum 2 years)</p>
Study rationale	<p>Standard of care (SOC) for palliative chemotherapy for SCCHN consists of a platinum-combination, mostly combined with cetuximab. However, platinum-therapy may not apply to a number of patients because of age (approx. 30% &gt;70y.) or comorbidities (36%) [Bøje et al. Radiother Oncol. 2014 Jan;110(1):91-7]. This fraction of patients is underrepresented in clinical trials. It remains a challenge to define the optimal palliative treatment benefit/risk ratio in the clinic and prospective data is scarce in order to guide the choice of the clinician. Hence, no SOC is defined and treatment recommendations for this cohort of patients vary among treating physicians (Mountzios et al. Head Neck Oncol. 2013 Feb 27;5(3):27).</p> <p>Comorbidities have been shown to be associated with a poor OS in SCCHN (Sanabria et al. Ann Surg Oncol. 2007 Apr;14(4):1449-57). The EORTC QLQ-H&amp;N35 questionnaire has been shown to be prognostic in localized disease (Osthus et al. Oral Oncol 47(10): 974-979, 2011). The ELAN-UNFIT trial tests the role of cetuximab or methotrexate in elderly patients (&gt;70 years) (NCT01884623) using a composite endpoint TTFS for efficacy and tolerability (Guigay J; ASCO 2014). However, age per se does not seem to affect treatment outcome, underscoring the relevance to differentiate fit and frail patients rather than an age limit for treatment selection (Mountzios et al. Head Neck Oncol. 2013 Feb 27;5(3):27).</p> <p>The Charlson Comorbidity Index (CCI) detected poor tumor specific survival in SCCHN with increasing comorbidities (Singh et al. Laryngoscope. 1997 Nov;107(11 Pt 1):1469-75). Based on these results an adapted version has been created for localized SCCHN - the HN-CCI, which includes 6 prognostic items: congestive heart failure, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, liver disease, and diabetes (Bøje et al. Radiother Oncol. 2014). This data underscores the relevance of non-cancer associated mortality in SCCHN patients. A more recent publication identified age, comorbidity, tumor recurrence, and secondary primaries to be prognostically relevant (Kwon et al. Ann Oncol 2014), emphasizing comorbidity as a key prognostic element. Clearly, novel therapeutic strategies are needed in order to deliver optimal palliation in patients who are not fit for platinum treatment.</p> <p>In bladder cancer, The EORTC 30986 study established an adapted regimen as a new standard in patients with WHO PS of 2 and/or impaired renal function (GFR &gt;30 but &lt;60 mL/min) (De Santis JCO 2012), which may serve as a backbone for the definition of cisplatin-ineligible patients.</p> <p>Criteria for cisplatin-ineligibility:</p> <ul style="list-style-type: none"> <li>• ECOG 2 and/or</li> <li>• CrCl &lt;60 mL/min</li> </ul> <p>The modulation of the immune system has been identified as a promising</p>



	<p>treatment approach in cancer patients. SCCHN has been shown to respond to checkpoint inhibitors in early clinical trials and have triggered a number of phase III studies, which explore PD-1 or PD-L1 inhibitors in patients with failure after platinum-based therapy. Pembrolizumab showed an ORR of 19.6%, irrespective of HPV status in PD-L1 positive SCCHN (Seiwert et al. ASCO 2014). Overall, tolerability remained good in this study, with an AE incidence of 58% (all grades), and 17% grade 3/4 AEs.</p> <p>We test the hypothesis that pembrolizumab is superior to methotrexate treatment in patients unfit to receive cisplatin-based chemotherapy.</p>
Rationale for sample size and tests to be used	In order for a chi-squared test to detect a difference of 25% vs. 50% (Methotrexate vs. Pembrolizumab) in the 1-year overall survival between the two treatment arms with 80% power and a one-sided significance level $\alpha=5\%$ , 46 evaluable patients per arm are needed. Hence, a total of 100 patients will be enrolled (incl. 9% uninformative drop-outs).
Interim analyses	No interim analyses planned.
Statistical analysis	<p><b>Primary endpoint and hypothesis:</b> 1-year overall survival rate We test the hypothesis that with regard to 1-year-OS, pembrolizumab is superior to methotrexate treatment in patients unfit to receive cisplatin-based chemotherapy (50% Arm 1 (Pembrolizumab) vs. 25% Arm 2 (MTX)).</p> <p><b>Key secondary:</b></p> <ul style="list-style-type: none"> <li>• Time to failure of strategy (TTFS) at 1 year, defined as death, progressive disease (PD), treatment discontinuation (due to toxicity) or deterioration of Instrumental Activities of Daily Living (IADL score) by 2 points</li> <li>• objective response rate (ORR) according to modified RECIST 1.1</li> </ul> <p><b>other secondary:</b></p> <ul style="list-style-type: none"> <li>• progression free survival (PFS)</li> <li>• median overall survival (OS)</li> <li>• ORR according to RECIST 1..1</li> <li>• duration of response</li> <li>• duration of treatment beyond progression</li> <li>• treatment discontinuation rate</li> <li>• safety and tolerability</li> </ul> <p>Exploratory:</p> <ul style="list-style-type: none"> <li>• predictive value of PD-L1 expression</li> <li>• prognostic value of tumor shrinkage</li> <li>• QoL response, defined as improvement of 5-10 points in QLQC30 and HN35</li> </ul>
Study plan	<p>Study start (FPI): Q1/2018  Recruitment end (LPI): Q4/2020  Reaching the primary endpoint: Q4/2021  Planned analysis of primary endpoint: Q1/2022  Publication date: Q4/2021  End of maximum treatment period for last patient [24 months]: Q4/2022  Follow up period for the last patient: 12 months  Study end (LPLV): Q4/2023  Data base lock: Q4/2024-Q1/2025  Completion of Clinical Study Report (CSR): Q3/2023  Publication date: Q2/2024</p>

**AIO-KHT-0117: A randomized phase II study on the OPTimization of IMMunotherapy in squamous carcinoma of the head and neck (OPTIM)**

Studiennummer/-Code	AIO-KHT-0117 - OPTIM
Status	in der Einreichungsphase
Rekrutierungszeitraum	2017 - 2019
Weitere Zentren	sind sehr erwünscht
Letzte Aktualisierung	April 2018

National Investigator	Coordinating Investigator	Professor Dr. med. Viktor Grünwald Medical School Hannover (MHH) Dept. of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation (OE6860) Carl-Neuberg-Str. 1 30625 Hannover, Germany Tel: +49-511/532-9196 or -4077 Fax: +49-511/532-8077 E-Mail: Gruenwald.viktor@mh-hannover.de
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Study design		Open label, randomized, multicenter phase II trial
Anticipated start date		Q4/2017
Duration of study		Enrollment: 24 month total study duration 34 month (incl. follow-up)
Indication		Second-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN)
Target population		Patients with R/M SCCHN progressing after prior platinum-based therapy (radiochemo-therapy or systemic chemotherapy)
Total number of sites		24
Primary objective		To test whether dual checkpoint blockade is superior to docetaxel chemotherapy as early salvage therapy in R/M-SCCHN.
Secondary objectives		Secondary objectives of this study are: <ul style="list-style-type: none"> <li>to assess efficacy, feasibility and safety of an intensified immunotherapy regimen.</li> </ul>
Planned sample size		N=280 enrolled to receive nivolumab mono-therapy N=154 randomized
Inclusion criteria		<ol style="list-style-type: none"> <li>Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>Age <math>\geq</math> 18 years at time of study entry</li> <li>Histological or cytological confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC) or nasal sinus not amenable to local therapies</li> <li>Availability of tumor tissue from biopsy for determination of PD-L1 and HPV status according to the following priority ranking: i) recent biopsy (<math>\leq</math>3 month old) without intervening therapy; ii) any recent biopsy (<math>\leq</math>3 month old); iii) any archival tumor tissue (<math>&gt;</math> 3 month old) [Biopsy should be excisional, incisional or core biopsy. Fine needle aspiration is not allowed.]</li> <li>Progression or recurrence during or after cetuximab+platinum-based 1<sup>st</sup> line palliative chemotherapy for relapsed or metastatic disease OR progression within 6 months after completion of definitive platinum-containing radiochemotherapy for locally advanced disease</li> </ol>

	<ol style="list-style-type: none"> <li>6. At least 1 measurable lesion according to RECIST 1.1</li> <li>7. ECOG performance status 0-1</li> <li>8. Completion of local therapy for brain metastases with discontinuation of steroids prior to start of study treatment</li> <li>9. Adequate blood count, liver-enzymes, and renal function: <ul style="list-style-type: none"> <li>• neutrophil count <math>&gt; 1.5 \times 10^6/\text{mL}</math></li> <li>• Platelet count <math>\geq 100 \times 10^9/\text{L}</math> (<math>&gt;100,000</math> per <math>\text{mm}^3</math>)</li> <li>• hemoglobin <math>\geq 9</math> g/dL</li> <li>• INR <math>\leq 1.5</math> and PPT <math>\leq 1.5 \times</math> lower limit during the last 7 days before therapy</li> <li>• AST (SGOT)/ALT (SGPT) <math>&lt; 3 \times</math> institutional upper limit of normal (5 x lower limit in case of liver metastases)</li> <li>• bilirubin <math>&lt; 1.5 \times</math> ULN</li> <li>• Serum Creatinine <math>\leq 1.5 \times</math> institutional ULN or creatinine clearance (CrCl) <math>\geq 40</math> mL/min (if using the Cockcroft-Gault formula below):  Female CrCl = <math>\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}</math>  Male CrCl = <math>\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}</math></li> </ul> </li> <li>10. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.</li> <li>11. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. [WOCBP should use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of nivolumab.]</li> <li>12. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational products (nivolumab, ipilimumab or docetaxel). Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception).</li> <li>13. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.</li> </ol> <p><b>Inclusion criteria for randomization</b></p> <ol style="list-style-type: none"> <li>1. progressive disease according to RECIST 1.1</li> <li>2. successful biopsy of tumor tissue at time of disease progression (if feasible, biopsy from the progressive lesion is preferred)</li> <li>3. known PD-L1 expression of most recent tumor tissue (primary, recurrence or metastasis)</li> <li>4. known HPV-status in oropharyngeal disease</li> <li>5. ECOG: 0-1</li> <li>6. adequate organ function, defined as: <ul style="list-style-type: none"> <li>• neutrophil count <math>&gt; 1.5 \times 10^6/\text{mL}</math></li> <li>• Platelet count <math>\geq 100 \times 10^9/\text{L}</math> (<math>&gt;100,000</math> per <math>\text{mm}^3</math>)</li> <li>• hemoglobin <math>\geq 9</math> g/dL</li> <li>• INR <math>\leq 1.5</math> and PPT <math>\leq 1.5 \times</math> lower limit during the last 7 days before therapy</li> <li>• AST (SGOT)/ALT (SGPT) <math>&lt; 3 \times</math> institutional upper limit of normal (5 x lower limit in case of liver metastases)</li> <li>• bilirubin <math>&lt; 1.5 \times</math> ULN</li> <li>• Serum Creatinine <math>\leq 1.5 \times</math> institutional ULN or creatinine clearance (CrCl) <math>\geq 40</math> mL/min</li> </ul> </li> <li>7. Immune related adverse events to prior nivolumab therapy have to resolve to grade <math>\leq 1</math> and may not require active treatment (prednisolone doses <math>\leq 10\text{mg}</math> or equivalent doses of steroids are allowed)</li> </ol>
<p>Global Exclusion criteria.</p> <p>Assessments at screening and re-assessment before randomization</p>	<p><b>Medical criteria:</b></p> <ol style="list-style-type: none"> <li>10. Nasopharynx carcinoma or carcinoma of salivary glands</li> <li>11. Live expectancy less than 3 months</li> <li>12. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to:</li> </ol>

- a) Minor surgery  $\leq$  24 hours prior first dose of nivolumab monotherapy
- b) Anticancer treatment during the last 30 days prior to start of nivolumab-monotherapy treatment, including systemic therapy, or major surgery [palliative radiotherapy has to be completed at least 2 weeks prior to start of study treatment]
- c) known active HBV, HCV or HIV infection
- d) active tuberculosis
- e) any other active infection requiring systemic therapy
- f) history of allogeneic tissue/solid organ transplant
- g) diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of nivolumab-monotherapy or randomization.
- h) Has an active autoimmune disease requiring systemic treatment within the past 3 months before enrollment or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo, hypothyroidism, diabetes mellitus type I or resolved childhood asthma/atopy are an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study. Psoriasis not requiring treatment is not excluded from the study.
- i) live vaccine within 30 days prior to the first dose of nivolumab-monotherapy treatment or during study treatment.
- j) Other active malignancy requiring treatment
- k) Clinically significant or symptomatic cardiovascular/cerebrovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment
- l) History or clinical evidence of CNS metastases  
 Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:
  - I. are asymptomatic and
  - II. have no requirement for steroids 6 weeks prior to start of nivolumab-monotherapy treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases

**Drug related criteria:**

- 13. Medication that is known to interfere with any of the agents applied in the trial.
- 14. Has known hypersensitivity to nivolumab or ipilimumab or docetaxel or any of the constituents of the products.
- 15. Any other efficacious cancer treatment except protocol specified treatment at study start.

**Safety criteria:**

- 16. Patient has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. [Subjects with  $\leq$  Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.]
- 17. Female subjects who are pregnant, breast-feeding or male/female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner]. Women of childbearing potential must have a negative pregnancy test (serum  $\beta$ -HCG) at screening.

**Methodological criteria:**

- 18. Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-Programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically

	<p>targeting T-cell co-stimulation or checkpoint pathways)</p> <p>19. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lives of previously used trial medication, whichever is longer</p> <p>20. Previous treatment in the present study (does not include screening failure). [Criterion is not applicable during re-assessment of eligibility for randomization]</p> <p><b>Regulatory and ethical criteria:</b></p> <p>21. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>22. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p>
Investigational agents	<ul style="list-style-type: none"> <li>• nivolumab</li> <li>• ipilimumab</li> <li>• docetaxel</li> </ul>
Treatment schedule	<p>Subjects enrolled in this trial will initiate palliative systemic treatment with nivolumab monotherapy (3 mg/kg Q2W). Tumor response will be assessed after 4, 8, 12, 18 and 24 weeks to capture early progressors. Patients with (radiologic) tumor progression during the first 6 months of NIVO mono will be randomized (1:1) to receive either docetaxel (75 mg/m<sup>2</sup> Q3W) or nivolumab+ipilimumab combination (NIVO 3mg/kg Q2W + IPI 1mg/kg Q6W) until PD or death.</p> <p>Randomization will be performed centrally.</p> <p>The stratification parameters are:</p> <ul style="list-style-type: none"> <li>• PD-L1 expression: <ul style="list-style-type: none"> <li>&lt; 1% vs ≥ 1%</li> </ul> </li> <li>• time point of PD during nivolumab monotherapy: <ul style="list-style-type: none"> <li>≤2 months vs &gt; 2 months</li> </ul> </li> <li>• HPV status (p16 IHC; mandatory for subjects with oropharynx carcinoma): <ul style="list-style-type: none"> <li>positive vs negative</li> </ul> </li> </ul> <p>Patients without PD within 6 months NIVO monotherapy continue treatment under study surveillance for a maximum of 12 months measured from first dose of NIVO or until documented disease progression. If disease progression occurs within the 12 months of study treatment a re-biopsy of the tumor will be conducted.</p> <p>Tumor assessment: Nivolumab monotherapy cohort:</p> <ul style="list-style-type: none"> <li>• from 1st dose of NIVO monotherapy until 12 weeks of treatment: Q4W</li> <li>• from weeks 13 until 6 months of NIVO monotherapy: Q6W</li> <li>• from 7<sup>th</sup> month until PD or end of study treatment: Q12W</li> </ul> <p>Randomized cohorts:</p> <ul style="list-style-type: none"> <li>• Q8W for the first 6 months and Q12W thereafter.</li> </ul> <p>Treatment will continue until</p> <ol style="list-style-type: none"> <li>a) progressive disease or death or a maximum of 12 months measured from randomization</li> <li>b) intolerable toxicity</li> <li>c) withdrawal of consent.</li> </ol> <p>Study subjects on NIVO monotherapy who do not progress during the first 6 months of treatment continue NIVO monotherapy for an additional 6 months under study surveillance. Thereafter, NIVO mono subjects continue treatment at the discretion of the treating physician and enter survival follow-up</p>
Primary endpoint	<ul style="list-style-type: none"> <li>• objective response rate in all randomized patients</li> </ul>
Secondary endpoints	<ul style="list-style-type: none"> <li>• OS (measured from begin of nivolumab-monotherapy therapy and from randomization; including sub-group analysis for HPV status; PD-L1 expression and tumor localization (i.e. oropharynx carcinoma))</li> <li>• PFS (measured from begin of nivolumab- monotherapy therapy and from</li> </ul>

	<p>randomization; including sub-group analysis for HPV status; PD-L1 expression and tumor localization (i.e. oropharynx carcinoma))</p> <ul style="list-style-type: none"> <li>• BOR, DOR</li> <li>• QoL (EORTC QLQC30; HN35; EQ-5D)</li> <li>• AEs/SAEs</li> </ul>
Translational research: Exploratory objectives and endpoints	<p>Tumor tissue analysis: All listed analysis are to be performed on pre-treatment tumor samples and in tissue material from re-biopsies taken at disease progression under - nivolumab monotherapy OR after 6 months of nivolumab monotherapy:</p> <ul style="list-style-type: none"> <li>• PD-L1</li> <li>• IFN – gamma signature (nano-string technology)</li> <li>• mutational load of the tumor</li> <li>• genetic alterations in the JAK signal transduction pathway</li> </ul>
Rationale Hypothesis	<p>Squamous cell carcinoma of the head and neck (SCCHN) is one of the most common cancers world-wide, accounting for more than 500,000 incident cases (Parkin et al. 2002: CA Cancer J Clin 2005; 55: 74–108). During recent years a substantial increase of the incidence of SCCHN has been detected in young adults, which is due to the wide spread of HPV16-infection among this patient population (Marur et al. Lancet Oncol 2010: 11(8), 781-789). For locally advanced SCCHN surgery and adjuvant radiotherapy, with or without chemotherapy or anti-EGFR antibody, remain the mainstay of therapy. Overall survival (OS) may achieve 20-42% after 5-year in these patients (Callais et al. Bull Cancer 2000; 87: 48–53). However, most patients will relapse and require subsequent palliative chemotherapy. Platin combined with fluorouracil and cetuximab is the GOLD standard in 1<sup>st</sup> line palliative systemic therapy which achieves a median OS of 10.1 months (Vermorken et al. 2008: NEJM 359(11), 1116-1127). Patients face tumor progression and subsequent therapies may be offered with limited clinical activity (Stewart et al. 2009: JCO, 27(11), 1864-1871). A contemporary phase III study comparing afatinib and methotrexate (MTX) confirmed the poor outcome in these patients (OS 6.8 vs. 6.0 mo.; P=0.70) (Machiels et al. (2015). Lancet Oncology, 16(5), 583–594). Recently, checkpoint inhibitors have demonstrated efficacy in R/M-SCCHN. Pembrolizumab has shown a high response rate of confirmed responses in 18% of patients and was associated with an median OS of 13 mo. (Chow et al. JCO 2016; Seiwert et al. Lancet Oncol. 2016). More recently, nivolumab reported a positive phase III study in R/M-SCCHN after platinum failure, which was superior in ORR and median OS in comparison to Investigator's Choice (IC) single-agent treatment (e.g. MTX, docetaxel or Cetuximab). This is the first study that achieved better clinical outcome, when compared to MTX and other single-agent treatments in previously treated patients in R/M-SCCHN. However, non-responder progress early on both IC and nivolumab, rendering a steep drop during the early slope of the progression free survival (PFS) curve. A pattern that is similar for pembrolizumab. Hence, early switch to an alternative therapy may improve outcome for these patients, possibly by introduction of chemotherapy or by intensification of immunotherapy. Based on the mechanism of action and the distinct outcome of patients with HPV-associated SCCHN, an enrichment strategy will be included in order to provide sufficient patients for subgroups analysis in these cohorts.</p> <p><b>Research hypothesis:</b> We hypothesize that patients with early failure of single agent nivolumab benefit from escalated immunotherapy given as a combination of nivolumab and ipilimumab when compared to docetaxel chemotherapy.</p>
Safety data	<ul style="list-style-type: none"> <li>• AEs, SAEs and treatment emergent adverse events according to CTC 4.03</li> <li>• Frequency of clinically significant abnormal laboratory parameters</li> </ul>
Sample size estimation and Statistical analysis considerations	<p>N=280 patients enrolled to receive NIVO monotherapy N=154 patients randomized after rapidly progressing disease.</p> <p>Sample size calculation is based on the assumptions:</p> <ul style="list-style-type: none"> <li>• that NIVO/IPI improves ORR to 25% in the randomized population compared to 10% with docetaxel treatment;</li> </ul>

	<ul style="list-style-type: none"> <li>• that approximately 85% of patients entering the study on a nivolumab monotherapy will develop a radiologic progression during the first 6 months of immunotherapy (becoming eligible for intensified treatment with NIVO/IPI combination)</li> <li>• approx. 30-35% drop-out before the possibility of randomization due to toxicity, withdrawal of consent or loss-to-follow-up</li> </ul> <p>Calculation for the randomized part:  Group sample sizes of 77 in each group achieve 80.3% power to detect a difference between the group proportions of 15%. The proportion in group A (the experimental treatment group NIVO/IPI) is assumed to be 10% under the null hypothesis and 25% under the alternative hypothesis. The proportion in group B (active comparator) is 10%. The test statistic used is the one-sided Z-Test with unpooled variance. The one-sided significance level of the test is 0.05. Thus the total sample size of the randomized part is N=154.  Total sample size of the trial is <math>N = 154 / 0.85 / 0.65 = 280</math></p> <p>Analysis strategies:  The primary objective will be measured by the primary endpoint of ORR (based on investigator assessments) among all randomized subjects.  It is defined as the number of subjects with a best overall response of CR or PR divided by the number of all randomized subjects per arm.  Best overall response is defined as the best response designation, as determined by investigator, recorded between the date of randomization and the date of progressive disease per RECIST v1.1 or the date of death or subsequent therapy, whichever occurs first. Patients who stop therapy for other reasons than progression should receive scheduled disease assessment as determined within the protocol and followed until documented disease progression occurs.</p>												
Study plan / time lines	<table style="width: 100%; border: none;"> <tr> <td style="width: 60%;">First Patient In (FPI):</td> <td>Q1/2018</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 24 month</td> </tr> <tr> <td>Last Patient Last treatment (LPLT):</td> <td>after max. 42 month</td> </tr> <tr> <td>End of follow-up period after LPI:</td> <td>after approx. 48 month</td> </tr> <tr> <td>Study report:</td> <td>after approx. 57 month</td> </tr> <tr> <td>Publication:</td> <td>after approx. 60 month</td> </tr> </table>	First Patient In (FPI):	Q1/2018	Last Patient In (LPI):	after approx. 24 month	Last Patient Last treatment (LPLT):	after max. 42 month	End of follow-up period after LPI:	after approx. 48 month	Study report:	after approx. 57 month	Publication:	after approx. 60 month
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Study report:	after approx. 57 month												
Publication:	after approx. 60 month												

## Arbeitsgruppe Lebensqualität und PRO – Patient Reported Outcomes

### Lebensqualität, metastasiertes kolorektales Karzinom (mCRC)

**AIO-LQ-0114/ass: Intravenöse Eisencarboxymaltose versus orale Eisensubstitution bei Patienten mit metastasiertem kolorektalem Karzinom (CRC) und Eisenmangelanämie: eine randomisierte, multizentrische Therapieoptimierungsstudie (FerInject)**

#### AIO-assozierte Studie

Studiennummer/-Code: AIO-LQ-0114/ass - FerInject  
 Status: in Rekrutierung  
 Rekrutierungszeitraum: 2015 – 2018  
 Weitere Zentren: sind sehr erwünscht  
 Letzte Aktualisierung: Oktober 2017

Art der Studie	Randomisierte, explorative Phase-II-Studie
Leiter der klinischen Prüfung	Institut für Klinisch-Onkologische Forschung (IKF) Ärztl. Direktor: Prof. Dr. Salah-Eddin Al-Batran Krankenhaus Nordwest GmbH UCT - Universitäres Centrum für Tumorerkrankungen Frankfurt Steinbacher Hohl 2-26 60488 Frankfurt E-Mail: albatran@aio-portal.de
Zentrale Studienkoordination	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Dr. Caroline Schönherr Steinbacher Hohl 2-26 60488 Frankfurt Tel: 069 7601 4094, FAX: 069 7601 3655 E-Mail: schoenherr.caroline@ikf-khnw.de www.ikf-nordwest.de
Ziele der Studie	<p>Primär</p> <p>Anstieg des Serum Hämoglobins um 2g/dl oder Normalisierung (12g/dl) des Serum Hämoglobins</p> <p>Sekundärparameter</p> <ul style="list-style-type: none"> <li>• Fatigue erhoben mittels EORTC-QLQ-FA13</li> <li>• Erfassung der Lebensqualität mittels des EORTC-C30 Fragebogens</li> <li>• Handkraftmessung mittels Hydraulic Hand Dynamometer</li> <li>• Anzahl der allogenen Bluttransfusionen insgesamt und Anzahl der Transfusionen pro Patient</li> <li>• Zeit bis zum Anstieg oder Normalisierung des Hämoglobins</li> <li>• Untersuchungen zur Genese der beobachteten Anämie (Eisenmangelanämie bei chronischen Erkrankungen vs. Absoluter Eisenmangel in Abgrenzung zur Anämie bei chronischen Erkrankungen)</li> <li>• Anzahl, Dosis und Dauer der Therapien mit rekombinantem Erythropoetin (r-HuEPO)</li> <li>• Begleitende korrelative Forschung: Erfassung relevanter Parameter (Hepcidin, CRP) der Inflammation und des Eisenstoffwechsels vor Therapie und Untersuchung auf deren Zusammenhang mit den o.g. Endpunkten unter Substitution (ggf. Definition von prädiktiven Markern).</li> <li>• Einfluss des Ernährungsstatus auf die Eisenmangelanämie und den Therapieerfolg</li> <li>• Verträglichkeit und Toxizität</li> <li>• Abbruchrate aufgrund von Toxizität oder Patientenwunsch</li> <li>• Gesamtüberleben (OS, gemessen ab Datum des Studieneinschlusses)</li> </ul>
Studiendesign	Patienten mit metastasiertem CRC unter palliativer Chemotherapie und diagnostizierter Eisenmangelanämie - nach Protokollvorgaben - werden nach



	<p>Randomisation in einem der folgenden Arme behandelt:</p> <p>Arm A: Parenterale Eisensubstitution mit Eisencarboxymaltose (Ferinject)  Der Patient erhält 500 mg bis 1000 mg Eisen in Form von Eisencarboxymaltose (Ferinject) intravenös pro Woche bis zu einer Gesamtdosis gemäß Tab.1. Die Gesamtdosis wird innerhalb von maximal 2 Wochen appliziert.  Tab.1: Dosierungsschema für die parenterale Eisensubstitution mit Eisencarboxymaltose (Ferinject)</p> <table border="1" data-bbox="513 450 1485 546"> <thead> <tr> <th>Hb (g/dl)</th> <th>Körpergewicht 35 -69 kg</th> <th>Körpergewicht <math>\geq</math>70 kg</th> </tr> </thead> <tbody> <tr> <td>&lt;10</td> <td>1500 mg</td> <td>2000 mg</td> </tr> <tr> <td><math>\geq</math>10</td> <td>1000 mg</td> <td>1500 mg</td> </tr> </tbody> </table> <p>Arm B: Per orale Eisensubstitution mit Eisen(II)-glycin-sulfat-Komplex (Ferro sanol Duodenal Kapseln)  Der Patient nimmt täglich 200 mg Eisen per oral verteilt auf zwei Dosen. Da durch die begrenzte Eisenresorption aus dem Magen-Darmtrakt bei oraler Eisengabe mit einem verzögerten Ansprechen zu rechnen ist, erfolgt die orale Eisensubstitution über die gesamte Studiendauer von 12 Wochen.  Zusätzlich erfolgt in beiden Gruppen - Arm A und Arm B - eine orale Folsäure- und Vitamin B12-Substitution. Die Folsäure-Substitution beträgt 400 <math>\mu</math>g pro Tag und die Vitamin B12-Substitution beträgt 10 <math>\mu</math>g pro Tag. Beide Vitamine werden in vorgeschriebener Dosis einmal täglich über den gesamten Studienzeitraum eingenommen.  Die Diagnostik der Eisenmangelanämie erfolgt über das Serum Hämoglobin (<math>\leq</math> 10.5 g/dl), über das Serum Ferritin und die Transferrin-Sättigung (TfS). In der Diagnostik wird zwischen einem absoluten Eisendefizit und einem Defizit an funktionell verfügbarem Eisen, welches häufig für die Anämie bei Patienten mit Tumoren verantwortlich ist, unterschieden. Ein absolutes Eisendefizit liegt vor bei einer Transferrin-Sättigung &lt; 20 % und einem Serum Ferritin &lt; 30 ng/ml. Ein Defizit an funktionell verfügbarem Eisen liegt vor bei einer Transferrin-Sättigung &lt; 20 % und einem Serum Ferritin &gt; 30 bis maximal 800 ng/ml.  Das Monitoring der Laborparameter (Eisen, Transferrin, Ferritin, Transferrinsättigung, Differentialblutbild (numerisches Blutbild, inkl. hypochromer Erythrozyten), Retikulozyten Hb-Wert, MCV, MCH, sTfR (löslicher Transferrin-Rezeptor), CRP, Hcpidin) erfolgt 4-wöchentlich über das Zentrallabor. Steigt die Transferrin-Sättigung &gt; 50 % wird die Eisensubstitution beendet. Die geplante Eisensubstitution wird wieder aufgenommen, sollte die Transferrin-Sättigung nach Absetzen der Eisensubstitution wieder unter 20 % sinken, sofern sich der Patient noch in der aktiven Studienphase befindet (3 Monate).  Zusätzlich wird der Einfluss der Tumorerkrankung auf den Eisenstoffwechsel erfasst. Hierzu wird Hcpidin, welches bei Tumorerkrankung oft erhöht vorliegt und direkten Einfluss auf den Eisenstoffwechsel hat, zu Beginn und am Ende der Studie erhoben. Die Fragenbögen zu Lebensqualität, Fatigue-Symptomatik und Ernährungszustand (NRS [Nutritional Risk Screening]), werden im 4-wöchentlichen Rhythmus erhoben. Die Messung der Muskelkraft mittels Handkraftmessung wird zusätzlich in zwei Zentren als funktioneller Parameter bestimmt. Das Serum Phosphat und die Thrombozyten werden zur Erfassung der Prävalenz und Bedeutung der Hypophosphatämie bzw. Reduktion der Thrombozytenzahl unter Eisensubstitution bei Tumorpatienten regelhaft mitbestimmt.</p>	Hb (g/dl)	Körpergewicht 35 -69 kg	Körpergewicht $\geq$ 70 kg	<10	1500 mg	2000 mg	$\geq$ 10	1000 mg	1500 mg
Hb (g/dl)	Körpergewicht 35 -69 kg	Körpergewicht $\geq$ 70 kg								
<10	1500 mg	2000 mg								
$\geq$ 10	1000 mg	1500 mg								
Rationale	<p>Der Eisenmangel hat bei Patienten mit Kolonkarzinom mit etwa 60 % eine hohe Prävalenz. Ein Großteil (70 %) der Patienten mit Eisenmangel weist auch eine Anämie auf. Eine Anämie ist mit einer eingeschränkten physischen und kognitiven Leistungsfähigkeit verbunden und vermindert somit die Lebensqualität der Patienten. Die Ursachen für die Anämie sind sehr unterschiedlich. Blutverluste, durch Therapie und Krankheit verminderte Erythropoese, Eisenmangel und krankheitsbedingt verminderte Eisensfreisetzung können für die Entstehung einer Anämie verantwortlich sein. Die Behandlung der Anämie erfolgt - je nach Ursache und Ausprägung - mit Eisensubstitution, rekombinantem Erythropoetin (r-HuEPO) und allogener Bluttransfusion. Der Einsatz von r-HuEPO und Bluttransfusionen hat aufgrund ihrer Nebenwirkungen Einfluss auf Morbidität und Mortalität und ist möglichst gering zu halten. Daten</p>									

	<p>zeigen, dass eine Eisensubstitution den Abfall des Serum Hämoglobins verhindern kann und somit den Einsatz von r-HuEPO und Bluttransfusion reduziert.</p> <p>In der klinischen Praxis erfolgt die Eisensubstitution bisher meist per oral. Durch eine geringe Eisenresorptionsrate und der - aufgrund der häufig auftretenden gastrointestinalen Nebenwirkungen - schlechten Compliance von Eisenpräparaten ist davon auszugehen, dass eine parenterale Eisensubstitution einen schnelleren und deutlicheren Effekt auf die Zielparameter (z.B. Hämoglobin) hat.</p> <p>Trotz der hohen Prävalenz des Eisenmangels bei Patienten mit Tumorerkrankung und den in den vergangenen Jahren neu dazugewonnenen wissenschaftlichen Erkenntnissen über den Eisenstoffwechsel ist sowohl die Diagnostik der Eisenmangelanämie bei chronischen Erkrankungen wie auch die Behandlung noch nicht in der klinischen Praxis regelhaft umgesetzt. Die Studie soll dazu beitragen, mehr Klarheit über Art, Dauer und Zeitpunkt der Eisensubstitution in der klinischen Praxis zu erlangen.</p>
<p>Therapieschemata</p>	<p>Arm A: Parenterale Eisensubstitution mit Eisencarboxymaltose (Ferinject)  Eisencarboxymaltose 10 ml in maximal 100 ml NaCl 0.9% (500 mg Eisen), 20 ml in maximal 250 ml NaCl 0.9% (1000 mg Eisen).  Infusion über mindestens 6 min (500 mg Eisen) bzw. 15 min (1000 mg Eisen).  500 mg bis 1000 mg pro Woche bis zu einer Gesamtdosis gemäß Tabelle 1. Die Gesamtdosis wird innerhalb von maximal zwei Wochen appliziert.  Therapiedauer in der Studie: 12 Wochen.  Anschließend entscheidet der behandelnde Arzt über die weitergehende antianämische Behandlung.</p> <p>Arm B: Eisensubstitution per oral mit Eisen(II)-glycin-sulfat-Komplex (Ferro sanol Duodenal Kapseln).  Die Eisensubstitution per oral mit Eisen(II)-glycin-sulfat-Komplex beträgt 200 mg Eisen pro Tag (entspricht zwei Kapseln) über einen Zeitraum von 12 Wochen. Die Einnahme sollte unzerkaut mit ausreichend Wasser (vorzugsweise ein Glas) - z. B. morgens bzw. abends nüchtern (ca. 1 Stunde vor dem Essen) bzw. in ausreichendem Abstand von etwa 2 Stunden vor oder nach einer Mahlzeit - erfolgen.  Therapiedauer in der Studie: 12 Wochen  Anschließend entscheidet der behandelnde Arzt über die weitergehende antianämische Behandlung.</p>
<p>Einschlusskriterien</p>	<ol style="list-style-type: none"> <li>1. Metastasiertes oder inoperables kolorektales Karzinom. Patienten, für die keine kurative Therapie möglich ist.</li> <li>2. Laufende palliative Chemotherapie. Potentiell resektable Patienten, die eine Konversionstherapie erhalten, können nicht in die Studie eingeschlossen werden.</li> <li>3. Eisenmangelanämie: Hb-Wert: <math>\leq 10.5</math> g/dl und Transferrinsättigung (TSAT) <math>&lt; 20\%</math> und/oder Serum Ferritin <math>&lt; 30</math> ng/ml</li> <li>4. Männliche und weibliche Patienten im Alter <math>\geq 18</math> Jahren; mündig</li> <li>5. ECOG <math>\leq 2</math></li> <li>6. Schriftliche Einverständniserklärung des Patienten</li> <li>7. Lebenserwartung des Patienten <math>&gt; 6</math> Monate</li> <li>8. Körpergewicht <math>\geq 40</math> kg</li> </ol>
<p>Ausschlusskriterien</p>	<ol style="list-style-type: none"> <li>1. Eisensubstitution oral oder i.v. bzw. Bluttransfusion in den letzten 4 Wochen</li> <li>2. Alter <math>&lt; 18</math> Jahre oder Körpergewicht <math>&lt; 40</math> kg</li> <li>3. Resorptionsstörung bei Kurzdarmsyndrom oder nach Magenentfernung</li> <li>4. Therapie mit rekombinantem Erythropoetin (r-HuEPO) in den letzten 4 Wochen</li> <li>5. Chronische Diarrhö</li> <li>6. Chronisch entzündliche Darmerkrankungen</li> <li>7. Ferritin <math>&gt; 800</math> ng/ml am Studienstart</li> <li>8. Bekannte Überempfindlichkeit gegen Eisencarboxymaltose und Eisen(II)-glycin-sulfat-Komplex oder Vorliegen von Kontraindikationen gegen Eisencarboxymaltose und Eisen(II)-glycin-sulfat-Komplex</li> </ol>

	<p>9. Bekannter Vitamin B12 oder Folsäure Mangel                  10. Notwendigkeit der parenteralen Ernährung                  11. Teilnahme an einer anderen interventionellen Studie                  12. Schwangerschaft oder Stillzeit</p>
<p>Fallzahl  Dauer der Studie</p>	<p>64 Patienten  Individuelle Beobachtungszeit pro Patient 12 Wochen ab Einschluss (Therapiebeginn) bzgl. des primären Endpunktes. Weitere Beobachtung bzgl. des Überlebens z.B. telefonisch bis zu 2 Jahre. Dauer der Studie insgesamt ca. 18 Monate plus bis zu 2 Jahren Nachbeobachtungszeit</p>
<p>The flowchart illustrates the study's stratification and randomization process. It begins with a box labeled 'Hb ≤ 10,5 g/dl'. An arrow points to a box containing 'Transferrinsättigung &lt; 20 % und/oder Serum Ferritin &lt; 20 ng/ml'. This leads to a 'STRATIFICATION' box containing three criteria: 'Ferritin ≤ 30 ng/ml vs &gt; 30 ≤ 800 ng/ml', 'ECOG 0 vs. ≥ 1 ≤ 2', and 'palliative Therapielinie = 1 vs. ≥ 2'. A vertical bar labeled 'RANDOMISATION' follows, leading to two treatment arms: 'Arm A: Fe-Substitution per i.v. (Eisencarboxymaltose)' and 'Arm B: Fe-Substitution per oral Eisen(II)-glycin-sulfat-Komplex'.</p>	
	<p>Initiierung des 1. Zentrums erfolgte am 30. März 2015.                  Rekrutierung: bis voraussichtlich 31. Dezember 2018.                  Teilnehmende Prüfzentren: 19                  Weitere Prüfzentren erwünscht: ja                  Rekrutierungsstand per 09.04.2018: 53</p>

**AIO-LQ-0113/ass: Nicht-interventionelle Studie zur Erfassung der Lebensqualität bei Patienten mit metastasiertem kolorektalem Karzinom unter Zaltrap® Therapie (QoLiTrap-Trial)**

**AIO-assoziierte Studie**

Studiennummer/-Code:	AIO-LQ-0113/ass - QoLiTrap-Trial
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 – Sep 2018
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Art der Studie	Prospektive, nicht-interventionelle Studie
Studienleitung	Arbeitsgruppe Lebensqualität der AIO Prof. Dr. R. Hofheinz Tages Therapie Zentrum (TTZ) am Interdisziplinären Tumorzentrum (ITM) III. Medizinische Klinik Universitätsklinikum Mannheim Theodor-Kutzer-Ufer 1-3, 68167 Mannheim Tel: 0621/383-2855; FAX 0621/383-3833 E-Mail: ralf.hofheinz@umm.de
Sponsor	Sanofi-Aventis Deutschland GmbH Klinische Forschung, Burkhard Linße Potsdamer Str. 8, 10785 Berlin Tel: 030/2575-2821
Studienziele	<u>Primäres Studienziel:</u> Als primäre Fragestellung der Nicht-Interventionellen Studie soll die Lebensqualität von Patienten mit metastasiertem Kolorektalkarzinom unter einer Therapie mit Zaltrap® in Kombination mit FOLFIRI in der täglichen Routine dokumentiert und analysiert werden. Separate Auswertungen hinsichtlich des RAS-Status sollen zeigen, ob es Unterschiede für Patienten mit RAS Wildtyp, RAS Mutation und unbestimmtem RAS-Typ gibt.  Sekundär sollen weitere wichtige Fragen untersucht werden, wie z.B. progressionsfreies Überleben (PFS), Ansprechrate (RR), Gesamtüberleben (OS) und Sicherheit sowie der Einfluss des RAS-Status auf die Therapie.  <u>Sekundäre Studienziele:</u> <ul style="list-style-type: none"> <li>• Auswirkung der Therapie auf andere Dimensionen/Skalen der Lebensqualität</li> <li>• Auswirkungen der Toxizitäten auf die Lebensqualität</li> <li>• Auswirkungen vorbestehender Symptome auf die Lebensqualität</li> <li>• Prädiktive Faktoren für die Verbesserung der Lebensqualität</li> <li>• Vergleich der Lebensqualität von Respondern und Non-Respondern</li> <li>• Ermittlung unerwünschter Arzneimittelwirkungen/Ereignisse</li> <li>• Vergleich der Lebensqualität in den Subgruppen RAS –WT und RAS- mt</li> </ul>
Zielparameter	Lebensqualität
Patientenzahl	Geplant: 1500 Patienten (D 1340, A 75, CH 85) Bereits eingeschlossen: 1098 (D 973; A 51, CH 74)
Studienstart	24.09.2013
Studienende	LPO März 2019

Weitere teilnehmende Zentren erwünscht?	ja
Einschlusskriterien	Patienten mit metastasiertem kolorektalem Karzinom, die für eine Behandlung mit Afibercept in Frage kommen
Therapieschema	4 mg Afibercept/ kg zusätzlich zur Chemotherapie
Evaluierung der Lebensqualität	<p>Die Daten zur Lebensqualität sollen mit dem validierten EORTC QLQ-C30-Fragebogen alle zwei Wochen unbeeinflusst vom Staging und von der Chemotherapie erhoben werden. Dieser Fragebogen enthält neben einem allgemeinen Score für den allgemeinen Gesundheitsstatus/QoL 5 funktionale Scores (physical, role, cognitive, emotional, social), 3 Symptom Scores (Fatigue, Schmerz, Übelkeit/Erbrechen), 6 einzelne Punkte, die Symptome erfassen, die von Tumorpatienten berichtet werden (Dyspnoe, Insomnie, Appetitlosigkeit, Konstipation, Diarrhoe, finanzielle Schwierigkeiten).</p> <p>Der behandelnde Arzt/das Studienpersonal händigt jedem Patienten nach Einschluss in die Studie ein Heft mit 20 EORTC QLQ-C30-Fragebögen aus. Jeder Patient wird gebeten, am Vortag jedes Chemotherapiezyklus die Fragen 1 bis 28 durch ein Kreuz auf einer Skala von 1 bis 4 („überhaupt nicht zutreffend“ bis „sehr zutreffend“) zu beantworten und seine(n) gegenwärtige(n) allgemeine(n) Gesundheitszustand/Lebensqualität (Fragen 29 und 30) durch ein Kreuz auf einer Skala von 1 („sehr schlecht“) bis 7 („ausgezeichnet“) einzuschätzen und zur nächsten Visite mitzubringen. Diese Einschätzung wird von dem behandelnden Arzt/der behandelnden Ärztin vom Patienten unabhängig vom Staging und von der Chemotherapie erbeten.</p> <p>Die Auswertung der QLQ-C30-Fragebögen erfolgt nach EORTC QLQ-C30 Scoring Manual. (Fayers et al. on behalf of the EORTC QoL Study Group. Brüssel 1995) „Missing Values“ werden nach den Vorgaben des EORTC QLQ-C30 Scoring Manual behandelt.</p>
Fallzahlbegründung	<p>Basierend auf vorangegangenen Studien kann davon ausgegangen werden, dass 80% der Datensätze von den behandelnden Ärzten zur Verfügung gestellt werden. Bei ca. 62% dieser Datensätze sind zum Zeitpunkt 12 Wochen nach Therapiebeginn wahrscheinlich auswertbare Lebensqualitätsbögen von den Patienten vorhanden. Um auswertbare Datensätze bei 750 Patienten zu erhalten, werden deshalb ca. 1500 Patienten in Deutschland, Österreich und in der Schweiz in die Studie eingeschlossen. Auswertbare und nicht auswertbare Kollektive werden bzgl. demographischer Daten und Tumorcharakteristika verglichen, um ggf. eine Bewertung von Selektionseffekten vornehmen zu können.</p> <p>Die Fallzahl von 750 auswertbaren Patienten begründet sich auch, um valide statistische Auswertungen für die Subgruppen nach RAS-Typ (RAS Wildtyp, RAS Mutation) durchzuführen. Nach aktuellen Marktdaten sind in Deutschland ca. 1/3 der mit Afibercept behandelten Patienten vom Typ RAS Wildtyp und ca. 2/3 der Patienten vom Typ RAS-Mutation. Bei 750 Patienten wären somit ca. 250 RAS Wildtyp-Patienten und ca. 500 RAS Mutation-Patienten zu erwarten. Eine administrative Auswertung von 250 Patienten der QoLiTrap-Studie ergab folgende Verteilung: 40,8% RAS-Wildtyp, 44,4% RAS-Mutation und 14,8% unbestimmt bzw. RAS-Typ fehlend. Bei 750 Patienten gesamt wären dies dann in den einzelnen Subgruppen 306, 333 und 111 Patienten.</p> <p>Die statistische Genauigkeit der Schätzungen für die Erfolgsraten werden mit Hilfe von 95% Konfidenzintervallen dargestellt.</p> <p>Auf der Basis von 750 auswertbaren Patienten mit vollständiger QoL-Dokumentation ergibt sich für die zu Grunde liegende Erfolgsrate von 65% ein 95%-Konfidenzintervall (nach Blyth-Still-Casella) von [61,6%; 68,5%], also mit einer Länge von 6,9 Prozentpunkten. Bei 250 Patienten ist das entsprechende 95% Konfidenzintervall [59,1%, 71,1%], hat also eine Länge von 12,0 Prozentpunkten. Bei 500 Patienten ist das entsprechende 95% Konfidenzintervall [60,8%, 69,2%], hat also eine Länge von 8,4 Prozentpunkten. Die entsprechenden Konfidenzintervalle für die Patientenzahlen 306, 333 und 111 sind in der nachfolgenden Tabelle</p>

	<p>enthalten.</p> <p>Sollte entgegen dieser Annahme die Erfolgsrate bei 50% liegen (worst case), sind die entsprechenden 95%-Konfidenzintervalle für 750, 250 und 500 Patienten: [46,4%; 53,6%], Länge 7,2 Prozentpunkte; [43,6%; 56,4%], Länge 12,8 Prozentpunkte und [45,5%; 54,5%], Länge 9,0 Prozentpunkte. Die entsprechenden Konfidenzintervalle für die Patientenzahlen 306, 333 und 111 sind in der nachfolgenden Tabelle enthalten.</p>																						
	<table border="1"> <thead> <tr> <th>Patientenzahl</th> <th>Erfolgsrate 65% 95% Konfidenzintervall (Blyth-Still-Casella)</th> <th>Erfolgsrate 50% 95% Konfidenzintervall (Blyth-Still-Casella)</th> </tr> </thead> <tbody> <tr> <td>750</td> <td>61,6% ; 68,5%</td> <td>46,4% ; 53,6%</td> </tr> <tr> <td>250</td> <td>59,1% ; 71,1%</td> <td>43,6% ; 56,4%</td> </tr> <tr> <td>500</td> <td>60,8% ; 69,2%</td> <td>45,5% ; 54,5%</td> </tr> <tr> <td>306</td> <td>59,6% ; 70,4%</td> <td>44,3% ; 55,7%</td> </tr> <tr> <td>333</td> <td>59,5% ; 70,0%</td> <td>44,7% ; 55,7%</td> </tr> <tr> <td>111</td> <td>55,7% ; 73,7%</td> <td>40,8% ; 60,1%</td> </tr> </tbody> </table>		Patientenzahl	Erfolgsrate 65% 95% Konfidenzintervall (Blyth-Still-Casella)	Erfolgsrate 50% 95% Konfidenzintervall (Blyth-Still-Casella)	750	61,6% ; 68,5%	46,4% ; 53,6%	250	59,1% ; 71,1%	43,6% ; 56,4%	500	60,8% ; 69,2%	45,5% ; 54,5%	306	59,6% ; 70,4%	44,3% ; 55,7%	333	59,5% ; 70,0%	44,7% ; 55,7%	111	55,7% ; 73,7%	40,8% ; 60,1%
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	<p>Die Auswertung umfasst alle Beobachtungskriterien und erfolgt nach deskriptiven und explorativen statistischen Methoden (tabellarisch und grafisch) einschließlich explorativ zu interpretierender Konfidenzintervalle und p-Werte. Die statistischen Auswertungen und deren Ergebnisse werden sowohl für das Gesamtkollektiv der auswertbaren Patienten als auch getrennt nach RAS-Status der Patienten (RAS Wildtyp, RAS-Mutation und unbestimmter RAS-Typ) durchgeführt und präsentiert. Die Erfolgsraten der verschiedenen RAS-Typen werden mit geeigneten (explorativ zu interpretierenden) statistischen Tests verglichen (z.B. mit Bernard's Test auf Überlegenheit)</p>																						

Lebensqualität: Metastasiertes Adenokarzinom des Pankreas

**AIO-LQ-0214/ass: Nicht-interventionelle Studie zur Erfassung der Lebensqualität, Wirksamkeit und Verträglichkeit bei Patienten mit metastasiertem Pankreaskarzinom unter Erstlinientherapie mit NabPaclitaxel und Gemcitabin – QoliXane.**

<b>AIO-assoziierte Studie</b>	
Studiennummer/-Code:	AIO-LQ-0214/ass - QoLiXane-Trial
Status:	Rekrutierung im Rahmen der QoliXane beendet. Folgeprojekt in Planung (Start: Q2/2018)
Rekrutierungszeitraum	2014 – 2017
Weitere Zentren:	Möglich für das Folgeprojekt.
Letzte Aktualisierung	April 2018

Art der Studie	Nicht-interventionelle Studie (NIS)
Verantwortlicher Studienleiter nach AMG	Institut für Klinisch-Onkologische Forschung (IKF) Ärztl. Direktor: Prof. Dr. Salah-Eddin Al-Batran Krankenhaus Nordwest GmbH UCT - Universitäres Centrum für Tumorerkrankungen Frankfurt

	Steinbacher Hohl 2-26 60488 Frankfurt E-Mail: albatran@aio-portal.de
Kontaktadresse/ Kontaktperson:	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Dr. Caroline Schönherr Steinbacher Hohl 2-26 60488 Frankfurt Tel: 069 7601 4094, FAX: 069 7601 3655 E-Mail: schoenherr.caroline@ikf-khnw.de www.ikf-nordwest.de
Studienziele/ Objectives	<p><u>Primäres Studienziel:</u> Verlauf der Lebensqualität bei Patienten mit einem metastasierten Pankreaskarzinom, die sich unter einer Therapie mit Gemcitabin und NabPaclitaxel befinden. Der Primäre Endpunkt ist der Anteil von Patienten, die nach 3 Monaten keine Verschlechterung (d.h. Verbesserung oder Stabilität) des Global Health Status/QoL-Score aufweisen. Dies wird mittels einer Kaplan-Meier-Analyse ermittelt.</p> <p><u>Sekundäre Studienziele:</u> <u>Lebensqualität</u></p> <ol style="list-style-type: none"> <li>1. Der Anteil von Patienten, die nach 6 Monaten keine Verschlechterung (stabil oder verbessert) des Global Health Status/QoL-Score aufweisen</li> <li>2. Der Anteil der Patienten mit einem eingeschränkten Allgemeinzustand (ECOG 2 oder 3) mit einem stabilen oder einem verbesserten Global Health Status/Lebensqualität und anderen EORTC QLQ-C30-Dimensionen/Skalen nach 3 und 6 Monaten</li> <li>3. Der Effekt der Therapie auf Global Health Status/Lebensqualität und auf andere Symptome und Skalen des EORTC-QLQ-C30 nach 3 Monaten (Anteil der Patienten mit einem besseren, stabilen oder schlechterem Score)</li> <li>4. Die prognostische Rolle von Global Health Status/Lebensqualität und von anderen Funktions- und Symptomskalen des EORTC-QLQ-C30</li> <li>5. Mediane Zeit bis zur definitiven Verschlechterung von Global Health Status/Lebensqualität und anderer Funktions- und Symptomskalen des EORTC-QLQ-C30</li> <li>6. Ermittlung des Effekts der Neuropathie auf die Lebensqualität im Vergleich mit anderen krankheitsbedingten Symptomen wie Schmerz, Anorexie und Fatigue. Auswertung erfolgt durch Korrelation von dokumentierten Adverse Events mit den Lebensqualitäts-Scores mittels univariater und multivariater Methoden</li> <li>7. Zusätzliche Analysen, die für den historischen Vergleich mit Gemcitabin nötig sind (Gourgou-Bourgade et al. 2013)</li> </ol> <p><u>Wirksamkeit</u></p> <ol style="list-style-type: none"> <li>1. Ansprech-Raten (RECIST-Kriterien sofern diese vorliegen), progressionsfreies Überleben (PFS) und Gesamtüberleben (OS) nach Studienende</li> <li>2. Wirksamkeit in speziellen Subgruppen wie z.B. ECOG PS &gt; 1 und Hyperbilirubinämie</li> </ol> <p><u>Sicherheit</u></p> <ol style="list-style-type: none"> <li>1. Nebenwirkungen (beurteilt nach den aktuell gültigen NCI-CTC Kriterien)</li> <li>2. Nebenwirkungen in speziellen Subgruppen wie z.B. ECOG PS &gt; 1 und Hyperbilirubinämie</li> </ol> <p><u>Translationale / Korrelative Begleitstudien</u> Assoziation vom Ansprechen und Überleben mit genetischen Alterationen mittels Next-Generation (NGS; Illumina HiSeq2000) und RNA Sequenzierungen</p>
Patientenzahl	Geplant: 600 Patienten Bereits eingeschlossen: 601 (Stand 20.10.2017)
Rekrutierungszeitraum	95 teilnehmende Zentren Oktober 2014 bis 30.09.2017

Weitere Zentren?	für Folgeprojekt möglich
Haupt-Einschlusskriterien /	<ul style="list-style-type: none"> <li>- metastasiertes Pankreaskarzinom</li> <li>- keine vorherige Therapie im metastasierten Stadium</li> <li>- eine Behandlung mit NabPaclitaxel/Gemcitabin ist durch den behandelnden Arzt geplant</li> </ul>
Haupt-Ausschlusskriterien	<ul style="list-style-type: none"> <li>- vorherige Chemotherapie im metastasierten Stadium</li> <li>- Unfähigkeit, die Studie zu verstehen und Patienteneinverständnis zu geben</li> <li>- Unfähigkeit des Patienten, QoL-Fragebogen auszufüllen bzw. die Fragen zu beantworten</li> </ul>
Therapieschema	NabPaclitaxel + Gemcitabin
Rationale	<p>Die Kombination von Gemcitabin und NabPaclitaxel stellt eine neue therapeutische Option für Patienten mit metastasiertem Pankreaskarzinom dar. In klinischen Studien konnte ein verlängertes Gesamtüberleben gegenüber der Monotherapie mit Gemcitabin statistisch signifikant nachgewiesen werden (medianes Gesamtüberleben 6,7 vs. 8,6 Monate). Die neue Kombination zeigte darüber hinaus auch Verbesserungen bei der Ansprechrate und dem progressionsfreien Überleben.</p> <p>Aufgrund der noch immer sehr schlechten Prognose, erhält die Lebensqualität von Patienten mit metastasiertem Pankreaskarzinom im palliativen Therapiesetting besondere Relevanz. Diese nicht-interventionelle Studie (NIS) ist speziell für die Evaluation der gesundheitsbezogenen Lebensqualität jener Patienten entwickelt worden, die unter dieser Indikation in Erstlinientherapie mit der Kombination aus NabPaclitaxel und Gemcitabin behandelt werden. Neben Sicherheit und Toxizität sollen zudem Ansprechrate, progressionsfreies Überleben und Gesamtüberleben als weitere wichtige Behandlungsparameter erfasst werden.</p> <p>Sofern vorhanden, soll im Rahmen dieser NIS für ein Begleitforschungsprojekt Tumormaterial der Patienten bei dem zuständigen Pathologen angefordert werden. Den Patienten wird kein neues Tumormaterial entnommen. Die Probe wird gezielt auf das Vorhandensein von Genvarianten untersucht, die potentiell mit dem Verlauf der Tumorerkrankung in Zusammenhang stehen, also eventuell als prognostische Marker dienen können.</p> <p>Diese NIS wird nach dem Empfehlungen des Verbandes der forschenden Arzneimittelhersteller (VfA) zur Verbesserung der Qualität und Transparenz von nicht-interventionellen Studien vom 17. August 2012 und nach den Gemeinsamen Empfehlungen des Bundesinstitutes für Arzneimittel und Medizinprodukte (BfArM) und des Paul-Ehrlich-Institutes (PEI) zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen vom 13. August 2013 durchgeführt</p>



## Arbeitsgruppe Mammakarzinom und Gynäkologische Tumoren

### Mammakarzinom – palliative Therapie, 2nd –line

**Multizentrische, prospektiv randomisierte Phase III Studie zum Vergleich einer antineoplastischen Therapie allein versus einer antineoplastischen Therapie plus Lapatinib bei Patientinnen mit initial HER2-negativem metastasiertem Brustkrebs und HER2-positiven zirkulierenden Tumorzellen (DETECT III)**

#### AIO-assozierte Studie

Studiennummer/-Code:	DETECT III
Status:	in Rekrutierung
Rekrutierungszeitraum	2012 – 2018
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	November 2017

Art der Studie	Phase-III, multizentrisch, prospektiv, randomisiert	
Sponsor's Responsible Person	Universitätsklinikum Ulm (AöR), Albert-Einstein-Allee 29, D-89081 Ulm Prof. Dr. med. Wolfgang Janni	
Leiter der klinischen Prüfung (LKP)	Prof. Dr. med. Tanja Fehm, Heinrich Heine Universität Düsseldorf, Frauenklinik, Moorenstraße 5, D-40225 Düsseldorf	
Sponsor's Study office	Universitätsfrauenklinik Ulm Studienzentrale Prittowitzstr. 43 D-89075 Ulm Germany	Physician: Dr. F. Schochter, Dr. S. Albrecht, Dr. A. Schramm, A.Polasik, Prof. Dr. J. Huber Studycoordinators: Evelyn Jäckel, Heike Karl & Jessica D'Andrea Tel: +49 (0) 731 500 58520/-58521 FAX: +49 (0) 731 500 58526 E-Mail: studienzentrale.ufk@uniklinik-ulm.de
Patientenzahl	Geplant: 120 Patientinnen randomisiert: 82 (Stand Nov. 2017)	
Studienrationale	Evaluation der Wirksamkeit von Lapatinib bei Patientinnen mit metastasiertem Brustkrebs, welche HER2-positive zirkulierende Tumorzellen (CTC) aufweisen, obwohl der Primärtumor und/oder Gewebeproben einer metastatischen Läsion auf ihren HER2-Status getestet wurden und HER2-Negativität zeigten. Evaluation der Toxizität bei Patientinnen mit ossären Metastasen, welche Denosumab in Kombination mit verschiedenen Studienmedikationen erhalten.	
Studienziele	<p>Primäres Zielkriterium:</p> <ul style="list-style-type: none"> <li>▪ CTC Clearance Rate: Anteil an Patientinnen mit mindestens einer vor Behandlungsbeginn in 7.5 ml peripherem Blut nachgewiesenen zirkulierenden Tumorzelle (CTC), bei denen nach der Behandlung keine CTCs im Blut mehr nachgewiesen werden können (CTC Nachweis erfolgt mit dem CellSearch® System; Veridex LLC, Raritan, USA)</li> </ul> <p>Sekundäre Zielkriterien:</p> <ul style="list-style-type: none"> <li>▪ Progressionsfreies Überleben (PFS)</li> <li>▪ Allgemeine Ansprechrate: Komplettremission (CR), Teilremission (PR)</li> <li>▪ Klinische Erfolgsrate</li> <li>▪ Gesamtüberleben</li> <li>▪ Dynamik der zirkulierenden Tumorzellen</li> <li>▪ Evaluation der Lebensqualität (EORTC QLQ-C30 und EORTC QLQ-BR23 Fragebögen)</li> </ul>	

	<ul style="list-style-type: none"> <li>▪ Toxizitätsanalyse von Lapatinib: Sicherheit und Verträglichkeit</li> <li>▪ Compliance</li> <li>▪ Schmerzanalyse: Messung anhand einer Numerischen Rating-Skala (NRS)</li> </ul>
Studiendesign	<p><b>DETECT</b></p> <p>Screening-Phase N = 2000 metastatic breast cancer, HER2-negative Primary tumor*</p> <p>CTC-determination Determination of the HER2 status on CTCs</p> <p>CTC+ [HER2+]</p> <p>R</p> <p>Standard treatment N = 60 + Denosumab**</p> <p>Standard treatment + Lapatinib N = 60 + Denosumab**</p> <p>CTC+ [HER2-] or CTC-negative</p> <p>Not eligible in D III</p> <p>* including HER2-negative metastatic disease in case a biopsy was performed ** in patients with bone metastases</p>
Einschlusskriterien	<ol style="list-style-type: none"> <li>1. Schriftliche Einverständnis zur Studienteilnahme</li> <li>2. Metastasiertes Mammakarzinom, das einer Operation oder der Strahlentherapie allein nicht zugänglich ist. Histopathologische Sicherung des primären Mammakarzinoms oder einer metastatischen Läsion des Mammakarzinoms und Bestimmung des Östrogen- und Progesteronrezeptorstatus</li> <li>3. Bestimmung des HER2-Status des primären Mammakarzinoms und/oder einer metastatischen Läsion. HER2-Negativität aller untersuchten Gewebeprobe(n), d.h. Immunhistochemie 0-1+ <u>oder</u> 2+ und Fluoreszenz in situ Hybridisierung (FISH) negativ <u>oder</u> nur FISH negativ.</li> <li>4. Nachweis HER2-positiver zirkulierender Tumorzellen (CTC) (HER2-Status ermittelt über IHC oder FISH)       <ul style="list-style-type: none"> <li>• Mindestens eine CTC/7.5 ml Blut (CellSearch® Circulating Tumor Cell Kit) und</li> <li>• Mindestens eine HER2-positive CTC</li> </ul> </li> <li>5. Indikation zur Standard-Chemo- oder endokrinen Therapie, deren Kombination mit Lapatinib zugelassen ist (Tyverb® 250 mg Tabletten) oder in klinischen Studien evaluiert wird</li> <li>6. Tumorevaluation innerhalb von 6 Wochen vor Studienrandomisierung</li> <li>7. Mindestens eine nach RECIST auswertbare metastatische Läsion, entsprechend den RECIST Leitlinien Version 1.1. Patienten mit messbaren und nicht-messbaren Läsionen können eingeschlossen werden. [Eisenhauer 2009]</li> <li>8. Alter <math>\geq 18</math> Jahre</li> <li>9. ECOG <math>\leq 2</math></li> <li>10. Adäquate Knochenmarksreserve und Organfunktion       <ul style="list-style-type: none"> <li>• Absolute Neutrophile <math>\geq 1500/\mu\text{L}</math>,</li> <li>• Thrombozyten <math>\geq 100000/\mu\text{L}</math>,</li> <li>• Hämoglobin <math>\geq 9\text{g/dL}</math>,</li> <li>• ALT (SGPT) <math>\leq 3.0 \times \text{ULN}</math>,</li> <li>• AST (SGOT) <math>\leq 3.0 \times \text{ULN}</math>,</li> <li>• Bilirubin (gesamt) <math>\leq 2 \times \text{ULN}</math> und <math>\leq 35\%</math> direkt</li> <li>• Kreatinin <math>\leq 2.0 \text{ mg/dl}</math> oder <math>177\mu\text{mol/L}</math>,</li> </ul> </li> </ol> <p><b>Cave:</b> Die oben genannten Angaben gelten nur für eine Therapie mit Lapatinib. Zur Verabreichung der Standard-Chemo- oder endokrinen Therapie muss die aktuelle Fachinformation zusätzlich berücksichtigt werden.</p> <ol style="list-style-type: none"> <li>11. Echokardiographischer Nachweis einer ausreichenden linksventrikulären Ejektionsfraktion innerhalb des Referenzbereichs der jeweiligen Institution</li> </ol>

	<p>12. Bei gebärfähigen Patientinnen gilt:</p> <ul style="list-style-type: none"> <li>• Negativer Schwangerschaftstest (minimale Sensitivität 25 IU/L oder äquivalente Einheiten des HCG) innerhalb von 7 Tagen vor Randomisierung</li> <li>• Sichere Kontrazeption (d.h. nicht-hormonelle Kontrazeption, IUP, Anwendung einer Doppelbarriere-Methode, Vasektomie des Geschlechtspartners, komplette sexuelle Abstinenz) andauernd über mindestens 28 Tage nach Komplettierung der Studientherapie.</li> </ul>
Ausschlusskriterien	<ol style="list-style-type: none"> <li>1. Anamnestisch bekannte Überempfindlichkeit gegenüber Lapatinib oder chemisch verwandten Substanzen</li> <li>2. Mehr als 3 palliative Chemotherapie-Linien (dabei ist eine Chemotherapie-Linie definiert als jede neue Chemotherapie und jede Modifikation eines bestehenden Chemotherapieregimes)</li> <li>3. Behandlung mit Prüfsubstanzen oder andere antineoplastische Therapie während der Studie oder innerhalb von 2 Wochen vor Randomisierung oder 6 Wochen im Fall von Nitrosourea oder Mitomycin C</li> <li>4. Persistierende, therapeutisch relevante Nebenwirkungen einer vorangegangenen antineoplastischen Therapie während des Randomisierungszeitraums &gt; Grad 1 (NCI CTCAE)</li> <li>5. Anti-retrovirale Therapie aufgrund einer HIV-Infektion</li> <li>6. Aktuelle Leber- oder Gallenwegserkrankung (mit Ausnahme von Patientinnen mit Gilberts-Syndrom, mit asymptomatischen Gallensteinen, Lebermetastasen oder stabiler chronischer Lebererkrankung)</li> <li>7. Vorliegen einer Erkrankung, die die adäquate Einschätzung oder Evaluation der Studiendaten stören könnte, oder Vorliegen einer anderen medizinischen Indikation, bei der die Patientin durch eine Studienteilnahme unverhältnismäßig gefährdet ist</li> <li>8. Zweitkarzinom innerhalb der letzten 3 Jahre (außer in-situ-Karzinom der Cervix uteri oder Basaliom der Haut)</li> <li>9. Unfähigkeit der oralen Aufnahme der Studienmedikation (z.B. bei Malabsorptionssyndrom, parenteraler Ernährung, vorangegangenen chirurgischen Eingriffen, die die Absorption beeinflussen (z.B. Dünndarm- oder Magenresektionen), oder bei unzureichend therapierten entzündlichen Darmerkrankungen (z.B. M. Crohn, Colitis ulcerosa))</li> <li>10. Manifeste kardiale Vorerkrankung, definiert als: <ul style="list-style-type: none"> <li>• instabile Angina pectoris in der Vorgeschichte,</li> <li>• therapiebedürftige oder klinisch relevante Arrhythmien in der Vorgeschichte (ausgenommen asymptomatisches Vorhofflimmern, welches einer Antikoagulation bedarf),</li> <li>• Z. n. Myokardinfarkt innerhalb der letzten 6 Monate vor Studieneintritt,</li> <li>• symptomatische Herzinsuffizienz,</li> <li>• Ejektionsfraktion &lt; 50% oder unterhalb des oberen Referenzbereichs der jeweiligen Institution</li> <li>• jede andere kardiale Begleiterkrankung, die nach Ansicht des behandelnden Arztes zu einer unverhältnismäßigen Gefährdung der Patientin bei Studienteilnahme führen würde</li> </ul> </li> <li>11. Demenz, veränderter mentaler Status oder andere psychiatrische oder soziale Einflüsse, die das Verständnis oder die Wiedergabe der informierten Einwilligung verhindern oder welche die Einhaltung des Studienprotokolls stören</li> <li>12. Lebenserwartung &lt; 3 Monate</li> <li>13. Männliche Patienten</li> <li>14. Schwangerschaft oder Stillzeit</li> <li>15. HER2-positiver Primärtumor oder HER2-positivem Gewebeprobe einer metastatischen Läsion</li> <li>16. Jede vorangegangene Behandlung mit anti-HER2-gerichteter Therapie</li> </ol>
Tumorevaluierung	Nach RECIST V 1.1 und CTC-Bestimmung sowie Bestimmung des HER2-Status der CTCs

Mammakarzinom – palliative Therapie – 1st und 2nd line.**AIO-MAM-0116/ass: Wirksamkeit und Lebensqualität in der Behandlung von postmenopausalen Frauen mit Hormonrezeptor-positivem, HER2-negativem, lokal rezidiviertem oder metastasiertem Brustkrebs mit Palbociclib (PD0332991) in Kombination mit Letrozol - eine offene, multizentrische, einarmige Phase 2 Studie (INGE-B)****AIO**-assoziierte Studie

Studiennummer/-Code:	AIO-MAM-0116/ass - INGE-B
Status:	in Rekrutierung
Rekrutierungszeitraum	2016 – 2018
Weitere Zentren:	keine weiteren Zentren erforderlich
Letzte Aktualisierung	April 2018

LKP Deutschland	Dr. med. Manfred Welslau
Sponsor	iOMEDICO AG
Studienpopulation	Patientinnen mit histologisch gesichertem lokal fortgeschrittenem oder metastasiertem hormonrezeptor-positivem, HER2/neu negativem Brustkrebs, die für eine Kombinationstherapie mit Palbociclib und einem Aromataseinhibitor oder Fulvestrant (Fulvestrant nach vorheriger endokriner Therapie) geeignet sind.
Anzahl Patientinnen	360 Patientinnen
Anzahl Zentren	85 Zentren in Deutschland
Studiendesign	<p>INGE-B ist eine prospektive, multizentrische, einarmige Phase II-Studie, in welcher die Wirksamkeit der Kombination aus Palbociclib und einem Aromatase-Inhibitor oder Fulvestrant bei postmenopausalen und prä-/perimenopausalen mit einem LHRH Agonisten behandelten Frauen mit HR+/HER2- fortgeschrittenem Brustkrebs getestet wird.</p> <p>Insgesamt werden 360 Patientinnen in die Studie aufgenommen. Ziel der Studie ist es, 60 (58-62) Patientinnen je Rekrutierungsgruppe (siehe Abbildung) einzuschließen.</p> <p>Die Behandlung wird fortgeführt bis zur Tumorprogression, nicht tolerierbarer Toxizität oder Tod. Falls die endokrine Therapie abgesetzt wird, muss auch Palbociclib abgesetzt werden. Falls die Behandlung mit Palbociclib gestoppt werden muss, kann die endokrine Therapie nach Ermessen des Prüfarztes weiter genommen werden. Unabhängig von der endokrinen Therapie ist in dieser Studie der Behandlungsstopp mit Palbociclib als Behandlungsende (<i>end of treatment</i>, EOT) definiert.</p> <p>Nach EOT folgt für die Patientin die Follow-up (FU) Phase. Diese beinhaltet:</p> <ul style="list-style-type: none"> <li>• die Palbociclib Sicherheits-FU Visite 30 Tage (+7 Tage) nach EOT,</li> <li>• die FU-Phase bis zur Krankheitsprogression mit fortgeführten Erhebungen (nur für die Patienten, die bei EOT keine Progression zeigten) und</li> <li>• die FU-Phase für Überleben bis zum Ende der Studie (<i>end of study</i>, EOS)</li> </ul> <p>EOS ist definiert als letzte Visite der letzten eingeschlossenen Patientin (<i>last patient last visit</i>, LPLV).</p>

	<div style="border: 2px solid orange; border-radius: 15px; padding: 10px; margin-bottom: 10px;"> <p><b>Frauen mit HR+/HER2-, lokal fortgeschrittenem, inoperablem oder metastasiertem Brustkrebs vorgesehen für eine Behandlung mit Palbociclib + Aromatase Inhibitor, oder Palbociclib + Fulvestrant nach vorheriger endokriner Therapie</b></p> <ul style="list-style-type: none"> <li>- Adjuvante Behandlung mit dem jeweiligen Kombinationspartner bis zu 12 Monate vor Studienbeginn erlaubt.</li> <li>- Keine vorherige palliative Behandlung mit dem geplanten endokrinen Kombinationspartner.</li> <li>- Nach maximal einer palliativen Chemotherapie</li> <li>- Keine Vorbehandlung mit CDK4/6 Inhibitor</li> </ul> </div> <div style="display: flex; justify-content: space-around; margin-bottom: 10px;"> <div style="text-align: center;"> <p><b>Erstlinientherapie</b></p> <p>↓</p> <div style="border: 1px solid gray; padding: 5px; width: 100px; margin: 0 auto;">Keine vorherige palliative systemische Therapie</div> <p>↓</p> <div style="border: 2px solid orange; border-radius: 10px; padding: 5px; width: 100px; margin: 0 auto;"> <p style="text-align: center;"><b>Gruppe 1</b></p> <p style="text-align: center; background-color: yellow;">Gruppe 1 geschlossen</p> </div> <div style="border: 2px solid orange; border-radius: 10px; padding: 5px; width: 100px; margin: 5px auto;"> <p style="text-align: center;"><b>Gruppe 2</b></p> <p style="text-align: center;">Palbociclib + Anastrozol; n ~ 60</p> </div> <div style="border: 2px solid orange; border-radius: 10px; padding: 5px; width: 100px; margin: 5px auto;"> <p style="text-align: center;"><b>Gruppe 3</b></p> <p style="text-align: center;">Palbociclib + Exemestan; n ~ 60</p> </div> <div style="border: 2px solid orange; border-radius: 10px; padding: 5px; width: 100px; margin: 5px auto;"> <p style="text-align: center;"><b>Gruppe 4</b></p> <p style="text-align: center;">Palbociclib + Fulvestrant; n ~ 60</p> <p style="text-align: center; font-size: small;">Nach vorheriger endokriner Therapie</p> </div> </div> <div style="text-align: center;"> <p><b>Zweite oder weitere Linien</b></p> <p>↓</p> <div style="border: 1px solid gray; padding: 5px; width: 100px; margin: 0 auto;">≥ 1 vorherige palliative systemische Therapie</div> <p>↓</p> <div style="border: 2px solid orange; border-radius: 10px; padding: 5px; width: 100px; margin: 0 auto;"> <p style="text-align: center;"><b>Gruppe 5</b></p> <p style="text-align: center; background-color: yellow;">Gruppe 5 geschlossen</p> </div> <div style="border: 2px solid orange; border-radius: 10px; padding: 5px; width: 100px; margin: 5px auto;"> <p style="text-align: center;"><b>Gruppe 6</b></p> <p style="text-align: center; background-color: yellow;">Gruppe 6 geschlossen</p> <p style="text-align: center; font-size: small;">Nach vorheriger endokriner Therapie</p> </div> </div> </div>
Zweck und Rationale	<p>Brustkrebs ist die häufigste bösartige Krebserkrankung bei Frauen in der westlichen Welt und die Hauptursache von Krebs Tod bei Frauen weltweit (WHO 2014). Hormonrezeptor-positiver (HR+)/humane epidermale Wachstumsfaktor-Rezeptor 2-negativer (HER2-) Brustkrebs ist der häufigste molekulare Subtyp und macht ungefähr drei Viertel aller Brusttumore aus.</p> <p>Endokrine Therapie ist eine Standardbehandlung für HR+ Brustkrebs und beinhaltet die Behandlung mit dem nicht-steroidalen Aromatase-Inhibitor Letrozol für postmenopausale Frauen.</p> <p>Palbociclib (PD-0332991) ist ein oral verabreichtes Prüfpräparat, das gezielt die cyclin-abhängigen Kinasen 4 und 6 (CDK4/6) hemmt. CDK4/6 sind Protoonkogene, die nach Aktivierung den Übergang des Zellzyklus von G1- zur S-Phase einleiten, und somit den Eintritt in die Mitose auslösen und damit Zellproliferation fördern. Änderungen im CDK4/6-Signalweg spielen eine wesentliche Rolle in der Brustkrebsentstehung.</p> <p>Präklinische Studien haben gezeigt, dass Palbociclib die Zellzykluskontrolle wiederherstellt und so die Proliferation der Tumorzellen, insbesondere bei Östrogenrezeptor-positiven (ER+) Brustkrebszelllinien blockiert. Xenograft Tumormodelle haben ebenso auf Palbociclib Behandlung angesprochen. Palbociclib zeigte synergistische Effekte mit Antiöstrogenen. In nachfolgenden frühen klinischen Prüfungen ließen sich vielversprechende Sicherheits- und pharmakokinetische Profile beobachten.</p> <p>Die Phase II-Studie PALOMA-1 vergleicht die Kombination von Palbociclib und Letrozol mit Letrozol Monotherapie bei postmenopausalen Frauen mit ER+/HER2- fortgeschrittenem/metastasiertem Brustkrebs als Erstlinientherapie. Die Kombinationsbehandlung verbesserte signifikant das mediane progressionsfreie Überleben (<i>progression-free survival</i>, PFS) in einem klinisch relevanten Ausmaß von 20,2 auf 10,2 Monate (HR 0,51). Die</p>

	<p>Gesamtansprechrates (<i>overall response rate</i>, ORR) betrug 48% im Vergleich zu 41%. Die klinische Benefitrate (<i>clinical benefit rate</i>, CBR) war mit 84% im Vergleich zu 70% ebenfalls verbessert [1].</p> <p>Im Februar 2015 bewilligte auf der Grundlage dieser Ergebnisse die FDA die beschleunigte Zulassung von Palbociclib (Ibrance®) in den USA zur kombinierten Verabreichung mit Letrozol als Erstlinientherapie dieser Patientinnenpopulation. Die korrespondierende Phase III-Studie PALOMA-2 (NCT01740427) läuft aktuell.</p> <p>Die Kombination Palbociclib und Anastrozol war im neoadjuvanten Setting in einer Phase II Studie bei Patientinnen mit ER+/HER2- Brustkrebs im Stadium II/III (n=50) wirksam. 31 von 41 Patienten, die mindestens mit 3 Zyklen behandelt wurden, hatten eine klinische Response (67%): 24% eine komplette Response, 43% eine partielle Response und 15% eine stabile Erkrankung.</p> <p>Die Kombination von Palbociclib und Exemestan im Vergleich zu Capecitabin wird zur Zeit in einer offenen, randomisierten Phase III Studie (PEARL; n=348) geprüft.</p> <p>Bei Patientinnen mit HR+/HER2- metastasiertem Brustkrebs nach vorheriger endokriner Therapie verbesserte die Kombination von Palbociclib und Fulvestrant im Vergleich zu Fulvestrant und Placebo das PFS signifikant (11,2 vs. 4,6 Monate; HR 0,497) (PALOMA-3) [2].</p> <p>Auf Grundlage dieser Ergebnisse wurde Palbociclib (Ibrance®) in Europa für die Behandlung von HR+/HER2- metastasiertem Brustkrebs nach endokriner Therapie für folgende Kombinationen zugelassen:</p> <ul style="list-style-type: none"> <li>• In Kombination mit einem Aromataseinhibitor, oder</li> <li>• In Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten.</li> </ul> <p>Bei prä- oder perimenopausalen Frauen ist die endokrine Therapie mit einem luteinisierenden Hormon Releasing-Hormon (LHRH) zu kombinieren.</p> <p>Die Kombination von Palbociclib und Fulvestrant verbesserte das PFS von 9,2 auf 3,8 Monate (HR 0,42) im Vergleich zu Fulvestrant bei Patientinnen mit HR+ metastasiertem Brustkrebs nach vorheriger endokriner Therapie (PALOMA-3) [2].</p>
Primärer Zielparameter	<p>Der primäre Zielparameter dieser Studie ist die Beurteilung der Effektivität über den klinischen Benefit nach 24 Wochen (<i>Clinical Benefit Rate</i>, CBR). CBR ist nach RECIST 1.1 definiert als komplette Remission (<i>complete response</i>, CR), partielle Remission (<i>partial response</i>, PR) oder stabile Erkrankung (<i>stable disease</i>, SD).</p>
Sekundäre Zielparameter	<p>Beurteilung der Sicherheit und Verträglichkeit durch Erfassung von</p> <ul style="list-style-type: none"> <li>• unerwünschten Ereignissen nach Art, Häufigkeit und Schweregrad (eingeteilt nach den Common Terminology Criteria for Adverse Events [CTCAE] des National Cancer Institutes v.4.03), sowie Schweregrade bis zur Progression (<i>progressive disease</i>, PD) bzw. bis zum Beginn der nächsten Krebstherapie, falls diese früher erfolgt.</li> <li>• jeglichen Laborwertabweichungen bis EOT</li> <li>• Häufigkeit und Dauer von Krankenhausaufenthalten bis zur Progression oder bis zum Beginn der nächsten Krebstherapie, falls diese früher erfolgt.</li> </ul> <p>Beurteilung der Behandlungswirksamkeit durch Bestimmung von</p> <ul style="list-style-type: none"> <li>• Progressionsfreies Überleben (PFS)</li> <li>• Gesamtüberleben (OS)</li> <li>• CBR nach 48 Wochen</li> <li>• PFS-Rate nach einer 48-wöchigen (für alle Patientinnen) und nach einer 2-jährigen Behandlung (nur für Erstlinienpatientinnen)</li> <li>• OS-Rate nach 48 Wochen (für alle Patientinnen) und danach jährlich bis Studienende (<i>end of study</i>, EOS) (nur für Erstlinienpatientinnen).</li> </ul> <p>Beurteilung der Adhärenz über die Erfassung der</p> <ul style="list-style-type: none"> <li>• Behandlungsdauer</li> <li>• Gründe für einen Behandlungsabbruch</li> </ul>

	<ul style="list-style-type: none"> <li>• Dosisanpassungen (Häufigkeit, Grund)</li> <li>• Patiententagebuch bis EOT</li> </ul> <p>Beurteilung der gesundheitsbezogenen Lebensqualität (<i>quality of life</i>, QoL), Fatigue, Angst und Depression</p> <ul style="list-style-type: none"> <li>• Die gesundheitsbezogene QoL wird mit Hilfe des FACT-B-Fragebogens (<i>Functional Assessment of Cancer Therapy - Breast</i>) erfasst, alle 12 Wochen bis zur PD (oder bis zum Beginn der folgenden Krebstherapie, falls diese früher erfolgt)</li> <li>• Fatigue wird mit dem BFI-Fragebogen (<i>Brief Fatigue Inventory</i>) erfasst, alle 12 Wochen bis zur PD (oder bis zum Beginn der folgenden Krebstherapie, falls diese früher erfolgt)</li> <li>• Depression und Angst werden mit dem HADS-D-Fragebogen (<i>Hospital Anxiety and Depression Scale</i>) erfasst, alle 12 Wochen bis zur PD (oder bis zum Beginn der folgenden Krebstherapie, falls diese früher erfolgt)</li> </ul> <p>Vergleich der QoL mit „Real-life“ Patientinnen, die eine Erstlinien-Chemotherapie im Rahmen der nicht-interventionellen MaLife Studie bekommen:</p> <ul style="list-style-type: none"> <li>• Gesundheitsbedingte Lebensqualität (FACT-B), Fatigue (BFI) sowie Depression und Angst (HADS-D) nach 12- und 24-wöchiger Behandlungsdauer bei Erstlinienpatientinnen der INGE-B Studie werden mit Patientinnen verglichen, welche eine Erstlinienchemotherapie innerhalb der nicht-interventionellen MaLife-Studie erhalten</li> </ul> <p>Ärztliche Beurteilung des allgemeinen Gesundheitszustands der Patientin sowie von Veränderungen im Gesundheitszustand im Vergleich zur vorangegangenen Visite</p> <ul style="list-style-type: none"> <li>• Beurteilung mit dem 2-Punkte-Fragebogen im Rahmen jedes Zyklus/bei dem vorgesehenen Patientenbesuch bis zur PD (oder bis zum Beginn der folgenden Krebstherapie, falls diese früher erfolgt)</li> </ul> <p>Untersuchung, ob organspezifische Symptome als Indikatoren für PD dienen können</p> <ul style="list-style-type: none"> <li>• Die folgenden organspezifischen Symptome werden ermittelt: Lungen (Husten, Dyspnoe), Leber (Appetitverlust, Gewichtsabnahme), Knochen (Schmerzen). Zusätzlich wird als generelles Symptom Fatigue bestimmt, als Indikator für PD.</li> </ul>
Tertiäre Zielparameter	Etablierung einer dezentralen, virtuellen Biobank für die zukünftige Erfassung und zentrale Analyse von prädiktiven Biomarkern des CDK4/6-Signalwegs.
Haupt-Einschlusskriterien	<ol style="list-style-type: none"> <li>1. Eine persönlich unterschriebene Einverständniserklärung muss vor Beginn der protokollspezifischen Abläufe, inklusive der voraussichtlichen Kooperation der Patientin für die Behandlung und das Follow-up eingeholt werden und gemäß der lokalen behördlichen Vorgaben aufgenommen und dokumentiert werden</li> <li>2. Frauen mit bestätigter Diagnose von fortgeschrittenem Adenokarzinom der Brust, als lokal fortgeschritten, inoperabel oder metastasiert definiert</li> <li>3. Hormonrezeptor-positive (HR+) Erkrankung, definiert als Östrogenrezeptor-positiv (ER+) und/oder Progesteronrezeptor-positiv (PgR+)</li> <li>4. Humaner epidermaler Wachstumsfaktor-Rezeptor 2-negative (HER2-) Erkrankung (HER2 neg/+ oder Her2++ mit CISH/FISH neg.)</li> <li>5. Postmenopausale Frauen oder prä-/perimenopausale Frauen, die eine begleitende Therapie mit einem luteinisierenden Hormon Releasing-Hormon (LHRH) Agonisten erhalten oder bei denen eine Ovarablation durchgeführt wurde.</li> <li>6. Alter <math>\geq</math> 18 Jahre</li> <li>7. Messbare Läsionen nach RECIST (<i>Response Evaluation Criterion in Solid Tumors</i>) oder nur Knochenmetastasen (bone-only)</li> <li>8. Geeignet für eine Kombinationstherapie mit Palbociclib und</li> </ol>

	<p>-Letrozol in der Erst und Folgelinien oder          -Anastrozol in der Erstlinie oder          -Exemestan in der Erstlinie oder          -Fulvestrant in der Erst- und Folgelinie (nach endokriner Therapie)</p> <p>9. ECOG Status 0-2          10. Ausreichende Organ- und Knochenmarksfunktion          11. Auflösung aller akuten toxischen Effekte von früheren Therapien, inklusive Radiotherapie, Grad <math>\leq 1</math> (ausgenommen Toxizitäten, die nicht als Sicherheitsrisiko für die Patientin eingestuft werden), sowie Erholung nach chirurgischen Eingriffen</p> <p>Deutschkenntnisse (fließend in Wort und Schrift)</p>
Haupt-Ausschlusskriterien	<ol style="list-style-type: none"> <li>1. Vorherige Behandlung mit einem CDK4/6-Inhibitor</li> <li>2. Vorherige adjuvante Therapie mit dem geplanten Kombinationspartner, wenn die letzte Einnahme &lt;12 Monate vor Einschluss in die Studie stattfand</li> <li>3. Vorherige palliative Therapie mit dem geplanten Kombinationspartner</li> <li>4. Mehr als eine vorherige palliative Chemotherapie</li> <li>5. Bekannte Hypersensitivität auf Letrozol, Anastrozol, Exemestan oder Fulvestrant oder einem seiner Trägerstoffe</li> <li>6. Verzehr von Nahrungsmitteln oder gegenwärtige Einnahme von Substanzen, welche als starke Inhibitoren oder Auslöser von CYP3A4 bekannt sind</li> <li>7. Gegenwärtige Einnahme von Substanzen, die Johanniskraut beinhalten</li> <li>8. Teilnahme an anderen interventionellen Studien innerhalb der letzten 2 Wochen vor Beginn der Behandlung im Rahmen der vorliegenden Studie</li> <li>9. QTc &gt; 480 msec im Screening-EKG (unter Verwendung der QTcF Formel und/oder der QTcB [Bazett] Formel); Vorgeschichte von QT-Syndrom, Brugada Syndrom oder bekannte Vorgeschichte von verlängerter QTc Zeit oder Torsade de Pointes</li> <li>10. Hohes kardiovaskuläres Risiko einschließlich, aber nicht beschränkt auf kürzlich erfolgten Herzinfarkt, schwere/instabile Angina und schwere Herzrhythmusstörungen in den letzten 6 Monaten vor Einschluss</li> <li>11. Patientinnen mit fortgeschrittener, symptomatischer, viszeraler Metastasenausbreitung, bei denen in kurzer Zeit lebensbedrohliche Komplikationen auftreten können, einschließlich Patientinnen mit massiven unkontrollierten pleuralen, perikardialen, peritonealen Ergüssen, pulmonarer Lymphangitis und Patientinnen bei denen die Leber über 50 % infiltriert ist</li> <li>12. Diagnose jeglicher sekundären malignen Erkrankung innerhalb der letzten 3 Jahre vor Einschluss, ausgenommen eines angemessen behandeltem Basalzell- oder Plattenepithelkarzinom, oder Carcinoma <i>in situ</i> des Gebärmutterhalses</li> </ol> <p>Bereits bekannte, nicht bestrahlte ZNS-Metastasen</p>
Voraussichtlicher Zeitplan	<p>Geplante Studiendauer: ca. 6 Jahre</p> <p>FPI: Sep 2016          LPI: Dez 2018          LPO: Dez 2022          Ende Follow-up: Dez 2022          Daten prim. Zielparame-ter: Juli 2019</p>
Studien- und Referenztherapie	<p>Die Studienbehandlung bestehend aus Palbociclib und endokrin wirksamem Kombinationspartner wird vom Prüfarzt verschrieben und über die lokalen Apotheken bezogen. Palbociclib wird einmal täglich oral in einer Dosis von 125 mg über insgesamt 21 Tage eingenommen, gefolgt von 7 Tagen Therapiepause (Behandlungsschema 3/1).</p> <p>Die Kombinationspartner werden gemäß Produktinformationen verabreicht:</p> <ul style="list-style-type: none"> <li>• Letrozol oral 2,5 mg 1 x täglich, kontinuierlich</li> </ul>



	<ul style="list-style-type: none"> <li>• Anastrozol oral 1mg 1 x täglich, kontinuierlich</li> <li>• Exemestan oral 25mg 1 x täglich, kontinuierlich</li> <li>• Fulvestrant intramuskulär: 1. Zyklus: 500mg 1x Tag 1 und Tag 15; jeder weitere Zyklus: Tag 1</li> </ul> <p>Bei prä- oder perimenopausalen Frauen ist die endokrine Therapie mit einem luteinisierenden Hormon Releasing-Hormon (LHRH) zu kombinieren.</p>
Datenanalyse	<p>Für diese klinische Prüfung gibt es keine formalen Hypothesen zu dem primären Zielparameter sowie zu den sekundären Zielparametern. Die Datenanalyse erfolgt deskriptiv innerhalb der Rekrutierungsgruppe unter Erstlinie bzw. späteren Therapielinien im Rahmen der Primäranalyse. Die Ergebnisse der primären Endpunkt CBR nach 24 Wochen werden in Häufigkeitstabellen mit der Angabe eines 95%-Konfidenzintervalls zusammengefasst.</p> <p>Die Patientengruppe, die hinsichtlich Sicherheit ausgewertet wird, umfasst alle Patientinnen, die mindestens eine Dosis der Studienmedikation erhalten und mindestens eine Sicherheitsbeurteilung in der nachfolgenden Untersuchung durchlaufen haben.</p> <p>Die Darstellung sämtlicher Listings und Tabellen erfolgt bezogen auf die jeweilige Rekrutierungsgruppe (Erstlinien-/Folgelinientherapie).</p> <p>Patientinnenbefragungen (<i>Patient-reported outcomes</i>, PROs) zur gesundheitsbezogenen QoL (FACT-B), Fatigue (BFI) sowie Angst und Depression (HADS-D) erfolgt im Rahmen der Screening-Untersuchungen und danach alle 12 Wochen bis zur PD oder bis zum Beginn der folgenden Krebstherapie, falls diese vor PD beginnt.</p> <p>Deskriptive Statistik wird für die Beurteilung von Messzeitpunkten und Veränderungen im Lauf der Zeit in den Rekrutierungsgruppen Erstlinie/spätere Therapielinien durchgeführt.</p> <p>Korrelationen zwischen CBR und QoL (FACT-B) sowie zwischen der ärztlichen Beurteilung und QoL werden ermittelt.</p> <p>Es wird eine vergleichende Analyse zu Fatigue (BFI-Gesamtscore), QoL (FACT-B-Gesamtscore) und Depressionshäufigkeit nach 12- und 24-wöchiger Behandlung bei Erstlinienpatientinnen der Studienpopulation und Patientinnen, welche eine Erstlinienchemotherapie innerhalb der nicht-interventionellen MaLife-Studie erhalten haben, durchgeführt. Eine Propensity-Score-Analyse zum Matching der MaLife-Subgruppe mit der INGE-B-Erstlinienbehandlungsgruppe hinsichtlich der Baseline-Charakteristika Alter, ECOG, Metastasen, krankheitsfreie Zeit, Art der vorherigen Behandlung und ausgewählte Begleiterkrankungen wird durchgeführt.</p> <p>Mögliche Indikatoren für PD werden durch Korrelation zwischen der Häufigkeit organspezifischer AEs und der PD-Häufigkeit in dem jeweiligen Organsystem zu bestimmten Zeitpunkten ermittelt.</p>

Mammakarzinom – palliative Therapie – 1st-line

**AIO-MAM-0117/ass: Randomisierte, offene, zwei-armige Phase III Studie zur Untersuchung der Wirksamkeit und der Lebensqualität von postmenopausalen Patientinnen mit metastasiertem HER2-negativem, Hormonrezeptor-positivem Brustkrebs unter Erstlinienbehandlung mit einer Ribociclib-Aromataseinhibitor-Kombinationstherapie oder Therapie mit Paclitaxel mit / ohne Bevacizumab. (RIBBIT-Trial)**

**AIO**-assoziierte Studie

Studiennummer/-Code:	AIO-MAM-0117/ass - RIBBIT (IOM-050371 CLEE011ADE04T)
Status:	in Vorbereitung
Rekrutierungszeitraum	2018 – 2020
Weitere Zentren:	Interessierte Zentren wenden sich bitte an den Sponsor
Letzte Aktualisierung	April 2018
Anzahl der initiierten Sites	20
Anzahl eingeschlossener Patienten	0

Leiter der klinischen Prüfung	<i>Prof. Dr. Thomas Decker Elisabethenstraße 19 88212 Ravensburg</i>
Sponsor	<i>iOMEDICO</i>
Studiendesign	<p>Dies ist eine prospektive, randomisierte, offene, zweiarmige, multizentrische interventionelle Phase III Studie in Deutschland. Die Studie wurde konzipiert, um die Wirksamkeit und Sicherheit der Erstlinientherapie mit einer Ribociclib-Aromataseinhibitor (AI)-Kombination im Vergleich zu Paclitaxel mit oder ohne Bevacizumab bei Patientinnen mit HR-positive, HER2-negativen Brustkrebs mit viszeralen Metastasen zu untersuchen.</p> <p>160 Patientinnen werden eingeschlossen und 1:1 randomisiert (stratifiziert nach dem Vorhandensein von Lungen- und/oder Lebermetastasen) um</p> <p>Arm A: eine Kombination aus Ribociclib mit AI; ODER</p> <p>Arm B: Paclitaxel mit/ohne Bevacizumab</p> <p>zu erhalten. Die Verabreichung von Paclitaxel als Monotherapie oder Kombinationstherapie mit Bevacizumab wird der Entscheidung des Arztes überlassen. Wenn jedoch 50% der Patienten in Arm B entweder eine Paclitaxel-Monotherapie oder eine Kombinationstherapie aus Paclitaxel und Bevacizumab erhalten haben, wird diese entsprechende Behandlungsoption geschlossen und es kann nur noch die andere Therapieoption gegeben werden. Sollten Patienten eine adjuvante AI-Therapie erhalten haben, wird empfohlen, dass Ribociclib mit einem steroidal AI kombiniert wird, wenn ein nicht-steroidaler AI in der Adjuvanz gegeben wurde und andersherum.</p> <p>Die Therapie wird bis zur Krankheitsprogression, nicht tolerierbarer Toxizität oder dem Tod fortgesetzt. Das progressionsfreie Überleben (PFS) wird basierend auf der Beurteilung des Tumors nach RECIST v1.1 durch den lokalen Radiologen/Prüfarzt bestimmt. Die Behandlung kann über einen nach RECIST definierten Progress hinaus weitergeführt werden, wenn dieser vernachlässigbar oder klinisch irrelevant ist und bis zur klinisch relevanten Krankheitsprogression oder bis zur symptomatischen Verschlechterung fortgesetzt werden.</p> <p>Die endokrine Therapie mit dem AI im Ribociclib + AI Arm kann nach Absetzen von Ribociclib fortgesetzt werden. Der Abbruch von Ribociclib und</p>

	<p>AI (oder AI, falls Ribociclib schon vorher beendet wurde) ist als Ende der Therapie (EOT) definiert. Die anti-VEGF Therapie im Paclitaxel-Arm kann nach Absetzen von Paclitaxel fortgesetzt werden. Wenn Paclitaxel für mehr als 4 Wochen verzögert wird, muss die Chemotherapie beendet werden. Die Beendigung von Paclitaxel und Bevacizumab (oder Bevacizumab, falls Paclitaxel vorher abgebrochen wurde) ist als EOT definiert.</p> <p>Nach EOT nehmen die Patienten an der Nachbeobachtung teil, welche für alle Patienten eine 30-tägige Sicherheitsnachbeobachtung und eine Überlebensnachbeobachtung bis zum Tod bzw. maximal bis 48 Monate nach Randomisierung des letzten Patienten, einschließt. Bei Patienten, die bei EOT keine Krankheitsprogression haben, wird außerdem die Tumorevaluation bis zum Progress oder dem Start der nachfolgenden Therapie fortgesetzt, je nach dem was zuerst eintritt.</p>
Indikation	Diese Studie schließt erwachsene weibliche, postmenopausale Patientinnen mit HR-positivem, HER2-negativem Brustkrebs mit viszeralem Metastasen ein, die keine vorangegangene Therapie in der fortgeschrittenen Situation erhalten haben.
Prüfpräparat und Vergleichstherapie	<p><i>Ribociclib (LEE011, Kisqali®) oral (an den Tagen 1 bis 21 eines 28-tägigen Zyklus) in Kombination mit einem oralen, einmal täglich eingenommenen AI oder Paclitaxel (an den Tagen 1, 8 und 15 eines 28-tägigen Zyklus) mit oder ohne Bevacizumab (an den Tagen 1 und 15 eines 28-tägigen Zyklus).</i></p> <p><i>Arm A: Ribociclib (600 mg/day) plus AI (entweder Letrozol (2.5 mg/Tag) ODER Anastrozol (1 mg/Tag) ODER Exemestan (25 mg/Tag))</i></p> <p><i>Arm B: Paclitaxel (90 mg/m<sup>2</sup>) ± Bevacizumab (10 mg/kg)</i></p>
Anzahl von Patienten und Studienzentren	160 Patientinnen in 30 Zentren (niedergelassene Onkologen und Gynäkologen, onkologische Ambulanzen und Kliniken)
Studienrationale	<p>Die endokrine Therapie stellt die wichtigste Therapiestrategie des HR-positiven, HER2-negativen Mammakarzinoms dar, da diese Zellen abhängig von Signalen des Östrogen-Rezeptors (ER) sind. Die Kombination aus endokriner Therapie mit zielgerichteter Therapie kann die Wirkung weiter verstärken.</p> <p>Ribociclib (LEE011, Kisqali®) ist ein oral bioverfügbarer, selektiver Inhibitor der Cyclin-abhängigen Kinasen CDK4/6. Diese sind Proto-Onkogene, die, wenn sie an ihr Regulatorprotein Cyclin D1 gebunden sind, die Progression des Zellzyklus aus der G1- zur S-Phase regulieren. Dies stellt einen Schlüsselschritt in der zellulären Proliferation dar. Änderungen im CDK4/6 Signalweg werden als wichtige Antreiber der Brustkrebsentstehung und auch der endokrinen Resistenz angesehen. In klinischen Studien wurde die antitumorale Aktivität von Ribociclib gezeigt. Die Phase III Studie in 668 Patientinnen (MONALEESA-2), welche die Kombinationstherapie aus Ribociclib mit Letrozol gegen Placebo mit Letrozol verglichen hat, zeigte, dass eine Zugabe von Ribociclib zu Letrozol das progressionsfreie Überleben (PFS) der HR-positiven, HER2-negativen Patientinnen mit fortgeschrittenem Brustkrebs inklusive derer mit Metastasen in der Lunge oder Leber verbessert (alle Patienten: HR 0,56; 95% CI 0,43-0,72; Patientinnen mit Leber- oder Lungenmetastasen: HR 0,57; 95% CI 0,41-0,79) (Hortobagyi et al. 2016). Die häufigsten unerwünschten Ereignisse (UE) von Grad 3/4, die im Zusammenhang mit der Ribociclib-Gabe auftraten, waren Neutropenie (59,3% vs. 0,9% in der Placebo-Gruppe) und Leukopenie (21,0% vs. 0,6%). Die meisten unerwünschten Ereignisse waren durch Dosisreduktionen oder Therapieunterbrechungen reversibel. Zusammenfassend stellt die Zugabe des CDK4/6-Inhibitors Ribociclib zu Letrozol eine vielversprechende chemotherapiefreie Behandlungsoption für metastasierten Brustkrebs dar.</p> <p>Daten aus dem deutschen Register zeigen, dass mehr als die Hälfte der Patienten mit einem HR-positiven Karzinom eine Chemotherapie als erste palliative Therapie erhalten. Dies gilt insbesondere für Patienten mit viszeralem</p>

	<p>Metastasierung (Fietz et al. 2017). Die am häufigsten eingesetzte Chemotherapie war Paclitaxel, welches eine der wirksamsten Substanzen bei Brustkrebs darstellt.</p> <p>Die Kombination von Paclitaxel mit dem anti-VEGF (vascular endothelial growth factor) Antikörper Bevacizumab verlängerte das mediane PFS im Vergleich zur Taxan-Monotherapie beim metastasierten Brustkrebs einschließlich der HR-positiven Subgruppe (Alle: 11,8 Monate vs. 5,9 Monate; ER-positiv, PgR-positiv: 14,4 Monate vs. 8,0 Monate) (Miller et al. 2007). In einer weiteren Phase III Studie (Alliance) resultierte die Kombination aus Paclitaxel mit Bevacizumab in einem medianen PFS von 11 Monaten in der Gesamtpopulation und 12,4 Monaten für die Subgruppe der Patienten mit HR-positiver Erkrankung (Rugo et al. 2015). Zusammenfassend stellt Paclitaxel als Monotherapie oder in Kombination mit Bevacizumab eine wirksame und dadurch auch häufig verwendete sowie empfohlene Therapieoption für Patienten mit metastasiertem Mammakarzinom dar.</p> <p>Das Ziel der RIBBIT Studie ist die Untersuchung der Wirksamkeit gemessen am PFS der Kombination von Ribociclib mit AI oder Paclitaxel mit / ohne Bevacizumab bei Patientinnen mit einem HR-positiven, HER2-negativen metastasierten Mammakarzinom mit viszeraler Metastasierung. Zusätzlich werden weitere Wirksamkeitsparameter sowie die Sicherheit und die Lebensqualität (QoL) untersucht. Zudem wird das symptomatische PFS (sPFS) untersucht, welches als Zeitraum von der Randomisierung bis zur symptomatischen Verschlechterung oder dem Tod definiert ist. Dies stellt einen patientenrelevanten Wirksamkeitsparameter dar.</p>
Zielparameter	<p><b>Primäres Studienziel:</b> Vergleich der Wirksamkeit gemessen am PFS der Kombination von Ribociclib mit AI gegen Paclitaxel mit / ohne Bevacizumab als Erstlinientherapie des HR-positiven, HER2-negativen Mammakarzinom mit viszeraler Metastasierung bei postmenopausalen Patientinnen.</p> <p><b>Sekundäre Studienziele:</b> Vergleich der beiden Studienarme hinsichtlich der folgenden Wirksamkeitsparameter: Ansprechraten (ORR), klinische Benefitrate (CBR), Zeit bis zum Ansprechen (TTR) und Gesamtüberleben (OS). Bestimmung der Sicherheit und Verträglichkeit der beiden Behandlungsarme hinsichtlich der (S)UEs, ECOG Performance Status, Routinelaboruntersuchungen und Elektrokardiogramm. Einschätzung und Vergleich der beiden Behandlungsarme in Bezug auf die gesundheitsbezogene Lebensqualität (QoL) mittels Auswertung des EORTC QLQ-C30 Fragebogen sowie weiterer Einzelfragen zur Belastung durch Nebenwirkungen der Therapie und Zeitaufwand für die Therapie</p> <p><b>Exploratives Studienziel:</b> Vergleich beider Therapiearme hinsichtlich des sPFS.</p>
Studienendpunkte	<p><b>Primärer Endpunkt:</b></p> <ul style="list-style-type: none"> <li>• PFS beurteilt durch den lokalen Untersucher mittels RECIST v1.1 Kriterien. PFS ist definiert als Zeit von der Randomisierung bis zur Krankheitsprogression oder Tod jeglicher Ursache, je nach dem, was zuerst auftritt.</li> </ul> <p><b>Sekundäre Endpunkte:</b> <i>Wirksamkeit:</i></p> <ul style="list-style-type: none"> <li>• ORR (komplettes oder partielles Ansprechen) erfasst durch den lokalen Untersucher mittels RECIST v1.1.</li> <li>• CBR (komplettes oder partielles Ansprechen oder stabile Erkrankung für mindestens 24 Wochen) erfasst durch den lokalen Untersucher mittels RECIST v1.1.</li> </ul>

	<ul style="list-style-type: none"> <li>• TTR (Zeit von der Randomisierung bis zum ersten Ansprechen (komplett oder partiell)) erfasst durch den lokalen Untersucher mittels RECIST v1.1.</li> <li>• Gesamtüberleben definiert als Zeit von der Randomisierung bis zum Tod jeglicher Ursache.</li> </ul> <p><i>Sicherheit und Verträglichkeit:</i></p> <ul style="list-style-type: none"> <li>• (Schwerwiegende) Unerwünschte Ereignisse ((S)UE): Häufigkeit und Schweregrad gemäß CTCAE v4.03 bis 30 Tage nach Ende der Therapie</li> <li>• Zeit bis zur Verschlechterung des ECOG Performance Status um mindestens einen Punkt</li> <li>• Routinelaboruntersuchungen bis zum Therapieende</li> <li>• Elektrokardiogramm (EKG) bis zum Therapieende</li> </ul> <p><i>Vom Patienten berichtete Lebensqualität:</i></p> <ul style="list-style-type: none"> <li>• Zeit bis zur Abnahme des Wertes der Skala „globaler Gesundheitsstatus“ des EORTC QLQ-C30 Fragebogens um mindestens 10 Punkte</li> <li>• Veränderung im Vergleich zur Baseline der Skala „globaler Gesundheitsstatus“ und aller funktionellen und Symptom –Skalen des EORTC QLQ-C30</li> <li>• Fläche unter der Kurve der Skala „globaler Gesundheitsstatus“ und aller funktionellen und Symptom-Skalen des EORTC QLQ-C30 unter Studienmedikation von Baseline bis Woche 24 und von Baseline bis 1, 2 und 3 Jahre danach</li> <li>• Belastung durch Nebenwirkungen der Therapie zu allen Fragebogenzeitpunkten (Einzelfrage)</li> <li>• Zeitliche Belastung durch die Therapie zu allen Fragebogenzeitpunkten (vier Einzelfragen)</li> </ul> <p><b>Explorativer Endpunkt:</b></p> <ul style="list-style-type: none"> <li>• sPFS, definiert als Zeit von der Randomisierung bis zur symptomatischen Verschlechterung (neue oder Verschlechterung bestehender Symptome) gemäß Beurteilung des lokalen Untersuchers oder Tod jeder Ursache</li> </ul>
<i>Haupt-Einschlusskriterien</i>	<ul style="list-style-type: none"> <li>• Alter <math>\geq</math> 18 Jahre.</li> <li>• Postmenopausale Frauen.</li> <li>• Frauen mit vor Ort bestätigter Diagnose eines metastasierten Adenokarzinom der Brust ohne vorangegangene systemische antineoplastische Therapie in der palliativen Situation.</li> <li>• Hormonrezeptor (HR)-positive Erkrankung, definiert als Östrogenrezeptor (ER)-positiv und / oder Progesteronrezeptor (PgR)-positiv.</li> <li>• Human epidermal growth factor receptor 2 (HER2)-negative Erkrankung, definiert als IHC-Status HER2 negativ/+ oder IHC HER2++ bei CISH/FISH negativem Befund.</li> <li>• Vorhandensein von viszerale Metastasen (zusätzlich können weitere nicht-viszerale Metastasen vorhanden sein).</li> <li>• Vorliegen von Zielläsionen und / oder nicht-Zielläsionen gemäß RECIST v1.1.</li> <li>• Patienten müssen gemäß der entsprechenden Fachinformationen für eine palliative Therapie mit Ribociclib + AI und Paclitaxel +/- Bevacizumab qualifizieren.</li> <li>• Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.</li> <li>• Ausreichende Organ- und Knochenmarksfunktion innerhalb 7 Tage vor Randomisierung.</li> <li>• Standard 12-Kanal EKG Werte: QTcF Intervall im Screening <math>&lt;</math> 450 msec; durchschnittlicher Ruhepuls von 50-90 bpm</li> <li>• Unterschriebene, schriftliche Einwilligung nach erfolgter Aufklärung vor Beginn von protokollspezifischen Maßnahmen.</li> </ul>
<i>Haupt-Ausschlusskriterien</i>	<ul style="list-style-type: none"> <li>• Jegliche vorangegangene Palliativtherapie.</li> <li>• Vorangegangene Therapie mit irgendeinem CDK4/6 Inhibitor.</li> </ul>

	<ul style="list-style-type: none"> <li>• Vorgegangene adjuvante Therapie mit einem AI, wenn die letzte Einnahme weniger als 12 Monate vor Studieneinschluss zurückliegt.</li> <li>• Vorgegangene adjuvante oder neoadjuvante Therapie mit einem Taxan, wenn die letzte Verabreichung innerhalb von 12 Monaten vor Studieneinschluss war.</li> <li>• Die Patientin erhält gleichzeitig eine andere anti-tumorale Therapie</li> <li>• Die Patientin hatte in den letzten 28 Tagen vor Randomisierung eine große Operation oder hat sich noch nicht von den bedeutenden Nebenwirkungen einer solchen erholt oder die Wunde ist noch nicht verheilt.</li> <li>• Die Patientin hat vor Randomisierung eine Bestrahlung erhalten (innerhalb von 4 Wochen eine extended-field Bestrahlung oder innerhalb von 2 Wochen eine limited-field Bestrahlung).</li> <li>• Bekannte Überempfindlichkeit gegen Ribociclib, AI, Paclitaxel, Bevacizumab oder irgendeinen ihrer Inhaltsstoffe.</li> <li>• Klinisch signifikante, unkontrollierte Herzerkrankung und / oder kardiale Repolarisationsanomalität (z.B. Vorgeschichte eines Myokardinfarktes innerhalb von 6 Monaten vor Studieneinschluss, verlängerte QT-Zeit, Long-QT-Syndrom, klinisch signifikante Herzrhythmusstörung oder systolischer Blutdruck von &gt; 150 oder &lt; 90 mmHg oder diastolischer Blutdruck von &gt; 100 mmHg).</li> <li>• Die Patientin hatte eine arterielle Thrombose, die weniger als 12 Monate zurückliegt.</li> <li>• Die Patientin hat eine Proteinurie (<math>\geq 2+</math> auf dem Protein Messstäbchen)</li> <li>• Die Patientin hat eine angeborene Blutungsneigung, eine erworbene Gerinnungsstörung oder nimmt die volle Dosis Anti-Koagulanzen ein</li> <li>• Die Patientin erhält gleichzeitig einen starken Induktor oder Inhibitor von CYP3A4/5 oder eine Medikation mit engem therapeutischen Fenster welches vorwiegend durch CYP3A4/5 metabolisiert wird und diese kann nicht innerhalb von 7 Tagen vor Beginn der Studienmedikation abgesetzt werden.</li> <li>• Bekanntes Vorhandensein zerebraler Metastasen mit Ausnahme, wenn der Abschluss der letzten Therapie (einschließlich Bestrahlung und / oder Operation) mindestens 4 Wochen vor Start der Studienbehandlung liegt und der ZNS Tumor zum Zeitpunkt des Screening klinisch stabil ist.</li> <li>• Patientin erhält gleichzeitig Warfarin oder ein anderes von Kumin abgeleitetes Anti-Koagulant in therapeutischer, prophylaktischer oder anderer Indikation. Eine Therapie mit Heparin, niedermolekularem Heparin oder Fondaparinx ist erlaubt.</li> <li>• Die Patientin erhält gleichzeitig oder innerhalb von 2 Wochen vor Beginn der Studienmedikation systemische Kortikosteroide oder andere chronische Immunsuppressiva.</li> <li>• Patientin mit fortgeschrittener, symptomatischer viszeraler Tumorausbreitung unter Risiko kurzfristiger lebensgefährlicher Komplikationen (einschließlich Patientinnen mit massivem, unkontrolliertem Erguss [pleural, perikardial, peritoneal], pulmonale Lymphangiosis carcinomatosa, und mehr als 50% Leberbefall).</li> <li>• Patientin mit bekannter Anamnese einer HIV Infektion (Testung ist nicht vorgeschrieben).</li> <li>• Patientin hat gleichzeitig eine andere schwere und / oder unkontrollierte Krankheit, welche im Ermessen des Prüfers ein nicht akzeptables Sicherheitsrisiko darstellt, gegen eine Studienteilnahme der Patientin spricht oder die Einhaltung des Protokolls gefährdet (z.B. chronische Pankreatitis, chronische aktive Hepatitis, aktive unbehandelte oder unkontrollierte Infektion durch Pilze, Bakterien oder Viren, etc.).</li> <li>• Vorgegangene Teilnahme an einer klinischen Prüfung innerhalb von 30 Tagen oder 5 Halbwertszeiten des Prüfpräparats vor Randomisierung, je nach dem was länger ist.</li> </ul>
Erfassung der Wirksamkeit	<ul style="list-style-type: none"> <li>• Tumorbeurteilung (CT/MRT und klinische Beurteilung) zu Baseline und anschließend alle 12 Wochen bis zur Tumorprogression oder, falls dies früher erfolgt, dem Beginn der nachfolgenden Therapie.</li> </ul>

	<ul style="list-style-type: none"> <li>• Ganzkörper-Knochen-Scan zu Baseline und bei klinischer Indikation.</li> <li>• Überlebensstatus alle 6 Monate unabhängig von Therapieabbruchgrund bis zum Tod oder, fall dies früher eintritt, dem Studienende</li> </ul>
<i>Erfassung der Sicherheit</i>	<ul style="list-style-type: none"> <li>• Kontinuierliche Erfassung und Einstufung aller UEs einschließlich der SUEs bis 30 Tage nach Therapieabbruch</li> <li>• ECOG Performance Status zu Baseline und anschließend alle 12 Wochen bis zur Tumorprogression.</li> <li>• Überwachung von Routinelaborparametern zu Baseline und jedem nachfolgenden Zyklus bis Therapieabbruch.</li> <li>• EKG zur Bestimmung der QT-Zeit zu Baseline und zusätzlich an Tag 15 des ersten und Tag 1 des zweiten Zyklus für Patienten, die in Arm A behandelt werden, sowie klinisch indiziert.</li> </ul>
<i>Erfassung der Lebensqualität</i>	<p><i>Die gesundheitsbezogene Lebensqualität (QoL) wird mittels des validierten European Organization for Research and Treatment of Cancer's core quality of life (EORTC QLQ-C30) Fragebogen erhoben. Zudem wird den Patientinnen eine Frage zur Belastung durch die Nebenwirkungen der Therapie und vier Fragen zur zeitlichen Belastung durch die Therapie gestellt.</i></p> <p><i>Alle Patientinnen werden zu Baseline vor Beginn der Studientherapie und anschließend alle 12 Wochen über einen Zeitraum von 36 Monaten befragt, sowie zum Zeitpunkt der Tumorprogression. Der Fragebogen zu Baseline und zum Zeitpunkt der Progression werden vom Zentrum ausgegeben, alle anderen werden 12-wöchentlich durch die iOMEDICO SMO GmbH bereitgestellt.</i></p>
<i>Andere Erfassungsparameter</i>	N.a.
<i>Data Analysis</i>	<p><i>Zwei Interims- und eine finale Analyse werden durchgeführt.</i></p> <p><i>Die erste Interimsanalyse (IA) wird durchgeführt nachdem 30 Patientinnen pro Arm rekrutiert und für 3 Monate beobachtet wurden. Der Fokus dieser IA liegt auf der deskriptiven Analyse der 3-Monats Ansprechrate. Die Analyse umfasst auch demographische Daten zu Baseline und Sicherheitsdaten (UEs).</i></p> <p><i>Eine zweite Interimsanalyse (IA) wird durchgeführt sobald 60 Patientinnen pro Arm rekrutiert und für 3 Monate beobachtet wurden. Diese IA umfasst eine deskriptive Analyse der 3-Monats Ansprechrate und der CBR. Die Analyse beinhaltet auch demographische Daten zu Baseline und Sicherheitsdaten (UEs).</i></p> <p><i>Die finale Analyse wird nach dem Ende der Studie durchgeführt und liefert Daten zu allen Endpunkten.</i></p> <p>Analyse Populationen:</p> <p>Die Analysen zur Wirksamkeit werden basierend auf der Intention-to-Treat (ITT) Population durchgeführt, welche aus allen randomisierten Patienten besteht. Die Patienten werden in dem Arm analysiert, in den sie randomisiert wurden unabhängig davon, ob sie die vorgesehene Therapie erhalten haben oder nicht.</p> <p>Das Per-Protokoll Set (PPS) besteht aus der Untergruppe der Patienten der ITT, welche den Anforderungen des Studienprotokolls entsprechen, d.h. die Patienten ohne irgendwelche schwerwiegenden Protokollverletzungen.</p> <p>Die Sicherheitspopulation (SAF) besteht aus allen Patienten, die Studienmedikation erhalten haben. Die Analyse wird stratifiziert nach der tatsächlich erhaltenen Therapie. Diese Population stellt die</p>

Analysepopulation für alle Sicherheitsanalysen dar.

Das QoL Set (QoLS) besteht aus der Untergruppe der Patienten aus der SAF, die den Fragebogen zu Baseline ausgefüllt und zurückgesendet haben (wobei mindestens eine Antwort gegeben worden sein muss). Alle Lebensqualitätsanalysen beruhen auf dieser Zusammenstellung.

Subgruppen:

Taxan-haltige Vortherapie

Die finale Analyse der Wirksamkeit und der Patientencharakteristika wird pro Studienarm stratifiziert nach vorangegangener Taxantherapie (ja/nein)

Lungen- oder Lebermetastasen

Die primäre Analyse wird stratifiziert nach dem Vorhandensein von Lungen- oder Lebermetastasen (Lunge und Leber / Lunge, aber keine Leber / Leber, aber keine Lunge / weder Lunge noch Leber)

Paclitaxel +/- Bevacizumab

Die finale Analyse der Wirksamkeit, Sicherheit und Patientencharakteristika im Paclitaxel +/- Bevacizumab-Arm wird stratifiziert nach Therapie mit Bevacizumab (ja/nein).

Analyses:

Primäre Wirksamkeitsanalyse:

PFS wird mittels der Kaplan-Meier Methode berechnet. Das PFS ist definiert als Zeit von der Randomisierung bis zur Krankheitsprogression oder dem Tod (vor Beginn der Nächstlinientherapie), je nach dem was zuerst eintritt. Falls vor Beginn der nächsten Therapie oder dem Ende der individuellen Beobachtung weder eine Progression noch der Tod eingetreten ist, wird mit dem Zeitpunkt der letzten Tumorevaluation vor Beginn der nachfolgenden Therapie zensiert. Für jeden Arm wird die Anzahl an Ereignissen und alle Quartile inklusive des 95%-Konfidenzintervalls dargestellt. Zudem werden die PFS-Raten nach 6 Monaten, 12 Monaten und 18 Monaten bestimmt. Das PFS der beiden Arme wird durch einen stratifizierten zweiseitigen Log-Rank-Test mit einem Signifikanzniveau von 0,05 verglichen. Stratifiziert wird entsprechend der Strata, die im Randomisierungsvorgang verwendet wurden.

Sekundäre Wirksamkeitsanalysen:

Absolute und relative Häufigkeiten der Gesamtansprechrates (ORR, komplettes oder partielles Ansprechen) nach 3 Monaten Therapie und gesamt werden für jeden Arm bestimmt.

Absolute und relative Häufigkeiten der CBR (komplettes oder partielles Ansprechen oder stabile Erkrankung für mindestens 24 Wochen) werden für jeden Arm bestimmt.

TTR wird mittels Kaplan-Meier-Methode berechnet. TTR ist definiert als Zeitraum von der Randomisierung bis zum ersten Auftreten eines Ansprechens jeder Art (komplettes oder partielles Ansprechen bestimmt durch den lokalen Untersucher). Wenn niemals ein Ansprechen erreicht wird, wird zensiert

mit der maximalen Beobachtungszeit (LPLV) für Patienten mit Krankheitsprogression oder die verstorben sind

mit dem Datum der letzten Tumorevaluation für Patienten, die zum Ende der Studie leben und deren Erkrankung nicht progredient ist.



	<p>TTR wird dargestellt mit Quartilen inklusive Median, sowie den Raten nach 3 Monaten und 6 Monaten. Für all diese Parameter wird das 95% Konfidenzintervall mit angegeben. Zusätzlich wird die Häufigkeit der Ereignisse (Anzahl von Patienten mit komplettem oder partiellem Ansprechen) dargestellt.</p> <p>Das OS wird mittels Kaplan-Meier Methode berechnet. Es ist definiert als Zeit von der Randomisierung bis zum Tod jeglicher Ursache. Patienten, die zum Ende der Studie noch leben, werden mit dem Datum des letzten Kontaktes zensiert. Die Häufigkeit der Ereignisse und die Quartile unter Angabe des 95% Konfidenzintervall werden dargestellt. Zusätzlich wird die OS-Rate nach 2 Jahren, 3 Jahren und 4 Jahren mit dem entsprechenden 95% Konfidenzintervall dargestellt.</p> <p>Explorative Wirksamkeitsanalyse:</p> <p>sPFS wird mittels Kaplan-Meier Methode berechnet. Das sPFS ist definiert als Zeitraum von der Randomisierung bis zur symptomatischen Verschlechterung (Aufreten neuer oder Verschlechterung bestehender Symptome) oder Tod (vor Beginn der nächsten Therapie), je nachdem, was zuerst eintritt. Falls vor Beginn der nachfolgenden Therapie oder am Ende der individuellen Beobachtung (je nachdem, was zuerst eintritt) keine symptomatische Verschlechterung oder Tod eingetreten ist, wird mit dem Datum des Beginns der nachfolgenden Therapie oder des letzten Kontaktes (was immer zuerst ist) zensiert. Für jeden Arm wird die Anzahl an Ereignissen und alle Quartile des sPFS einschließlich der 95%-Konfidenzintervalle dargestellt.</p> <p>Sicherheitsanalyse:</p> <p>Patienten- und Fall-bezogene Häufigkeiten und Anteile in jedem Therapiearm werden hinsichtlich des Auftretens der folgenden Ereignisse berechnet</p> <p>UEs</p> <p>SUEs</p> <p>UEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab</p> <p>SUEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab</p> <p>UEs, die zum Abbruch von Ribociclib, AI, Paclitaxel, Bevacizumab führen</p> <p>gesamt sowie nach CTCAE Schweregrad.</p> <p>Auftretenshäufigkeit von UE (MedDRA-Preferred Term nach Systemorganklasse) in jeder Therapiegruppe wird berechnet für</p> <p>UEs</p> <p>SUEs</p> <p>UEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab</p> <p>SUEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab</p> <p>UEs, die zum Abbruch von Ribociclib, AI, Paclitaxel, Bevacizumab führen</p> <p>gesamt sowie nach CTCAE Schweregrad</p> <p>Verschlechterung des ECOG Performance Status wird mittels Kaplan-Meier Methode berechnet. Eine Abnahme um mindestens einen Punkt verglichen mit der Baseline wird als Ereignis erachtet. Falls der ECOG Performance Status bis zum Ende der Beobachtung nicht abgefallen ist, dann wird mit dem Zeitpunkt der letzten ECOG Bestimmung zensiert. Die mediane Zeit bis zur Verschlechterung (einschließlich 95%-Konfidenzintervall), Häufigkeiten</p>
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	<p>von Ereignissen und Rate zu 12 Monaten (mit 95%-Konfidenzintervall) werden für beide Therapiearme angegeben.</p> <p>Ergebnisse aus Routinelaboruntersuchungen werden auf Patienten-Ebene in Listings dargestellt.</p> <p>QoL Analysen:</p> <p>Die Zeit bis zur Abnahme des globalen Gesundheitsstatus Skalenwerts des EORTC QLQ-C30 um 10 Punkte wird mittels Kaplan-Meier Methode berechnet. Eine Abnahme von mindestens 10 Punkten im Vergleich zum Baseline Wert wird als Ereignis erachtet. Daten von Patienten, die keine Abnahme von mindestens 10 Punkten haben, werden mit Datum des letzten ausgefüllten Fragebogens zensiert. Die Analyse wird in der Subgruppe der Patienten ohne fehlende Fragebogen zwischen zwei ausgefüllten Fragebogen durchgeführt. Die mediane Zeit bis zur Verschlechterung (einschließlich 95% Konfidenzintervall), Häufigkeiten der Ereignisse und 12 Monatsrate (mit 95% Konfidenzintervall) wird für jede Behandlungsgruppe dargestellt.</p> <p>Veränderung von der Baseline im globalen Gesundheitsstatus Skalenwert und den funktionellen und Symptomskalen des EORTC QLQ-C30 werden für jede Behandlungsgruppe mittels deskriptiver Statistik beschrieben.</p> <p>Die Fläche unter der Kurve in den Skalenwerten des EORTC QLQ-C30 werden mittels deskriptiver Statistik für die Behandlungsgruppen zu den nachfolgenden Zeitpunkten dargestellt:</p> <p>Baseline bis 24 Wochen nach Therapiebeginn</p> <p>Baseline bis 1 Jahr nach Therapiebeginn</p> <p>Baseline bis 2 Jahre nach Therapiebeginn</p> <p>Baseline bis 3 Jahre nach Therapiebeginn</p> <p>Die Analysen werden für alle Patienten durchgeführt, für die die Baseline und der jeweilig letzte Fragebogen vorhanden ist und für die weniger als die Hälfte der Fragebogen / Skalen fehlt. Fehlende Werte werden mittels eines Regressionsmodells unter Berücksichtigung der Baseline Charakteristika ersetzt.</p> <p>Eine Sensitivitätsanalyse wird für die Fläche unter der Kurve in denjenigen Versuchspersonen durchgeführt, für die alle Fragebogen / Skalen bis zum jeweiligen Zeitpunkt vorhanden sind. Jede der genannten Analysen wird nur dann berechnet, falls mindestens 20 Patientinnen pro Behandlungsgruppe auswertbar sind.</p> <p>Die Belastung durch Nebenwirkungen (Einzelfrage) wird pro Arm und Zeitpunkt mit Häufigkeiten und Anteil dargestellt</p> <p>Die zeitliche Belastung durch die Therapie (vier Einzelfragen) wird pro Behandlungsarm und Fragebogenzeitpunkt mit Häufigkeiten und Anteil dargestellt.</p>								
<i>Geplante Studiendauer</i>	<table> <tr> <td><i>Einschluss des ersten Patienten</i></td> <td><i>Q2/2018</i></td> </tr> <tr> <td><i>Einschluss des letzten Patienten</i></td> <td><i>Q4/2020</i></td> </tr> <tr> <td><i>Letzte Visite des letzten Patienten</i></td> <td><i>Q4/2024</i></td> </tr> <tr> <td><i>Finale Analyse / Studienbericht</i></td> <td><i>Q4/2025</i></td> </tr> </table>	<i>Einschluss des ersten Patienten</i>	<i>Q2/2018</i>	<i>Einschluss des letzten Patienten</i>	<i>Q4/2020</i>	<i>Letzte Visite des letzten Patienten</i>	<i>Q4/2024</i>	<i>Finale Analyse / Studienbericht</i>	<i>Q4/2025</i>
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Schlüsselworte	<p><i>Metastasierter Brustkrebs; viszerale Metastasen; HR+; HER2-; ER+; PgR+; CDK4/6 Inhibitor; Ribociclib; Aromataseinhibitor; Erstlinie; PFS; Lebensqualität Zeitliche Belastung durch die Therapie (einzelner Punkt)</i></p>								



## Arbeitsgruppe Neuroendokrine Tumoren/ Karzinoide

### Neuroendocrine Carcinomas, Neuroendocrine tumors NET G3 with progression after first line chemotherapy

**AIO-NET-0217/ass: A phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in patients with advanced, metastatic high grade neuroendocrine carcinomas NEC G3 (WHO 2010) progressive after first line chemotherapy (AveNEC-Trial)**

#### AIO-assozierte Studie

Studiennummer/-Code:	AIO-NET-0217/ass - AveNEC-Trial
Status:	In Rekrutierung
Rekrutierungszeitraum:	Nicht bekannt
Weitere Zentren:	Sind leider nicht möglich
Letzte Aktualisierung	April 2018

APPLICANT/ COORDINATING INVESTIGATOR	Univ.-Prof. Dr. Matthias M. Weber, Unit of Endocrinology, I. Med. Department Langenbeckstraße 1, 55131 Mainz Sponsor Johannes Gutenberg-University Mainz
CONDITION	Patients with advanced neuroendocrine carcinomas NEC G3 (WHO 2010) (excluding SCLC and Merkel cell carcinomas) who experienced tumor progression within 9 months after prior chemotherapy
OBJECTIVE(S)	To assess the clinical activity of avelumab as determined by the disease control rate (DCR) according to RECIST1.1 from start of study drug until documented disease progression (PD), assessed every 8 weeks for the first 6 month and every 12 weeks thereafter. Secondary objectives; objective reponse rate, best overall response, duration of disease control, progression-free survival overall survival, quality of life, safety and tolerability.
INTERVENTION(S)	Avelumab at a dose of 10 mg/kg as a 1h intravenous (i.v.) infusion every two weeks (Q2W).
KEY EXCLUSION CRITERIA	Small cell lung cancer and Merkel cell carcinomas Typical or Atypical Carcinoid of the lung with a Ki67 < 20% Prior therapy with any antibody/drug targeting T-cell co-regulatory proteins Major surgery within 4 weeks of first dose of study medication. TACE, TAE, SIRT or PRRT within 3 months of starting study treatment Patients pretreated with Interferon as last treatment line prior to study entry Concurrent anticancer treatment within 28 days before the start of trial treatment active infection requiring systemic therapy including, HIV/AIDS, HBV or HCV Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent Pregnancy or lactation Vaccination within 4 weeks of the first dose of avelumab and while on trial Abnormal kidney function (eGRF < 60 ml/min)

KEY INCLUSION CRITERIA	<p>male or female patient <math>\geq</math> 18 years</p> <p>Histologically proven neuroendocrine neoplasia NEC G3 (WHO 2010)</p> <p>One block or 20 slides (4 microns) of archival tumor tissue to perform central pathological review and biomarker assessment</p> <p>No curative option available</p> <p>Progressive disease within 9 months after prior first line chemotherapy (platinum based chemotherapy or STZ/TEM/DTIC based chemotherapy in NET G3)</p> <p>Presence of measurable disease as per RECIST1.1 criteria</p> <p>ECOG Performance Status 0 – 2</p> <p>Written informed consent</p>
OUTCOME(S)	activity and safety of avelumab in patients with advanced, metastatic high grade neuroendocrine carcinomas NEC G3
STUDY TYPE	phase II, open-label, multicenter trial
STATISTICAL ANALYSIS	<p>The primary parameter will be analyzed by an exact binomial test with a one-sided level of significance of 5%. The study uses a Simon's design with a futility stop. An interim analysis of response will be performed 16 weeks after the start of the 20th patient and the study will be stopped if the disease control rate with complete remission (CR), partial remission (PR) or stable disease (SD) according to RECIST1.1 is below or equal to 10 % in the first 20 patients. Dichotomous variables will be displayed by absolute and relative frequencies. For rates 95% Clopper-Pearson confidence intervals will be calculated. Time to event data will be displayed by median time to event times and 95% confidence intervals together with Kaplan Meier plots. The QoL data and duration of disease control and response will be assessed by sample characteristics and 95% confidence intervals.</p>
SAMPLE SIZE	60 patients
TRIAL DURATION	66 months
PARTICIPATING CENTERS	Marburg, Essen, Heidelberg, Halle

Progressive pancreatic neuroendocrine neoplasms**AIO-NET-0117/ass: A multicenter single-arm pilot study of ramucirumab in combination with dacarbazine in patients with progressive well-differentiated metastatic pancreatic neuroendocrine tumors (RamuNet-Trial)****AIO-assoziierte Studie**

Studiennummer/-Code:	AIO-NET-0117/ass – RamuNET-Trial
Status:	in Vorbereitung (Ethikvotum und Verträge)
Rekrutierungszeitraum:	Studienstart Q1/2018-Q1/2019
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	20.09.2017

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Patrick Michl Universitätsklinikum Halle Universitätsklinik für Innere Medizin I Ernst-Grube-Straße 40 06120 Halle (Saale) Phone: +49 (0) 345 - 557 2661 Fax: +49 (0) 345 - 557 2253 E-Mail: patrick.michl@uk-halle.de
CONDITION	Pancreatic neuroendocrine tumors (pNET)
OBJECTIVE(S)	The aim of this study is to investigate whether ramucirumab in combination with dacarbazine has an effect on the disease-control rate at 6 months in patients with progressive pancreatic NET.
INTERVENTION(S)	During the study each patient with progressive PNET will receive chemotherapy with DTIC (650mg/m <sup>2</sup> d1 every 4 weeks iv) plus ramucirumab (8mg/kg d1 + d15 iv)
KEY EXCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Pregnancy (positive urin or blood pregnancy test) or lactation.</li> <li>• Secondary malignancy in patient's history with the exception of: disease-free period &gt; 5 years before randomization or non-melanoma skin cancer or curatively treated cervical carcinoma in situ or other noninvasive in situ neoplasm.</li> <li>• Allergy against dacarbazine or ramucirumab</li> <li>• Current enrolment or participation within the last 4 weeks in a clinical drug trial</li> <li>• Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol therapy.</li> <li>• Insufficient liver function: cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.</li> <li>• Uncontrolled or poorly-controlled hypertension (&gt;160 mmHg systolic or &gt; 100 mmHg diastolic for &gt;4 weeks) despite standard medical management</li> <li>• Chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted</li> <li>• Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy.</li> <li>• History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to first dose of protocol therapy</li> <li>• Uncontrolled severe physical or mental disorders such as: neurological or</li> </ul>

	<p>psychiatric disorders including seizure, advanced dementia, psychosis, active uncontrolled infections or sepsis, HIV, replicative hepatitis B or C infection</p> <ul style="list-style-type: none"> <li>• History of gastrointestinal perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.</li> <li>• Major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to first dose of protocol therapy. Elective or planned major surgery to be performed during the course of the clinical trial.</li> <li>• Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy.</li> </ul>
KEY INCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Histologically confirmed unresectable metastatic G1-G2 differentiated PNET excluding neuroendocrine carcinomas (NEC). Both non-functional and functional NET can be included.</li> <li>• Age: 18-75 years</li> <li>• Measurable disease (RECIST 1.1)</li> <li>• Progressive disease under treatment with either non-DTIC-based chemotherapy (e.g. 5-FU/ Streptozotocin, capecitabine), SSA analogues, everolimus or sunitinib. No prior therapy with DTIC or temozolomide is allowed. Prior TACE and SIRT are allowed with a minimum of 3 months before study entry, prior PRRT is allowed with a minimum of 12 months before study entry.</li> <li>• If the tumor biopsy is older than 6 months in progressive disease a rebiopsy is mandatory</li> <li>• ECOG 0-1</li> <li>• Life expectancy &gt; 12 weeks</li> <li>• Adequate renal function (serum creatinine <math>\leq 1.5 \times</math> ULN, or creatinine clearance (measured via 24-hour urine collection) <math>\geq 40</math> mL/minute (if serum creatinine is <math>&gt; 1.5 \times</math> ULN, a 24-hour urine collection to calculate creatinine clearance must be performed). Urinary protein is <math>\leq 1+</math> on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is <math>\geq 2+</math>, a 24-hour urine collection for protein must demonstrate <math>&lt; 1000</math> mg of protein in 24 hours to allow participation in this protocol).</li> <li>• Adequate hepatic function (total bilirubin <math>\leq 1.5</math> mg/dL (25.65 <math>\mu</math>mol/L), and aspartate transaminase (AST) and alanine transaminase (ALT) <math>\leq 3.0 \times</math> ULN; or <math>5.0 \times</math> ULN in the setting of liver metastases)</li> <li>• Adequate bone marrow function (absolute neutrophil count <math>&gt; 1,500/\text{mm}^3</math>, platelets <math>&gt; 100,000/\text{mm}^3</math>, hemoglobin <math>&gt; 9</math> g/dL)</li> <li>• Adequate coagulation function (INR <math>\leq 1.5</math> and PTT <math>\leq 5</math> seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.</li> <li>• Pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices)</li> <li>• The patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods, Pearl Index <math>&lt; 1</math>). Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of protocol therapy.</li> <li>• Written informed consent</li> </ul>
OUTCOME(S)	<p><u>Primary endpoint</u></p> <ul style="list-style-type: none"> <li>• Disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria</li> </ul> <p><u>Secondary endpoints</u></p> <ul style="list-style-type: none"> <li>• Objective tumor response (ORR)</li> <li>• progression-free survival (PFS)</li> <li>• overall survival (OS)</li> <li>• toxicity</li> <li>• biochemical response (tumor marker chromogranin A; in cases of functional NET: gastrin, insulin etc.)</li> <li>• QoL (EORTC QLQ-C30 questionnaire)</li> <li>• translational research for predictive biomarkers (e.g. circulating VEGF,</li> </ul>

	ANGPT1/2 and IL8 levels, immunohistochemical VEGFR2 expression)
STUDY TYPE	Prospective single-arm multi-center phase IIa trial
STATISTICAL ANALYSIS	<p>This trial is planned as a pilot study to evaluate the efficacy of combination treatment of ramucirumab and dacarbazine.</p> <p>Primary endpoint is the disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria</p> <p>The sample size calculation follows an exact binomial single-stage design (A'Hern 2001)</p> <p><math>H_0: p \leq p_0 = 60\%</math> versus <math>H_1: p &gt; p_1 = 80\%</math>, <math>\alpha = 0.05</math>, <math>\beta = 0.1</math></p> <p>The design requires 45 subjects recruited to decide whether the disease control rate, <math>p</math>, is less than or equal to <math>p_0 = 60\%</math> or greater than or equal to <math>p_1 = 80\%</math>. Disease control rate (DCR) and two-sided 95% confidence intervals will be calculated (DCR = percentage of patients with CR, PR or SD and binomial proportion confidence interval).</p>
SAMPLE SIZE	To be allocated to trial: 46
TRIAL DURATION	<p>Recruitment period: 12 months</p> <p>Treatment per patient: until disease progression or intolerable toxicity</p> <p>Follow-up per patient: 24 months after begin of treatment.</p> <p>First patient in to last patient out (months): 36</p> <p>Duration of the entire trial (months): 42 months</p> <p>Intended start date: 1<sup>st</sup> quarter 2018</p> <p>Expected end of the study: 3<sup>rd</sup> quarter 2021</p>
PARTICIPATING CENTERS	<ul style="list-style-type: none"> <li>- UK Halle</li> <li>- UKE Hamburg</li> <li>- Zentralklinik Bad Berka</li> <li>- Charité</li> <li>- UKGM Standort Marburg</li> <li>- UK Ulm</li> <li>- UK Göttingen</li> </ul>



Neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET)/

**AIO-NET-0417/ass: A prospective, randomised, Controlled, Open-label, Multicentre phase III study to evaluate efficacy and safety of Peptide Receptor Radionuclide Therapy (PRRT) with <sup>177</sup>Lu-Edotreotide compared to targeted molecular therapy with Everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR pos.), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).**

**<sup>177</sup>Lu-edotreotide vs. everolimus in GEP-NET (COMPETE-Trial)**

**AIO-assozierte Studie**

Studiennummer/-Code: AIO-NET-0417/ass – COMPETE-Trial

Status: in Rekrutierung

Rekrutierungszeitraum: 24 Monate

Weitere Zentren: leider nicht möglich

Letzte Aktualisierung April 2018

APPLICANT/ COORDINATING INVESTIGATOR	ITM Solucin GmbH/ Prof. Dr. Richard Baum Zentralklinik Bad Berka GmbH
CONDITION	Well-differentiated neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET), with positive SSTR expression
OBJECTIVE(S)	<p><b>Primary objective</b> To demonstrate the efficacy of PRRT with <sup>177</sup>Lu-edotreotide to prolong median progression-free survival (mPFS) in patients with inoperable, progressive, SSTR+ GEP-NET, compared to everolimus</p> <p><b>Secondary objectives</b></p> <ol style="list-style-type: none"> <li>1. To assess overall survival (OS) during study period, defined as the date from randomisation until death</li> <li>2. To determine objective response rates (ORR), defined as the proportion of patients achieving partial (PR) or complete response (CR) as best outcome</li> <li>3. To determine disease control rates (DCR), defined as the proportion of patients achieving stable disease (SD), PR or CR as best outcome</li> <li>4. To determine the duration of disease control (DDC), measured from the time of initial diagnosis of response (SD, PR or CR), until diagnosis of progression</li> <li>5. To determine functional response rates (FRR), considering Cg-A and specific hormones (where increased at baseline)</li> <li>6. To assess the safety and tolerability of <sup>177</sup>Lu-edotreotide in GEP-NET patients</li> <li>7. To determine the health-related quality of life (HRQL) in GEP-NET patients during and after therapy (EORTC QLQ-C30 questionnaire)</li> <li>8. To evaluate symptomatic tumour response (EORTC GI.NET21 questionnaire)</li> <li>9. To evaluate the impact of patient characteristics (time from primary diagnosis, time from diagnosis of progression, number of prior therapies (1st vs 2nd line), type of prior therapies, KPS at randomisation) on tumour response</li> <li>10. To evaluate the impact of tumour histology (histological entity, tumour grade, Ki-67 expression, SSTR expression, functional state) as determined in primary or current bioptic tumour specimen on tumour response</li> </ol> <p><b>Tertiary objectives (in <sup>177</sup>Lu-edotreotide patients)</b></p> <ol style="list-style-type: none"> <li>1. To assess differences in tumour and kidney radiation dose estimates, obtained with conventional 2D (planar), compared to hybrid (2D/3D), and 3D (SPECT) imaging</li> <li>2. To evaluate the value of pre-therapeutic SSTR imaging (SRI) to predict tumour response (globally/at lesion level)</li> </ol>

	3. To evaluate the relationship between PRRT radiation dose (in Gy)
INTERVENTION(S)	<ul style="list-style-type: none"> <li>- Slow intravenous infusion/injection (IV) of <math>^{177}\text{Lu}</math>-edotreotide, an octreotide-derived somatostatin analogue containing the chelator DOTA, radiolabelled with n.c.a. lutetium-177, a radio-lanthanide, emitting <math>\beta</math>- and <math>\gamma</math>-radiation</li> <li>- A maximum of four cycles of <math>7.5 \pm 0.7</math> GBq <math>^{177}\text{Lu}</math>-edotreotide</li> </ul>
KEY EXCLUSION CRITERIA	<p>A patient will be excluded from participation in the trial if one or more of the following criteria are met:</p> <ol style="list-style-type: none"> <li>1. Known hypersensitivity to edotreotide or everolimus</li> <li>2. Known hypersensitivity to DOTA, lutetium-177, or any excipient of edotreotide or everolimus or any other Rapamycin derivative</li> <li>3. Known hypersensitivity to lysine, arginine, or any excipient of the nephroprotective amino acid solution</li> <li>4. Prior exposure to any peptide receptor radionuclide therapy (PRRT), including <math>^{177}\text{Lu}</math>-edotreotide, <math>^{90}\text{Y}</math>-edotreotide or other SSTR-targeting agents (e.g. <math>^{177}\text{Lu}</math>-octreotate or high-dose <math>^{111}\text{In}</math>-pentetretotide)</li> <li>5. Prior therapy with mTor inhibitors</li> <li>6. Prior EFR (extended field radiation) to GEP-NET lesions or radioembolisation therapy (e.g. <math>^{90}\text{Y}</math> microspheres, <math>^{131}\text{I}</math>-lipiodol) with administration to the liver</li> <li>7. Therapy with an investigational compound and/or medical device within 30 days or 5 half-life periods (whichever is longer) prior to randomisation</li> <li>8. Subjects who have received a live vaccine up to 4 weeks prior to first dose</li> <li>9. Current therapy with any prohibited medication</li> <li>10. Ongoing toxicity grade 2 according to CTCAE version 4.03 from previous standard or investigational therapies</li> <li>11. Indication for surgical lesion removal with curative potential</li> <li>12. Planned (for the period of study participation): chemotherapy, immunotherapy, radiation therapy, chemo-embolisation, bland embolisation, radio-embolisation, treatment with cyclosporine-A</li> <li>13. Neuroendocrine tumours, not meeting the inclusion criteria: <ul style="list-style-type: none"> <li>• With known non-GEP-NET origin (e.g. pulmonary or gonadal primaries)</li> <li>• Functional GE-NET</li> <li>• NET with unknown primaries (CUP), manifesting as liver metastases</li> <li>• Poorly differentiated neuroendocrine carcinomas(G3)</li> <li>• NET for which no histological specimen for secondary histological analysis can be obtained</li> </ul> </li> <li>14. Total hepatic tumour burden &gt; 70%</li> <li>15. Brain metastases</li> <li>16. Secondary malignoma within previous 5 years (except basalioma)</li> <li>17. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator</li> <li>18. Renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments, as follows: <ul style="list-style-type: none"> <li>• Renal <ul style="list-style-type: none"> <li>○ Serum potassium &gt; 5.0 mmol/L</li> <li>○ Renal obstruction</li> <li>○ Known nephropathy from any cause</li> </ul> </li> <li>• Hepatic <ul style="list-style-type: none"> <li>○ Total bilirubin &gt;1.5 x ULN</li> <li>○ AST or ALT &gt; 2.5 x ULN</li> <li>○ Alkaline phosphatase &gt; 5 x ULN</li> <li>○ Albumin &lt; 3 g/dL, unless prothrombin time is within normal range</li> <li>○ Known cirrhosis or other distinctly restricted liver function</li> </ul> </li> <li>• Cardiovascular <ul style="list-style-type: none"> <li>○ New York Heart Association classification III &amp; IV</li> <li>○ Uncontrolled hypertension</li> </ul> </li> <li>• Haematopoietic</li> </ul> </li> </ol>

	<ul style="list-style-type: none"> <li>○ Platelets <math>\leq 80 \times 10^9/L</math></li> <li>○ Absolute neutrophil count (ANC) <math>&lt; 1 \times 10^9</math> cells/L</li> </ul> <p>19. Pregnant or breast-feeding women. Female patients of childbearing potential or male patients with female partners of childbearing potential, unless willing to practice full and true sexual abstinence or being surgically/permanently sterile or with a history of hysterectomy for women, not willing to practice effective contraception by using: a non-oral, injected or implanted non-oestrogen progesterone based hormonal method, male condom, vaginal diaphragm, cervical cap, intrauterine device, during the study period and for 56 days after treatment in the everolimus group and 66 days in the PRRT group (10 half-lives of <math>^{177}\text{Lu}</math>) after the last treatment cycle.</p> <p>20. Subjects not able to declare meaningful informed consent on their own (e.g. with legal guardian for mental disorders) or any other vulnerable population to that sense (e.g. persons institutionalised, incarcerated etc.).</p>
KEY INCLUSION CRITERIA	<p>All patients must meet all of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Written informed consent</li> <li>2. Male or female <math>\geq 18</math> years of age</li> <li>3. Histologically and clinically confirmed diagnosis of well-differentiated neuro-endocrine tumour of non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET), tumour grade G1 or G2 (Ki-67 <math>&lt; 20\%</math>), unresectable or metastatic</li> <li>4. Availability of existing biopsy specimen from primary tumour or metastasis or, if unavailable, willingness to undergo current biopsy for secondary central analysis</li> <li>5. Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with <math>\geq 1</math> cm in longest diameter, and <math>\geq 2</math> radiological tumour lesions in total. A maximum of 5 target lesions visible on CT/MRI will be defined, thereof not more than 2 lesions per organ</li> <li>6. Somatostatin receptor positive (SSTR<sup>+</sup>) disease, as evidenced by SSTR imaging (SRI) within 4 months prior to randomisation, by: <ul style="list-style-type: none"> <li>• <math>^{68}\text{Ga}</math>-based SSTR PET imaging (e.g. using <math>^{68}\text{Ga}</math>-edotreotide or <math>^{68}\text{Ga}</math>-DOTATATE), or</li> <li>• <math>^{111}\text{In}</math>-pentetreotide SSTR SPECT/planar imaging, or</li> <li>• <math>^{99\text{m}}\text{Tc}</math>-octreotide SSTR SPECT/planar imaging</li> </ul> <p>All target lesions and <math>\geq 90\%</math> of non-target lesions need to be positive for SSTR, demonstrated by adequate tracer uptake, being defined as being “clearly differentiable from background”</p> </li> <li>7. Radiological disease progression, defined as: <ul style="list-style-type: none"> <li>• Progressive disease per RECIST 1.1. criteria, evidenced by consecutive morphological imaging (CT or MRI) with <math>\geq 90</math> days interval during the 12 months prior to randomisation</li> </ul> </li> <li>8. Karnofsky performance status (KPS) scale <math>\geq 70</math></li> <li>9. Life expectancy of at least 6 months</li> <li>10. Glomerular filtration rate (GFR, MDRD) <math>\geq 60</math> mL/min/1.73 m<sup>2</sup></li> <li>11. For patients included in France only, verification and confirmation of their affiliation with a <u>social security</u></li> </ol>
OUTCOME(S)	To demonstrate the efficacy of PRRT with $^{177}\text{Lu}$ -edotreotide to prolong median progression-free survival (mPFS) in patients with inoperable, progressive, SSTR+ GEP-NET, compared to everolimus.
STUDY TYPE	This will be a confirmatory, prospective, randomised, controlled, parallel group, open-label, multi-centre phase III study to evaluate the efficacy and safety of $^{177}\text{Lu}$ -edotreotide in comparison to molecular targeted therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).

STATISTICAL ANALYSIS	<p><b>Primary Variable:</b>  <b>Progression-free survival</b>  Median progression-free survival (mPFS)</p> <p><b>Secondary variables:</b>  <b>Efficacy</b></p> <ol style="list-style-type: none"> <li>Percentage patients progression-free at 2 years (% 2y-PFS)</li> <li>Objective response rate (ORR), % patients achieving PR and CR</li> <li>Disease control rate (DCR), % patients achieving PR, CR and SD</li> <li>Median duration of disease control (mDDC)</li> <li>Median overall survival (mOS)</li> <li>Percentage overall survival at 2 years (% 2y-OS)</li> <li>Percentage patients experiencing functional tumour response (CgA, specific hormones), classified as functional SD, PR, CR</li> <li>Median duration of functional response</li> <li>Percentage of patients experiencing symptomatic tumour response (EORTC GI.NET21 questionnaire), classified as symptomatic SD, PR, CR</li> <li>Median duration of symptomatic response</li> </ol> <p><b>Safety and tolerability</b></p> <ol style="list-style-type: none"> <li>Calculated GFR, percentage depart from baseline value</li> <li>Measured TER, percentage depart from baseline value</li> <li>Renal volume (<math>V_{\text{kidney}}</math>), percentage depart from baseline value</li> <li>General safety parameters:  Frequency of occurrence and severity of abnormal findings in safety investigations (physical examination, vital signs, 12-lead ECG, clinical laboratory, adverse events, concomitant medication)</li> </ol> <p><b>Health-related quality of life (HRQL)</b></p> <ol style="list-style-type: none"> <li>Maximum HRQL improvement (EORTC QLQ-C30 questionnaire) total scores, relative to baseline</li> <li>Median duration of maximum HRQL improvement</li> </ol> <p><b>Tumour dosimetry measures</b>  Cumulative absorbed dose (Gy) from <math>^{177}\text{Lu}</math>-edotreotide to target tumour lesions, estimated from <math>^{177}\text{Lu}</math>-edotreotide dosimetry after first dose.</p> <p>Stratified randomisation will be used to control for primary tumour origin (GE-NET vs. P-NET) and for prior medical therapy (1<sup>st</sup> line vs. 2<sup>nd</sup> line, as well as types of previous therapies).  The primary variable progression-free survival (PFS) will be analysed using confirmatory statistics. All survival data will be analysed using the Kaplan-Meier method, which takes into account the impact of censored observations and the Log-rank test. Likewise, the secondary variable overall survival (OS) and progression-free survival in the treatment groups, adjusted for the co-variables primary tumour origin, prior medical treatment, tumour grade and baseline KPS, will be compared using exploratory statistics.  All other secondary variables will be analysed descriptively by treatment group.</p>
SAMPLE SIZE	<p>In total, 300 GEP-NET patients will be randomised in 2:1 fashion to receive either</p> <ul style="list-style-type: none"> <li>PRRT with <math>^{177}\text{Lu}</math>-edotreotide consisting of a maximum of four cycles (<math>7.5 \pm 0.7 \text{ GBq } ^{177}\text{Lu}</math>-edotreotide each), administered as IV infusion at 3-monthly intervals for 9 months, or until diagnosis of progression (200 patients), or</li> <li>10 mg everolimus (Afinitor<sup>®</sup>) daily, administered orally as a tablet until diagnosis of progression (100 patients)</li> </ul>
TRIAL DURATION	<p>Study duration per patient will be 24 months. Collection of survival data and information on further antineoplastic treatments will be continued after EOS.</p> <ul style="list-style-type: none"> <li>Screening period: 90 days (day -90 to day -1)</li> <li>Study period: <ul style="list-style-type: none"> <li>Treatment period <u>IMP</u>: Four single doses administered on days 0, 90, 180 and 270, unless diagnosis of progression or EOS</li> <li>Treatment period <u>RP</u>: Daily oral administration from day 0 until diagnosis of progression or EOS.</li> <li>Follow-up period: day 0 – month 24 (or until diagnosis of progression, whichever is earlier).</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>• Post-study period follow-up: <ul style="list-style-type: none"> <li>- <sup>177</sup>Lu-edotreotide therapy for patients (having progressed under everolimus therapy): Administration and follow-up as for study patients, until secondary progression.</li> <li>- All patients: collection of overall survival (OS) data.</li> </ul> </li> </ul>
PARTICIPATING CENTERS	30-35 centres/10-12 countries (Europe, North America, South Africa, Australasia)

*Neuroendocrine Tumors G3 and neuroendocrine carcinoma G3 of gastroenteropancreatic origin with progression on first line platinum-based chemotherapy*

**AIO-NET-0112: Safety and Tolerability of Everolimus as second–line treatment in poorly differentiated neuroendocrine carcinoma / neuroendocrine carcinoma G3 according to WHO 2010 and neuroendocrine tumor G3 – an investigator initiated Phase II study. (EVINEC-Trial)**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-NET-0112 - EVINEC
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 – 2017 (wird verlängert)
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Study Type	Phase-II, open-label, prospective, single arm, multicenter study
Study design	The study is designed as an open-label, prospective, single arm, multicenter study of everolimus in histologically confirmed, neuroendocrine carcinoma G3 / neuroendocrine tumor G3 after failure of first-line platin-based chemotherapy (open-label pilot study).
Principal investigator	Prof. Dr. Marianne Pavel Charité Universitätsmedizin Berlin, Campus Virchow Klinikum (CVK) Medical Department, Division of Hepatology and Gastroenterology CVK Augustenburger Platz 1, 13353 Berlin, Germany Tel: +49 30 450 553 022, FAX: +49 30 450 553 977 E-Mail: marianne.pavel@charite.de
Sponsor/ Study coordinator	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Tel: +49 30 814534431; FAX: +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Study Objectives	<p><u>Primary objective:</u></p> <ul style="list-style-type: none"> <li>• To evaluate tolerability and safety of everolimus in second-line treatment of poorly differentiated neuroendocrine carcinoma / neuroendocrine carcinoma G3 according to WHO 2010 and neuroendocrine tumors G3. Incidence of adverse events (AEs) overall and by severity, and serious adverse events (SAEs). Severity will be assessed using the National Cancer Institute-Common Toxicity Criteria (CTCAE) for Adverse Events, v. 4.03 (CTCAE v4.03). Safety and tolerability of Everolimus can be inferred if type, frequencies and seriousness of observed AEs are comparable to those determined in</li> </ul>

	<p>previous everolimus trials in NET (Radiant-1, 2 and 3).</p> <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> <li>• To estimate progression free survival (PFS) Progression free survival (PFS) as the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse as per local radiology assessment using RECIST 1.1.)</li> <li>• To estimate Objective Response Rate (ORR) Objective response rate defined as the rate of best overall response (CR+PR), determined by RECIST V 1.1.</li> <li>• To estimate Disease control rate (DCR) Disease control rate defined as the rate of best overall response and stable disease (CR+PR+SD), determined by RECIST V 1.1.</li> <li>• To estimate Duration of Response (DR) and Time to Progression (TTP) Duration of response is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause. Time to progression (TTP) is the time from date of start of treatment to the date of event defined as the first documented progression due to underlying cancer.</li> <li>• To estimate Overall Survival (OS) OS is defined as the time from date of randomization to the date of death from any cause. If a patient is not known to have died at the date of analysis cut-off, the OS will be censored at the last date of contact.</li> <li>• To evaluate Quality of Life Quality of life (HRQoL) will be evaluated using the EORTC QLQ-C30.</li> <li>• To explore blood levels of tumor markers (chromogranin A &amp; B, neuronspecific enolase, progastrin releasing peptide) as correlative tumor markers for clinical outcome in NET patients Percentage of patients showing normalization or a decrease of chromogranin A &amp; B, neuronspecific enolase, progastrin releasing peptide.</li> <li>• To explore expression of mTOR pathway components in tumor tissue (archive) in correlation to tumor response</li> </ul>
Number of patients	<p><b>Enrolled: 33</b></p> <p>A total of 40 patients will be enrolled.</p> <p>The planned sample size is based on previous chemotherapy trials in NEC G3. Since no data in this subpopulation of NET are available, no precise calculation of response rate and time to progression is feasible, and thus primary objective is restricted to safety and tolerability. With a sample size of N = 40 patients AEs with an incidence rate <math>\geq 7.2\%</math> will be observed at least once in a patient with a 95 % probability. This observation limit will exclude most rare SAEs but covers most AEs and the most frequent SAE stomatitis reported in previous trials (Radiant-2 and Radiant-3).</p> <p>A drop-out rate of 30 % will be assumed.</p>
Anticipated start date	Q2 2015
Study Centers	12
Duration of study	1.5 years
More centers?	No
Key inclusion criteria	<ol style="list-style-type: none"> <li>1. Signed written informed consent</li> <li>2. Male or female <math>\geq 18</math> years of age</li> <li>3. Patients with poorly differentiated neuroendocrine carcinoma, neuroendocrine carcinoma G3 (NEC - G3 according to WHO 2010) or well or moderately differentiated neuroendocrine tumor (NET – G1 / G2) that switched to G3 (confirmed by histology) or neuroendocrine tumor G3 (NET G3) and disease progression as measured by RECIST 1.1</li> <li>4. Progression during or after treatment with first-line platinbased</li> </ol>

	<p>chemotherapy. In NET G3 that switched from NET G2 the line of therapy is determined from the time of revised histology (confirming a G3 NEN)</p> <ol style="list-style-type: none"> <li>5. Measurable disease according to RECIST 1.1</li> <li>6. ECOG status 0 - 2 (Karnofsky Performance status <math>\geq</math> 80 %)</li> <li>7. Women of child-bearing potential must have a negative pregnancy test</li> <li>8. Laboratory requirements:       <ul style="list-style-type: none"> <li>• Hematology           <ul style="list-style-type: none"> <li>- Absolute neutrophil count <math>\geq</math> <math>1.5 \times 10^9/L</math></li> <li>- Platelet count <math>\geq</math> <math>100 \times 10^9/L</math></li> <li>- Leukocyte count <math>\geq</math> <math>3.0 \times 10^9/L</math></li> <li>- Hemoglobin <math>\geq</math> 9 g/dL or 5.59 mmol/L</li> </ul> </li> <li>• Hepatic Function           <ul style="list-style-type: none"> <li>- Total bilirubin <math>\leq</math> 1.5 time the upper limit normal (ULN)</li> <li>- AST <math>\leq</math> 3 x ULN in absence of liver metastases, or <math>\leq</math> 5 x ULN in presence of liver metastases</li> <li>- ALT <math>\leq</math> 3 x ULN in absence of liver metastases, or <math>\leq</math> 5 x ULN in presence of liver metastases</li> </ul> </li> <li>• Renal Function           <ul style="list-style-type: none"> <li>- Creatinine clearance <math>\geq</math> 50 mL/min according to Cockcroft-Gault formula</li> </ul> </li> <li>• Metabolic Function           <ul style="list-style-type: none"> <li>- Magnesium <math>\geq</math> lower limit of normal</li> <li>- Calcium <math>\geq</math> lower limit of normal</li> </ul> </li> <li>- Others:           <ul style="list-style-type: none"> <li>o CRP (PCT if CRP is elevated to exclude infection),</li> <li>o negative Urinary screening test for leukocytes and nitrite (U - stix) to exclude urinary tract infection</li> </ul> </li> </ul> </li> </ol>
Key exclusion criteria	<ol style="list-style-type: none"> <li>1. Known or suspected allergy or hypersensitivity reaction to any of the components of study treatment or their excipients.</li> <li>2. Previous therapy with mTOR inhibitor</li> <li>3. Radiotherapy:       <ul style="list-style-type: none"> <li>• Concurrent radiotherapy involving target lesions used for this study.</li> <li>• Concurrent palliative radiation (but radiation for non-target lesions is allowed if other target lesions are available outside the involved field)</li> <li>• previous pre-operative or post-operative radiotherapy within 3 months before study treatment</li> </ul> </li> <li>4. History of other malignant tumours within the last 5 years, except basal cell carcinoma or curatively excised cervical carcinoma in situ</li> <li>5. Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids</li> <li>6. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) <math>\leq</math> 1 year before enrolment</li> <li>7. Inadequate pulmonary function according to the Investigator's judgment, history of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan</li> <li>8. Known active HBV, HCV or HIV infection</li> <li>9. Serious concomitant disease or medical condition that in the judgment of the investigator renders the patient at high risk from treatment complication</li> <li>10. Any systemic disease requiring oral intake of corticosteroids (except for replacement therapy of corticosteroids – hydrocortisone in case of adrenal or pituitary insufficiency)</li> <li>11. Hearing loss <math>\geq</math> Grade 3 (CTCAE v4.03)</li> <li>12. Patient pregnant or breast feeding, or planning to become pregnant within 8 weeks after the end of treatment</li> <li>13. Patient (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 8 weeks (male or female) after the end of treatment.</li> <li>14. Concurrent treatment with other experimental drugs or participation in</li> </ol>

	<p>another clinical trial with any investigational drug within 28 days prior to treatment start</p> <ol style="list-style-type: none"> <li>15. Concurrent treatment with inhibitors (e.g. itraconazol, ketoconazol) and inducers (e.g. phenytoin, rifampicin) of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP).</li> <li>16. Known drug abuse/alcohol abuse</li> <li>17. Peripheral polyneuropathy <math>\geq</math> Grade 2 (CTCAE v4.03)</li> <li>18. Active chronic inflammatory bowel disease</li> <li>19. Any condition which might interfere with study objectives (e.g. infections) or would limit the patient's ability to complete the study in the opinion of the investigator</li> <li>20. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities. (AMG § 40, Abs. 1 No. 4)</li> <li>21. Affected persons who might be dependent on the sponsor or the investigator</li> </ol>
Investigational drug	<p>Name/Substance: <b>Everolimus</b>          Formulation: 10 mg/day          Administration route: oral (tablet)</p>
Scheme of therapy	<p>Everolimus (Afinitor®) should be administered orally once daily at the same time every day, consistently either with or without food. Everolimus (Afinitor®) tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.</p> <p>The recommended dose is 10 mg everolimus (Afinitor®) once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.</p> <p>If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose.</p>
Study rationale	<p>The mTOR inhibitor everolimus has proven antitumoral efficacy in phase II / III studies in neuroendocrine tumors of the pancreas (RADIANT 1 and 3 studies) as well as neuroendocrine tumors of different sites (carcinoids) associated with the carcinoid syndrome (RADIANT2 study). Whereas tumor remissions are rare with these small molecules, disease stabilization is observed in a high proportion of patients (60 – 80 percent). Neuroendocrine carcinoma G3 has been excluded from these studies.</p> <p>However, there is an unmet medical need to improve therapeutic options in NEC G3 / NET G3. NEC G3 are often metastatic at the time of diagnosis and have an aggressive clinical behavior with a poor prognosis. Established first-line therapy is cisplatin and etoposide. Although remission rates are between 40 and 67 percent, there is no long-lasting effect [19, 20]. Time to tumor progression is 4 - 8 months. A retrospective study of 305 patients with NEC G3 (NORDIC NEC study) showed very recently that the median survival is 11 months only under first-line therapy with cisplatin and etoposide or carboplatin and etoposide [21]. Objective remission rates were around 30 % and PFS is 4 months only. There is no established second-line therapy [22]. More efficient drugs are urgently needed.</p> <p>The investigator evaluated phosphorylated mTOR and effectors in a series of NEC G3 at the Charité Center. Expression of components of the mTOR pathway was associated with poor survival. 64 % of the tissues showed positivity with IRS score <math>\geq</math> 2, (data in review).</p> <p>Everolimus showed antiproliferative effects in bronchial NET (NCI-H727) that display a rather aggressive growth [23]. In individual patients with high grade histology and proliferative activity of more than 20 % there is first evidence of anti-tumor activity of everolimus in this type of tumor [23]. Therefore the antitumoral efficacy of everolimus should be further investigated in poorly differentiated neuroendocrine carcinoma where there are no alternative treatment options after failure of platin-based chemotherapy. The aim of this study is to provide a second line therapy to patients with any type of platinum-based first-line chemotherapy, to gather data on disease control rate and progression free survival. In a second approach these data should be the basis to generate another study to further explore everolimus as maintenance</p>



	therapy in NEC G3 / NET G3.
Rationale for sample size and tests to be used	No exact sample size estimation is performed for this exploratory phase II study. Since no data in this subpopulation of NET are available, no precise calculation of response rate and time to progression is feasible, and thus the primary objective is restricted to safety and tolerability. (see also sample size calculation above)
Statistical analysis	<p>For the analysis of Adverse Events (primary objective), summary tables will be generated for the incidence of AEs overall and by severity. This will also be done for Serious Adverse Events. The AE summary tables will provide the number and percentage of patients with adverse events and the 95 % confidence intervals for the event rates.</p> <p>The secondary objectives – progression free survival, objective response rate, duration of response, time to progression and overall survival – will be described using Kaplan-Meier methods. In the evaluation of the influence of prognostic factors, Cox regression models will be used. A two-sided significance level of 10 % will be applied for these exploratory tests.</p> <p>Descriptive statistics will be used for the analysis of the following:</p> <ul style="list-style-type: none"> <li>• Quality of Life Data (HRQoL)</li> <li>• Demographic Data</li> </ul> <p>For laboratory parameters, the distribution over time (mean values) as well as changes from baseline will be calculated and reported with descriptive statistics.</p> <p>Percentage of patients showing normalization or a decrease of chromogranin A &amp; B, neuron-specific enolase, progastrin releasing peptide will be evaluated by measures of descriptive statistics.</p> <p>The details of the statistical analysis will be defined in a Statistical Analysis Plan, which will be prepared before database closure.</p>

### Progressive pancreatic neuroendocrine tumors G1/G2

**AIO-NET-0215/ass: Randomized open label study to compare the efficacy and safety of everolimus followed by chemotherapy with STZ-5FU upon progression or the reverse sequence, chemotherapy with STZ-5FU followed by everolimus upon progression, in advanced progressive pNETs (SEQTOR study)**

#### AIO-assozierte Studie

Studiennummer/-Code:	AIO-NET-0215/ass - SEQTOR-Study
Status:	in Rekrutierung
Rekrutierungszeitraum	2014 - 2018
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Art der Studie Study Type	Phase-II Randomized phase III open label and <i>cross-over</i> study to compare the efficacy and safety of everolimus followed by chemotherapy upon progression or the reverse sequence, in advanced progressive pNETs.
Verantwortlicher Studienleiter nach AMG	Prof. Dr. Marianne Pavel (DL) Prof. Ramon Salazar, Barcelona, Spain (international Study Lead)
Kontaktadresse/ Kontaktperson:	Prof. Dr. Marianne Pavel Charité Universitätsmedizin Berlin, Campus Virchow Klinikum (CVK) Medical Department, Division of Hepatology and Gastroenterology Augustenburger Platz 1, 13353 Berlin, Germany

	Tel: +49 30 450 553022, FAX: +49 30 450 553977 E-Mail: marianne.pavel@charite.de
Studienziele/ Objectives	<p><u>Primary</u> To compare the efficacy of the combination STZ-5FU chemotherapy followed by Everolimus 10 mg/day upon progression versus the reverse sequence in the treatment of advanced pancreatic neuroendocrine tumours (pNET), in terms of rate of patients with second progression free survival at 84 weeks of treatment, assessed by local investigator using RECIST criteria 1.0.</p> <p><u>Secondary</u></p> <ul style="list-style-type: none"> <li>• To describe the efficacy of the two sequences of treatment STZ-5FU and everolimus 10 mg/day, as a continuous variable Hazard Ratio (HR), in advanced pNETs.</li> <li>• To determine whether the overall survival of patients with advanced pNETs could be modified by the upfront administration of each other treatment, STZ-5FU and everolimus 10 mg/day, upon progression.</li> <li>• To compare the clinical activity of STZ-5FU and everolimus 10 mg/day treatment given in 1st or 2nd place in advanced pNETS, in terms of time to first and second progression, response rate (RR), and early biochemical response (4 week CgA levels), Quality of Life and cost-efficacy of each sequence, and to investigate the criteria for measuring progression free survival (RECIST 1.0, RECIST 1.1, composite RECIST 1.0 and composite RECIST 1.1) that correlates better with overall survival.</li> <li>• To compare the safety and tolerability of treatment with STZ-5FU and everolimus 10 mg/day, given upfront each other upon progression, in patients with advanced pNET.</li> <li>• To compare the cost-efficacy of treatment with STZ-5FU and everolimus 10 mg/day, given upfront each other upon progression, in advanced pNET patients.</li> </ul>
Patientenzahl Number of patients	Geplant: 180 Patienten Bereits eingeschlossen: 108 (Stand Okt. 2017)
Rekrutierungszeitraum	04/2014 - 12/2018
Weitere teilnehmende Zentren erwünscht?	Approximately 50 centres planned
Haupt-Einschlusskriterien / Key inclusion criteria	<ul style="list-style-type: none"> <li>• Adult patients <math>\geq</math> 18 years old.</li> <li>• Histologically proven diagnosis of unresectable or metastatic, advanced pancreatic NET.</li> <li>• Documented confirmation of pancreatic NET G1 or G2 as per ENETS classification system: <ul style="list-style-type: none"> <li>• G1: <math>&lt;2</math> mitoses per 2 mm<sup>2</sup> and/or Ki-67 index <math>\leq</math> 2%</li> <li>• G2: 2–20 mitoses per 2 mm<sup>2</sup> and/or Ki-67 index <math>&gt;2\%</math> and <math>\leq</math> 20%</li> </ul> </li> <li>• Patients from whom a paraffin-embedded primary tumour or metastasis block is available and sent by courier (Section 7.2.10). Patient should give his/her consent for its use in future investigations.</li> <li>• Before study inclusion, patients must show progressive disease documented by radiology within 12 months prior to study inclusion. If patient received anti-tumour therapy during the past 12 months, he/she must have radiological documentation of progressive disease while on or after receiving that anti-tumour therapy. Naive patients can be also included if, under investigator's judgement, the patient needs active treatment with either chemotherapy or everolimus.</li> <li>• Before starting with the second treatment in sequence, patients must show documented disease progression by RECIST 1.0 (local assessment) while on anti-tumour therapy or in case of toxicity caused by the first treatment period.</li> <li>• ECOG Performance status score 0 - 2.</li> <li>• Life expectancy <math>&gt;</math> 12 months.</li> <li>• Presence of measurable disease as per RECIST criteria 1.0, documented by a Triphasic Computed Tomography (CT) scan or multiphase MRI radiological</li> </ul>

	<p>assessment.</p> <ul style="list-style-type: none"> <li>• Previous treatment with somatostatin (SS) analogues is allowed. Only those patients with active functioning syndrome at entry can continue with SS analogues during the study.</li> <li>• Adequate bone marrow function, documented by ANC &gt; 1.5 x 10<sup>9</sup>/L, platelets &gt; 100 x 10<sup>9</sup>/L, haemoglobin &gt; 9 g/dL.</li> <li>• Adequate liver function documented by: serum bilirubin ≤ 2.0 mg/dL, INR ≤ 2, ALT and AST ≤ 2.5 x ULN (≤ 5 x ULN in patients with liver metastasis).</li> <li>• Adequate renal function documented by: serum creatinine &lt; 1.5 x ULN.</li> <li>• Fasting serum cholesterol &lt; 300 mg/dL or &lt; 7.75 mmol/L and fasting triglycerides &lt; 2.5 x ULN. If one or both thresholds are exceeded, the patient may only be included after starting treatment with an adequate lipid-lowering agent.</li> <li>• Women with child-bearing potential must have a negative serum pregnancy test within 14 days prior to enrolment and/or a urine pregnancy test 48 hours before the administration of the first study treatment.</li> <li>• Written Informed Consent obtained according to local regulations.</li> </ul>
<p>Haupt-Ausschlusskriterien / Key exclusion criteria</p>	<ul style="list-style-type: none"> <li>• Patients with poorly differentiated pancreatic neuroendocrine tumor; this is, pNET G3 as per ENETS classification system:</li> <li>• G3: 21 or more mitoses per 2 mm<sup>2</sup> and/or Ki-67 index &gt;20%</li> <li>• Previous treatment with chemotherapy and/or mTOR inhibitors (sirolimus, temsirolimus, everolimus, deforolimus) or tyrosine kinase inhibitors (sunitinib, sorafenib, axitinib, pazopanib, regorafenib).</li> <li>• Immune therapy or radiation therapy within 4 weeks prior to the patient entering the study.</li> <li>- Hepatic artery embolization within the last 6 months (1 month if there are other sites of measurable disease), or cryoablation/radiofrequency ablation of hepatic metastasis within 2 months of enrolment.</li> <li>• Previous treatment with Peptide-Receptor Radionuclide Therapy (PRRT) within the last 6 months and/or without progression following PRRT.</li> <li>• Uncontrolled diabetes mellitus defined as: fasting serum glucose &gt; 1.5 x ULN.</li> <li>• Patients with any severe and/or uncontrolled medical conditions such as: <ul style="list-style-type: none"> <li>• unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, serious uncontrolled cardiac arrhythmia,</li> <li>• active or uncontrolled severe infection,</li> <li>• severe hepatic impairment (Child Pugh C) is not allowed; moderate hepatic impairment (Child Pugh B and A) requires a reduced dose of everolimus (5mg and 7.5 mg daily respectively). Positive HBV-DNA and or HBsAg patients at screening should receive prophylaxis treatment.</li> <li>• severely impaired lung function (spirometry and DLCO 50% or less of normal and O<sub>2</sub> saturation 88% or less at rest on room air),</li> <li>• active, bleeding diathesis</li> </ul> </li> <li>• Treatment with potent inhibitors or inducers of CYP3A isoenzyme (rifabutin, rifampicin, clarithromycin, ketoconazole, itraconazole, voriconazole, ritonavir, telithromycin) within 5 days immediately before the start of treatment (a list of clinically significant drug interactions is shown in section 6. Concomitant Medication).</li> <li>• Patients on chronic treatment with corticosteroids or any other immunosuppressive agent.</li> <li>• Patients known to be HIV seropositive.</li> <li>• Known intolerance or hypersensitivity to everolimus or its excipients or other rapamycin analogues. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.</li> <li>• Known intolerance or hypersensitivity to 5FU or STZ or its excipients.</li> <li>• Participation in any other clinical trial or concomitant treatment with any other investigational drug.</li> <li>• No other prior or concurrent malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for ≥ 3 years.</li> </ul>

	<ul style="list-style-type: none"> <li>• Pregnant, lactating women or fertile adults not using effective birth control methods. If barrier contraceptives are used, these must be continued to be used throughout the trial by both sexes and for up to 8 weeks after the end of treatment.</li> <li>• For administrative matters (insurance) patients <math>\geq 95</math> are not allowed.</li> </ul>
Therapieschema Scheme of therapy	<p><b>Everolimus</b> The recommended dose for everolimus is 10 mg once a day while a clinical benefit is observed or until unacceptable toxicity occurs. The length of cycles is 4 weeks (28 days).</p> <p><b>STZ-5FU</b> - STZ 0.5 g/m<sup>2</sup> days 1–5 and 5-FU 400 mg/m<sup>2</sup> days 1–5 every 6 weeks (<i>Moerte!</i>) or, - 0.5 g/m<sup>2</sup> STZ on days 1–5 and 400mg/m<sup>2</sup> 5-FU on days 1-3 and then, 1-day treatment with 1g/m<sup>2</sup> STZ and 1 day treatment with 400mg/m<sup>2</sup> 5-FU every 3 weeks (<i>Uppsala</i>).</p>
Tumorevaluierung Criteria for evaluation	<p>Rate of patients with second progression free survival at 84 weeks of treatment, assessed by local investigator using RECIST criteria 1.0.</p> <p>Rate of second progression free survival is defined as: PFS of Course 1 + interval between treatments + PFS of Course 2, where PFS1 represents progression free survival of Course 1 and PFS2 represents progression free survival of Course 2.</p> <p>Number of adverse events, dose reductions, and total dose administered on patients treated with STZ-5FU followed by everolimus 10 mg/day or the reverse sequence, in advanced pNETs.</p>
Rationale	<p>STZ 5-FU chemotherapy is the actual standard of care for advanced pNETS in the European Union (ENETS guidelines; Neuroendocrinology 2012). Everolimus has been recently approved for its use in advanced pNETs by the FDA and in Europe by the EMA. A randomized study is needed to have a clear knowledge about the best sequence for its administration; this is, before or after palliative chemotherapy.</p> <p>The purpose of this study is to elucidate which sequence of STZ based chemotherapy and the mTOR inhibitor, everolimus, gives better results. in terms of second PFS in well differentiated and advanced pancreatic NETs.</p>

Typical and atypical Lung carcinoids, therapy naïve, first line therapy

**AIO-NET-0116/ass: A Phase 3, prospective, randomized, double-blind, multi-center study of the efficacy and safety of lanreotide Autogel/Depot 120 mg plus BSC vs. placebo plus BSC for tumour control in subjects with well differentiated, metastatic and/or unresectable, typical or atypical, lung neuroendocrine tumours. (SPINET-Trial)**

**AIO-assozierte Studie**

Studiennummer/-Code:	AIO-NET-0116/ass - SPINET-Trial
Status:	in Rekrutierung
Rekrutierungszeitraum	2016 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Sponsor Name	IPSEN Biopharmaceuticals <u>Contact:</u> <ul style="list-style-type: none"> <li>Philipp Hoffmanns, Director Global Medical Affairs, philipp.hoffmanns@ipsen.com</li> <li>Elodie Blouquit, Global Project Leader, elodie.blouquit.ext@ipsen.com</li> </ul>
Study sites in Germany	<ul style="list-style-type: none"> <li>Zentralklinik Bad Berka GmbH Principal Investigator: Dieter Hoersch</li> <li>Evangelische Lungenklinik Berlin Principal Investigator: Christian Grohe</li> <li>Charite Universitätsmedizin Berlin, Campus Virchow-Klinikum Principal Investigator: Marianne Pavel</li> <li>Universitätsklinikum Essen Principal Investigator: Harald Lahner</li> <li>Johann Wolfgang Goethe-Universitätsklinikum Frankfurt Principal Investigator: Jörg Bojunga</li> </ul>
Study Objectives	<p>Objectives</p> <p>Primary Objective</p> <ul style="list-style-type: none"> <li>To compare the antitumour efficacy of LAN monotherapy plus BSC every 28 days versus placebo plus BSC, in terms of progression free survival (PFS), measured by central review using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, every 12 weeks</li> </ul> <p>Secondary Efficacy Objectives</p> <ul style="list-style-type: none"> <li>To compare the objective response rate (ORR) of LAN monotherapy plus BSC every 28 days versus placebo plus BSC, as assessed by RECIST v 1.1 criteria (proportion of subjects with a best overall response of partial response (PR) or complete response (CR)),</li> <li>To compare the overall survival (OS) of subjects randomised to LAN monotherapy plus BSC every 28 days versus subjects randomised to placebo plus BSC,</li> <li>To compare time to treatment failure (Kaplan Meier estimates) of LAN monotherapy plus BSC every 28 days versus placebo plus BSC,</li> <li>To compare the changes from Baseline in the biomarker chromogranin A (CgA),</li> <li>To describe the change in Quality of Life (QoL) from baseline, as assessed by the EORTC QLQ-C30 questionnaire,</li> <li>To describe the time to deterioration of QoL (using EORTC QLQ-C30),</li> <li>To describe the changes in urinary 5-hydroxyindoleacetic acid (5-HIAA) in subjects with elevated urinary 5-HIAA (<math>\geq 2 \times</math> ULN) at Baseline,</li> </ul>

	<ul style="list-style-type: none"> <li>To assess the pharmacokinetics (PK) of LAN</li> </ul>
Study Timelines	<p>Start: Feb 2016 Estimated completion date: August 2019</p>
Study Design	<p>This is a Phase 3, prospective, multi-center, randomized, double-blind study evaluating the efficacy and safety of LAN plus BSC vs. placebo plus BSC for the treatment of well-differentiated typical or atypical, metastatic and/or unresectable lung NETs.</p> <p>The study contains two phases, the DB Phase, and the OL Extension Phase. The DB Phase will include: Screening, Baseline and Treatment periods and the Extension Phase will consist of two periods: Treatment Period and Follow-Up Period.</p>
Number of Patients	Aktuell eingeschlossen: 1 Patient (Stand Okt. 2016)
Study Population	<p>Study population will consist of 216 eligible subjects who meet the selection criteria specified below:</p> <p>Inclusion criteria (selected)</p> <ol style="list-style-type: none"> <li>(1) Have metastatic and/or unresectable pathologically confirmed well-differentiated, typical or atypical neuroendocrine tumour of the lung,</li> <li>(2) Histologic evidence of well differentiated NETs of the lung (typical and atypical according to the WHO criteria evaluated locally),</li> <li>(3) Has a mitotic index &lt;2 mitoses/2 mm<sup>2</sup> for typical carcinoid (TC) and &lt;10 mitoses/2 mm<sup>2</sup> and/or foci of necrosis for atypical carcinoid (AC),</li> <li>(4) At least one measurable lesion of the disease on imaging (CT or MRI; RECIST v1.1),</li> <li>(5) Positive somatostatin receptor imaging (SRI) (Octreoscan<sup>®</sup> ≥ grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background),</li> </ol> <p>Exclusion criteria (selected)</p> <ol style="list-style-type: none"> <li>(1) Poorly differentiated or high grade carcinoma, or patients with neuroendocrine tumors not of lung origin are excluded</li> <li>(2) Has been treated with an Somatostatin analogs (SSA) at any time prior to randomization, except if that treatment was for less than 15 days (e.g. peri-operatively) of short acting SSA or one dose of long acting SSA and the treatment was received more than 6 weeks prior to randomization</li> <li>(3) Has been treated with Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization</li> <li>(4) Has been treated with more than two lines of cytotoxic chemotherapy or molecular targeted therapy or interferon for Lung NET</li> </ol>
Study Treatment	<p>Lanreotide Autogel/Depot 120mg (LAN) plus BSC every 28 days administered via deep subcutaneous (s.c.) injection until disease progression confirmed centrally, development of unacceptable toxicity or premature withdrawal for any reason.</p> <p>OR</p> <p>Placebo plus BSC every 28 days administered via deep s.c. injection until disease progression confirmed centrally, development of unacceptable toxicity or premature withdrawal for any reason.</p>

Progressive midgut or pancreatic NET G1/ G2 after progression on standard dose lanreotide

**AIO-NET-0216/as: Efficacy and safety of lanreotide Autogel® 120 mg administered every 14 days in well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut neuroendocrine tumours having progressed radiologically while previously treated with lanreotide Autogel® 120 mg administered every 28 days. (CLARINET FORTE-Trial)**

**AIO-assozierte Studie**

Studiennummer/-Code:	AIO-NET-0216/ass - CLARINET FORTE-Trial
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Sponsor Name,	IPSEN Pharma <u>Ipsen Contact:</u> <ul style="list-style-type: none"> <li>• Ali Majdi, Senior Director Global Medical Affairs, abdelali.majdi@ipsen.com</li> <li>• Catherine Viollet, Global Project Manager, catherine.viollet@ipsen.com</li> </ul>
Zentren in Deutschland	<ul style="list-style-type: none"> <li>• Charite, Berlin Principal Investigator: Marianne Pavel</li> <li>• Nationales Centrum für Tumorerkrankungen, Heidelberg Principal Investigator: Leonidas Apostolidis</li> </ul>
Study Objectives	<p>Primary</p> <ul style="list-style-type: none"> <li>• To assess progression free survival (PFS) when treated with lanreotide Autogel® 120 mg administered every 14 days based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.0, and according to central review.</li> </ul> <p>Secondary</p> <ul style="list-style-type: none"> <li>• To evaluate the clinical and biological safety profile.</li> <li>• To evaluate time to progression.</li> <li>• To evaluate PFS rate every 12 weeks.</li> <li>• To evaluate overall survival at Week 48 and at the end of the study period in each cohort.</li> <li>• To evaluate the objective response rate (ORR) as per RECIST v1.0 every 12 weeks.</li> <li>• To evaluate the disease control rate (DCR) as per RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort.</li> <li>• To evaluate the best overall response as per RECIST v1.0.</li> <li>• To evaluate the duration of stable disease (SD) as per RECIST v1.0.</li> <li>• To evaluate the effect on symptoms (diarrhoea, flushing).</li> <li>• To evaluate quality of life.</li> <li>• To evaluate the changes in tumour biomarkers</li> <li>• To evaluate the pharmacokinetic (PK) profile</li> </ul>
Study Timelines	Study Start Date: November 2015 Estimated Study Completion Date: October 2019
Study Design	This is a phase II, multicentre, prospective, open label, noncomparative, exploratory study. (pNET and intestinal NET cohort)
Number of Patients	aktuell eingeschlossen: 65 Pts. davon 1 Pt. in Deutschland (Stand Nov. 2017)
Study Population	Study population will consist of 100 eligible subjects who meet the selection

	<p>criteria specified below:</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"><li>1) Histopathologically confirmed, grade 1 or 2, metastatic or locally advanced, unresectable pNET (pNET cohort) or midgut NET (midgut cohort) with or without hormone related syndromes, with a proliferation index (Ki67) <math>\leq 20\%</math>.</li><li>2) Positive somatostatin receptors type 2</li><li>3) Progression as assessed by an independent central reviewer according to RECIST v1.0 while receiving first line treatment with lanreotide Autogel® at a standard dose of 120 mg every 28 days for at least 24 weeks</li></ol> <p>Exclusion Criteria:</p> <ol style="list-style-type: none"><li>1) Grade 3 or rapidly progressive (within 12 weeks) NET</li><li>2) Any NET other than pancreatic and midgut</li><li>3) Previous treatment with any antitumour agent for NET other than lanreotide Autogel® 120 mg every 28 days</li><li>4) Gallbladder lithiasis at Screening echography or history of cholelithiasis with no cholecystectomy since then.</li></ol>
Study Treatment	Lanreotide Autogel® will be administered by deep subcutaneous (s.c.) injection at a dose of 120 mg every 14 days.



## Interdisziplinäre Arbeitsgruppe Nierenzellkarzinom

### Nierenzellkarzinom, 1st-line

**AIO-NZK-0117/ass : A Phase 2, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Sunitinib Monotherapy in Subjects with Previously Untreated and Advanced (unresectable or metastatic) non-clear Cell Renal Cell Carcinoma (SUNNIFORECAST)**

#### AIO-assozierte Studie

Studiennummer/-Code:	AIO-NZK-0117/ass - SUNNIFORECAST
Status:	in Rekrutierung
Rekrutierungszeitraum	11/2017 – 12/2021
Weitere Zentren:	Interessierte Zentren können sich auf Warteliste setzen lassen
Letzte Aktualisierung	Oktober 2017

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Lothar Bergmann Universitätsklinikum Frankfurt Medizinische Klinik II Theodor-Stern-Kai 7 60590 Frankfurt
Studienziele	<p><b>Primäres Studienziel:</b></p> <p>OS Rate nach 12 Monate</p> <p><b>Sekundäre Studienziele:</b></p> <p>OS Rate nach 6 und 12 Monaten Dauer der Response (DOR) Progressionsfreie Überleben (PFS) Mediane Gesamtüberleben (mOS) Ojektive Responserate (ORR) Sicherheit und Tolerabilität der Therapien</p>
Patientenzahl	Geplant: 306 Bereits eingeschlossen:
Haupt-Einschlusskriterien	<p><b>Inclusion:</b></p> <p>a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.</p> <p>b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.</p> <p>2. Target Population</p> <p>a) Histological confirmation of non-clear RCC with at least 50% non-clear cell component according to actual WHO classification<sup>36</sup></p> <p>b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC</p> <p>c) Karnofsky &gt; 70% (See Appendix 2, 14.2)</p> <p>d) Measurable disease</p>
Haupt-Ausschlusskriterien	<p>Exclusion Criteria:</p> <p>a) Any active brain metastases requiring systemic corticosteroids. Baseline imaging of the brain by MRI is required in patients with</p>

	<p>clinical signs of potential CNS involvement within 28 days prior to randomization.</p> <p>a) Tumors with a clear-cell component of &gt; 50%</p> <p>Medical History and Concurrent Diseases</p> <p>b) Prior systemic treatment with VEGF or VEGF receptor targeted therapy (including, but not limited to, Sunitinib, pazopanib, axitinib, tivozanib, and bevacizumab) or prior treatment with an mTOR inhibitor or cytokines.</p> <p>c) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.</p> <p>d) Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (&gt; 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.</p> <p>e) Any condition requiring systemic treatment with corticosteroids (&gt; 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses &gt; 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.</p> <p>f) Uncontrolled adrenal insufficiency.</p> <p>g) Ongoing symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation, or prolongation of the Fridericia corrected QT (QTcF) interval defined as &gt; 450 msec for males and &gt; 470 msec for females, where <math>QTcF = QT / \sqrt{RR}</math></p> <p>h) Poorly controlled hypertension (defined as systolic blood pressure (SBP) of <math>\geq 150</math> mmHg or diastolic blood pressure (DBP) of <math>\geq 90</math></p> <p>i) mmHg), despite antihypertensive therapy.</p> <p>j) History of any of the following cardiovascular conditions within 12 months of enrollment: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association.</p> <p>k) History of cerebrovascular accident including transient ischemic attack within the past 12 months.</p> <p>l) History of deep vein thrombosis (DVT) unless adequately treated with low molecular weight heparin</p> <p>m) History of pulmonary embolism within the past 6 months unless stable, asymptomatic, and treated with low molecular weight heparin for at least 6 weeks.</p> <p>n) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months.</p> <p>o) Serious, non-healing wound or ulcer.</p> <p>p) Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 30 days.</p> <p>q) Any requirement for anti-coagulation, except for low molecular weight heparin.</p> <p>r) Prior malignancy active within the previous 3 years except for locally</p>
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	<p>curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.</p> <ul style="list-style-type: none"> <li>s) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).</li> <li>t) Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.</li> <li>u) Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.</li> <li>v) Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug.</li> <li>w) Anti-cancer therapy less than 28 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug.</li> <li>x) Receiving concomitant CYP3A4 inducers or strong CYP3A4 inhibitors (See Appendix 4, <b>Fehler! Verweisquelle konnte nicht gefunden werden.</b>).</li> <li>y) Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of Sunitinib (eg, malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection).</li> <li>z) Hypersensitivity to sunitinib or any of the excipients</li> <li>aa) Patients who were vaccinated with a live vaccine 2 weeks prior to the start of the CT</li> </ul>
Tumorevaluierung Criteria for evaluation	Tumor assessment with CT/MRT according to RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria and immune-related response criteria (irRECIST)
Rationale	<p>SUNNIFORECAST (Sunitinib vs. Nivolumab + Ipilimumab as First line treatment Of RENal cell CAncer of non-clear cell SubTypes) is a Phase II, randomized, open-label study of Nivolumab (BMS-936558) combined with Ipilimumab vs. Sunitinib monotherapy in subjects with previously untreated and advanced (unresectable or metastatic) non-clear cell renal cell carcinoma (ncRCC). In the Phase I setting, Nivolumab combined with Ipilimumab has demonstrated substantially greater clinical activity, as measured by objective response rate (ORR), than either agent alone. Given the durability of responses associated with immunotherapies, Nivolumab combined with Ipilimumab is hypothesized to lead to greater clinical benefit, as measured by overall survival (OS) rate at 12 months as primary endpoint and OS at 6 months and 18 months, progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) as secondary endpoints compared to Sunitinib, a widely used standard-of-care agent in this patient population. This study will allow for direct comparison of OS rate at 12 months between both arms.</p>

**AIO-NZK-0116/ass: A randomized phase II study with NIVolumab or continuation of therapy as an early SWITCH approach in patients with advanced or metastatic renal cell carcinoma (RCC) and disease control after 3 months of treatment with a tyrosine kinase inhibitor (NIVOSWITCH)**

**AIO-assozierte Studie**

Studiennummer/-Code:	AIO-NZK-0116/ass - NIVOSWITCH
Status:	in Rekrutierung
Rekrutierungszeitraum	Q4 / 2016 – Q4 / 2019
Weitere Zentren:	erwünscht für Deutschland
Letzte Aktualisierung	April 2018

National Coordinating Investigator	Prof. Dr. med. Viktor Grünwald Medizinische Hochschule Hannover Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation Carl-Neuberg-Straße 1, 30625 Hannover Telefon: +49 511 532 2301 E-Mail: gruenwald.viktor@mh-hannover.de
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Study design	Open label, randomized, phase II trial
Duration of study	Approx. 72 month
Indication	Adult patients of at least 18 years of age and any gender and metastatic or advanced RCC will be included. Patients must have received first line therapy with a VEGFR-TKI prior to study inclusion for 10-12 weeks with documented disease control (PR/SD) according to RECIST 1.1 at time of study entry
Total number of sites	Approx. 35 in Germany and Austria
Primary objective	To assess the survival benefit from an early switch approach from sunitinib or pazopanib to nivolumab (anti-angiogenic to immunotherapy switch)
Secondary objectives	<ul style="list-style-type: none"> <li>• to compare efficacy of early switch to nivolumab vs. continuation of either sunitinib or pazopanib</li> <li>• to compare health-related quality of life (HR-QoL) during TKI and nivolumab treatment after early switch</li> <li>• to assess the influence of response to previous TKI treatment on nivolumab efficacy</li> <li>• to assess safety and toxicity</li> </ul>
Exploratory objectives	<ul style="list-style-type: none"> <li>• To explore predictive biomarkers in the tumor and serum</li> <li>• ORR, PFS, and OS in subgroups (MSKCC risk categories; previous response, type of TKI administered)</li> <li>• To assess efficacy, safety and HR-QoL in patients who treated beyond progression as assessed by RECIST 1.1.</li> </ul>
Planned sample size	N=244
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.</li> <li>2. Subject is willing and able to comply with the protocol for the duration of</li> </ol>

	<p>the study including undergoing treatment and scheduled visits and examinations including follow up.</p> <ol style="list-style-type: none"> <li>3. Age <math>\geq</math> 18 years at time of study entry</li> <li>4. ECOG performance status 0-2.</li> <li>5. Metastatic or locally advanced RCC with clear cell component, not amenable to surgery with curative intention.</li> <li>6. First-line treatment with a TKI for 10-12 weeks (limited to sunitinib or pazopanib).</li> <li>7. Patients with measurable disease (at least one uni-dimensionally measurable target lesion by CT-scan or MRI) according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). If prior palliative radiotherapy to metastatic lesions: <math>\geq</math> 1 measurable lesion that has not been irradiated. Patients with bone lesions as the only measurable lesion are eligible, provided that lesions consist of soft tissue, which is assessed via CT or MRI.</li> <li>8. Documented partial response or stable disease to first-line TKI exposure at 10-12 weeks.</li> <li>9. Prior therapies other than indicated in the exclusion criteria and surgeries are allowed if completed 4 weeks (for minor surgery and palliative radiotherapy for bone pain: 2 weeks) prior to start of treatment and patient recovered from toxic effects.</li> <li>10. Adequate blood count, liver-enzymes, and renal function (obtained no later than 14 days prior to start of study treatment): <ul style="list-style-type: none"> <li>▪ WBC <math>\geq</math> 2000/<math>\mu</math>L</li> <li>▪ Neutrophils <math>\geq</math> 1500/<math>\mu</math>L</li> <li>▪ Platelets <math>\geq</math> 100 <math>\times 10^3</math>/<math>\mu</math>L</li> <li>▪ Hemoglobin <math>&gt;</math> 9.0 g/dL</li> <li>▪ Serum creatinine <math>\leq</math> 1.5 x ULN or creatinine clearance (CrCl) <math>\geq</math> 40 mL/min (if using the Cockcroft-Gault formula below): <math display="block">\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}</math> <math display="block">\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}</math> <ul style="list-style-type: none"> <li>▪ AST/ALT <math>\leq</math> 3 x ULN</li> <li>▪ Total Bilirubin <math>\leq</math> 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin <math>&lt;</math> 3.0 mg/dL)</li> </ul> </li> </ul> </li> <li>11. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. <i>WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of nivolumab.</i></li> <li>12. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab</li> <li>13. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic) men do not require contraception.</li> </ol>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Prior systemic therapy other than 10-12 weeks SOC TKI treatment for advanced or metastatic RCC.</li> <li>2. Standard of care 1<sup>st</sup>-line TKI treatment for advanced or metastatic RCC for longer than 12 weeks.</li> <li>3. Complete remission (CR) or progression during SOC TKI 1<sup>st</sup>-line treatment.</li> <li>4. Termination of first-line treatment with TKI due to intolerance</li> <li>5. Previous malignancy (other than renal cell cancer), requiring active</li> </ol>

	<p>treatment or diagnosed in metastatic state. Basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a prostate carcinoma or superficial bladder tumor [T<sub>a</sub>, T<sub>is</sub> and T<sub>1</sub>] are exempted.</p> <ol style="list-style-type: none"> <li>6. Brain metastases mandating active treatment. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for 4 weeks after treatment is completed and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (&gt; 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.</li> <li>7. Prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents.</li> <li>8. Administration of a live, attenuated vaccine within 4 weeks of start of therapy</li> <li>9. Any previous treatment with a an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways</li> <li>10. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.</li> <li>11. Patients should be excluded if they have an active, known or suspected autoimmune disease. NOTE: Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger</li> <li>12. Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (&gt; 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. NOTE: Inhaled or topical steroids and adrenal replacement doses &gt; 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.</li> <li>13. Known chronic infection (i.e. hepatitis B or C, HIV)</li> <li>14. Patients should be excluded if they have been positively tested for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.</li> <li>15. Patients should be excluded if they have a known history of testing positive for human immunodeficiency virus (HIV) or a known acquired immunodeficiency syndrome (AIDS).</li> <li>16. History of severe hypersensitivity reaction to any monoclonal antibody or any constituent of the product.</li> <li>17. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have a psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent</li> <li>18. Uncontrolled severe hypertension (failure of diastolic blood pressure to fall below 95 mmHg under adequate medication)</li> <li>19. Current cardiac events such as arrhythmias, myocardial infarction, CHF, apoplexy, lung embolism</li> <li>20. Idiopathic pulmonary fibrosis or other risk for pneumonitis</li> <li>21. History of allogeneic solid organ or tissue transplant including allogeneic hematopoietic stem cell transplantation.</li> <li>22. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year)</li> <li>23. Any other serious or uncontrolled medical disorder, active infection, physical examfinding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially</li> </ol>
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	<p>increase risk to the subject, or impact the interpretability of study results.</p> <p>24. Previous enrollment or randomization in the present study. (Not applicable to screening failures)</p> <p>25. Involvement in the planning and/or conduct of the study (applies to both BMS staff and/or staff of sponsor and study site)</p> <p>26. Patient who might be dependent on the sponsor, site or the investigator.</p> <p>27. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p> <p>28. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p>
Investigational agents	<ul style="list-style-type: none"> <li>• Nivolumab</li> </ul> <p><b>Active comparators</b></p> <ul style="list-style-type: none"> <li>• Sunitinib</li> <li>• Pazopanib</li> </ul>
Treatment schedule	<p>Dosage/Time points Nivolumab arm: 240 mg fixed dose Q2W for 16 weeks, then 480 mg Q4W</p> <p>Continuous TKI arm: Previous TKI will be continued according to SOC</p> <ul style="list-style-type: none"> <li>• Sunitinib: recommended dose of sunitinib is 50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.</li> <li>• Pazopanib: The recommended dose of pazopanib for the treatment of RCC is 800 mg once daily.</li> </ul> <p>Adaption of original dose and scheme of sunitinib or pazopanib due to toxicity is permitted at study entry. Cross-over between nivolumab and SOC TKI arms is not allowed.</p> <p>Treatment with nivolumab or TKI will be administered until disease progression, unacceptable toxicity or patient withdrawal up to a maximum of 3 years.</p> <p><b>Study procedures (and routine procedures):</b></p> <ul style="list-style-type: none"> <li>• Tumor assessment time points: Screening (Day -21 to 1 from initiation of study treatment), Week 12, and then every 12 weeks until disease progression is documented</li> <li>• FKSI-15 will be assessed after 4 weeks, 8 weeks, 12 weeks and every 12 weeks thereafter until end of treatment.</li> </ul>
Primary endpoint	<ul style="list-style-type: none"> <li>• OS</li> </ul>
Secondary endpoints	<p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> <li>• Best overall response (PR+CR) throughout the 1<sup>st</sup>-line treatment according to modified RECIST</li> </ul> <p>Additional secondary endpoints:</p> <ul style="list-style-type: none"> <li>• PFS and OS from time of randomization to death from any cause</li> <li>• OS rates at 24 and 36 months</li> <li>• PFS and OS from start of 1<sup>st</sup> line TKI therapy</li> <li>• Duration of response (DoR)</li> <li>• Health related-Quality of Life (Functional Assessment of Cancer Therapy-Kidney Symptom Index FKSI 15 score and changes in the FKSI 15 score)</li> <li>• proportion of subjects with increase from baseline in FKSI 15 (MID 3 points)</li> <li>• time to deterioration, measured as a composite endpoint consisting of decrease of QoL (defined by the minimal clinical relevant difference) or death (TUDD)</li> <li>• tumor shrinkage, i.e. relative change from baseline in sum of longest</li> </ul>

	<p>diameter</p> <ul style="list-style-type: none"> <li>• AEs / SAEs / Treatment Emergent Adverse Events according to CTCAE 4.03</li> </ul>
Randomization procedure	<p>1:1 (Arm A: Nivolumab; Arm B: SOC-TKI) randomization will be performed centrally.</p> <p>Stratification according to:</p> <ul style="list-style-type: none"> <li>• Response characteristics: OR vs. SD</li> <li>• Modified MSKCC score: risk poor vs. other</li> <li>• TKI: sunitinib vs. pazopanib</li> </ul>
Rationale	<p>Today, targeted therapies represent the standard of care (SOC) in metastatic RCC. Inhibition of the VEGF axis remains the cornerstone of first line therapy, with pazopanib and sunitinib being the predominant choices (Motzer et al., 2013). Objective response rates (ORR) are within the range of 25-31%. The depth of remission has been shown to be a prognostic factor in RCC (Seidel et al., 2013), which has been recently validated in 2749 RCC patients (Grünwald et al., 2015). Objective response was achieved in 30%, half of which occurred within a 3 months window. Summarized, deep remission predicts overall survival (OS) in mRCC patients and may serve as a surrogate marker.</p> <p>Combination therapies have explored cytokines and targeted agents as combinational partners in order to improve quality of response in RCC. However, such combinations were prohibitive due to excessive toxicity and resulting dose-compromises (Négrier et al., 2011; Ryan et al., 2007).</p> <p>Inhibitors of programmed death -1 (PD-1) have been recently shown in early clinical trials in RCC to be active (Topalian et al., 2012). The initial phase I study detected clinical activity at any dose-level without reaching a formal maximum tolerated dose (MTD). Adverse events (AE) occurred in 41% of patients, with 6% of grade 3/4 AEs. The most common treatment-related events consisted of fatigue, rash, diarrhea, pruritus, anorexia, and nausea. About 50% of the responders derive sustained benefit (Topalian et al., 2013). A recent phase II study confirmed the favorable tolerability and clinical activity of nivolumab in RCC (Motzer et al., 2014). Based on this data, it is hypothesized that nivolumab is better tolerated and beneficial in terms of health-related Quality of Life (HR-QoL). A recent phase III study investigating nivolumab vs. everolimus in the second-line setting for mRCC demonstrated clear superiority of nivolumab in terms of overall survival (25.0 vs 19.6 mo; HR=0.73;p=0.002), response rate (25% vs. 5% p&lt;0.001) and frequency of TEAEs (19% vs. 37%) [1]. The afore-mentioned results constituted the basis for the market approval of nivolumab in the U.S. and in the E.U.</p> <p>The concomitant combination with targeted agents or Ipilimumab have set a new benchmark for response, but at the expense of toxicity (Amin et al., 2014; Hammers et al., 2014).</p> <p>Today, it remains unknown whether a tyrosine-kinase inhibitor (TKI) may boost response of subsequent checkpoint inhibitors. It is known however, that resistance to antiangiogenic therapy is associated with an immunosuppressive tumor microenvironment in mRCC and the effect can be mechanistically explained by an increase of PD-L1 expression (Liu et al. CIR 2015). Pretreatment with cytotoxic agents has been reported to boost immune response in cancer (Honeychurch, Dive, &amp; Illidge, 2013), but whether a rapid sequence or simultaneous treatment with TKI and nivolumab will yield improved immune response remains unknown.</p> <p>The goal of our study is to investigate whether an early switch from TKI to nivolumab may improve clinical outcome, in particular survival and tumor response, compared to the continuation of VEGFR inhibition in RCC. In subgroup analyses, efficacy of nivolumab for different patient populations is explored.</p>



	<p>Hypothesis: A brief exposure (10-12 wks.) with a TKI will boost immune responsiveness to nivolumab in mRCC patients and, hence, improve OS in mRCC patients to an early switch of therapy. As a key secondary endpoint, overall response rate will be assessed and analyzed. We hypothesize that nivolumab treatment is associated with improved overall survival and ORR as compared to TKI treatment.</p>
Interim analysis	<p>A first interim analysis will be conducted after 183 patients have been enrolled and followed-up for progression for 6 month (approx. 33 month after FPI). The read-out of the interim analysis will consist of:</p> <ul style="list-style-type: none"> <li>• ORR</li> <li>• PFS</li> <li>• AEs/SAEs</li> </ul> <p>The interim analysis does not include provisions for early termination and the study will continue recruitment until the required sample size for OS analysis has been reached.</p>
Safety data	<ul style="list-style-type: none"> <li>• AEs / SAEs / Treatment Emergent Adverse Events according to CTC 4.03</li> <li>• Frequency of abnormal laboratory parameters</li> </ul>
Sample size estimation	<p>In order to detect a difference between groups in the primary endpoint overall survival using a log-rank test with a two-sided significance level of 5% and assuming a 2-year survival of 75% vs. 60% (corresponding to a hazard ratio of 1.78), a total of 128 events is necessary to achieve 90% power. Under the assumption of a total study duration of 72 month (36 month accrual + 36 month treatment and FU) and a 5% drop-out rate per year the required number of observable events translates into 122 patients per treatment arm. To reach this recruitment goal in 36 month 35 sites with an average total enrollment of 6-7 patients per month are required.</p> <p>Key secondary endpoint and interim analysis: Because patients without response to pazopanib or sunitinib are excluded from study participation, a 35% ORR is estimated in eligible mRCC patients (i.e. those who have CR/PR/SD after 10-12 weeks of TKI treatment). It is expected that with the early switch to nivolumab, the ORR can be increased by 20%. A total sample size of N=244 achieves 89% power to detect a difference of 0.2 between the group proportions of 0.35 and 0.55 at a global significance level (alpha) of 0.05 using a one-sided z-test with continuity correction. These results assume that 2 sequential tests (one interim analysis + final analysis) are made using the Pocock spending function to determine the test boundaries. The interim analysis will achieve 81.1% power at a nominal alpha=0.041 after the accrual and follow-up for tumor response for at least 6 month of n=183 patients (75%).</p>
Biomarker measurements	<p>Biomarkers will consist of tumor tissue and soluble markers. Tumor tissue is mandatory and must be taken from metastatic disease prior to start of TKI (≤6 mo.). In the case of synchronous metastases, tissue from the primary is an acceptable alternative. If no tissue was obtained prior to start of TKI, a biopsy is mandatory prior to randomization.</p> <p>Markers will be tested for its predictive and prognostic value.</p> <p><b>Work package 1 - tumor tissue analysis:</b></p> <ul style="list-style-type: none"> <li>• Tumor blocks of the primary tumor and optional re-biopsies before and during treatment will be collected centrally</li> <li>• Standardized histopathological examination will be performed including immunohistochemistry and molecular pathology if necessary (Tumor type according to WHO 2016, WHO grade)</li> <li>• DNA and RNA will be isolated using automatized and standardized methods</li> <li>• Tumors will be tested for PD-L1, PD-L2 and PD-1 expression using immunohistochemistry (antibody PD-L1 28-8, DAKO, approved for Nivolumab, 3 other antibodies for comparison) and qPCR</li> </ul>

	<p>(Checkpointtyper)</p> <ul style="list-style-type: none"> <li>• Immune cell infiltrate (T-cells, cytotoxic T-cells, NK cells) will be characterized on protein and RNA level (CD3, CD8, CD57) and customized Nanostring Immunotyper test (48 genes).</li> <li>• VEGFR polymorphisms will be characterized using pyrosequencing</li> </ul> <p><b>Work package 2 – blood and serum analysis:</b></p> <ul style="list-style-type: none"> <li>• Quantification of serum markers including angiogenesis and cytokine/chemokine related proteomics, prior to and during treatment.</li> <li>• monitor CD4/CD8 T-cell populations and their functional subgroups as well as the T<sub>reg</sub> and their different functional subgroups</li> <li>• quantification of PD-1 expression on these T-cell populations</li> <li>• Isolation and quantification of circulating exosomes from serum prior and during therapy</li> </ul>												
QoL measurements	FKSI15												
Study plan / time lines	<table> <tr> <td>First Patient In (FPI):</td> <td>Q4 / 2016</td> </tr> <tr> <td>Interim analysis for ORR</td> <td>after approx. 33 month</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 36 month</td> </tr> <tr> <td>End of treatment and follow-up for LPI:</td> <td>after approx. 72 month</td> </tr> <tr> <td>Study report:</td> <td>after approx. 81 month</td> </tr> <tr> <td>Publication (OS data):</td> <td>after approx. 84 month</td> </tr> </table>	First Patient In (FPI):	Q4 / 2016	Interim analysis for ORR	after approx. 33 month	Last Patient In (LPI):	after approx. 36 month	End of treatment and follow-up for LPI:	after approx. 72 month	Study report:	after approx. 81 month	Publication (OS data):	after approx. 84 month
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**AIO-NZK-0115/ass: A phase III study testing the role of proactive coaching on patient reported outcome in metastatic renal cell carcinoma treated with sunitinib [PREPARE]**

**AIO-assozierte Studie**

Studiennummer/-Code:	AIO-NZK-0115/ass - PREPARE
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 - 2020
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	Oktober 2017

Study Type	Open-label, randomized, observational phase III study
Coordinating investigator (LKP)	<p>Prof. Dr. med. Viktor Grünwald          Medizinische Hochschule Hannover          Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation          Carl-Neuberg-Straße 1, 30625 Hannover          Telefon: +49 511 532 2301, E-Mail: gruenwald.viktor@mh-hannover.de</p>
Sponsor:	<p>AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin          Phone: +49 30 814534431, info@aio-studien-ggmbh.de</p>
Objectives	<p><u>Primary objective:</u></p> <p>To determine the impact of a 24 weeks concomitant coaching on patient reported outcomes of patients receiving standard treatment for mRCC with sunitinib.</p> <p><u>Secondary objectives:</u></p> <p>Assessment of the impact of a 24 weeks concomitant coaching on additional QoL measures, patient compliance, efficacy and safety.</p>

	<p><u>Exploratory objectives:</u></p> <p>Assessment of inflammatory markers in tumor samples and serum.</p>
Endpoints	<p><u>Primary endpoint:</u></p> <p>QoL assessment during sunitinib treatment: Rate of responders to concomitant coaching assessed by the FKSI-15 questionnaire</p> <p><u>Secondary endpoints:</u></p> <ul style="list-style-type: none"> <li>• ORR according to RECIST 1.1 criteria</li> <li>• OS</li> <li>• PFS</li> <li>• Duration of treatment</li> <li>• Dose density of sunitinib</li> <li>• Rate of hospitalization irrespective of TEAEs</li> <li>• Treatment beyond progression</li> <li>• Further cancer treatment and time to first subsequent therapy (TFST)</li> <li>• Patient adherence / drug-related treatment discontinuation rates: percentage of patients with treatment discontinuation due to specific ADRs (e.g. hand-foot syndrome, diarrhea, stomatitis, fatigue, hypertension)</li> <li>• Treatment Emergent Adverse Events according to CTC 4.03:</li> <li>• Frequency/incidence, severity, percentage reduction, time-to-event of ADRs, SAEs and specific TEAEs (e.g. hand-foot syndrome, diarrhea, stomatitis, fatigue, hypertension)</li> <li>• Reduction of grade 3/4 ADRs</li> <li>• Health related Quality of Life (FACT-G, EQ-5D)</li> <li>• Time to improvement or deterioration measured by HRQoL</li> <li>• Assessment of comorbidities by Charlson Comorbidity Index (CCI) and social status</li> </ul>
Number of patients	N=430 total    Currently recruited: 10
Start date	Q1/2017
More centres?	Target number: 100 / Yes
Key inclusion criteria	<ol style="list-style-type: none"> <li>1. Written informed consent and any locally required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.</li> <li>2. Age <math>\geq</math> 18 years at time of study entry.</li> <li>3. Advanced or metastatic renal cell carcinoma, not amendable to surgery with curative intent, rendering the patient eligible for TKI treatment with sunitinib.</li> <li>4. Intended first-line treatment with sunitinib.</li> <li>5. Documented progressive disease within 6 months prior to study inclusion.</li> <li>6. Patients with measurable disease (at least one unidimensionally measurable target lesion by CT-scan or MRI) according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and non-measurable disease are eligible.</li> <li>7. Prior radiotherapy and surgery are allowed if completed 4 weeks (for minor surgery and palliative radiotherapy for bone pain: 2 weeks) prior to start of treatment and patient recovered from toxic effects.</li> <li>8. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: <math>\geq</math>60 years old and no menses for <math>\geq</math>1 year without an alternative medical cause; OR history of hysterectomy, OR history of</li> </ol>

	<p>bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.</p> <p>9. Subject is willing to receive additional concomitant coaching and able to comply with the QoL/PRO assessments specified in the protocol for the duration of the study including scheduled visits, examinations and follow up.</p>
Key exclusion criteria	<ol style="list-style-type: none"> <li>1. Any other anti-cancer treatment aside of sunitinib for mRCC (except palliative radiotherapy).</li> <li>2. Previous malignancy (other than mRCC) which either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial bladder tumor [Ta, Tis and T1].</li> <li>3. CNS metastases, unless local therapy has been for at least 3 month and patient does not require the use of steroids.</li> <li>4. Chronic liver disease with Child-Pugh B or C score</li> <li>5. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year).</li> <li>6. Any condition that, in the opinion of the investigator, would interfere with evaluation of the concomitant coaching or QoL assessments or interpretation of patient safety or study results.</li> <li>7. Participation in another clinical study with an investigational product during the last 30 days before inclusion.</li> <li>8. Any previous treatment with a tyrosine kinase inhibitor for metastatic disease. Adjuvant or neoadjuvant therapy for localized disease is permitted, provided that relapse occurred at least 6 months after last exposure.</li> <li>9. Previous enrollment or randomization in the present study (does not include screening failure).</li> <li>10. Involvement in the planning and/or conduct of the study (applies to both Pfizer staff and/or staff of sponsor and study site).</li> <li>11. Patient who might be affiliated or otherwise dependent on the sponsor, site or the investigator.</li> <li>12. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities [§ 40 Abs. 1 S. 3 Nr. 4 AMG].</li> <li>13. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</li> </ol>
Scheme of therapy	<p>Cancer treatment Standard treatment of mRCC according to the prescribing information of sunitinib: recommended dosage is 50 mg sunitinib once daily for 4 weeks followed by 2 weeks off treatment [4/2 schedule; total cycle length = 6 weeks]. Cancer treatment management, dosage, dose modifications (in particular schedule adjustments during therapy) and concomitant treatment and medication are at the discretion of the treating physician.</p> <p>Concomitant coaching [primary intervention]: The corner stones of the pro-active coaching are as follows:</p> <ul style="list-style-type: none"> <li>• Patient education <ul style="list-style-type: none"> <li>○ Information on nature and severity of treatment emergent AEs</li> <li>○ Information about remedies for TEAEs</li> <li>○ Propagation and explanation of tests and treatment decisions</li> <li>○ Patient instruction on self-care and preventive measures</li> </ul> </li> <li>• Preemptive AE treatment strategies <ul style="list-style-type: none"> <li>○ Proactive assessment of treatment emergent AEs with emphasis on predefined ADRs of special interest (fatigue, diarrhea, stomatitis, skin toxicities, hypertension)</li> </ul> </li> <li>• Supervision of reported ADR severity, ADR mitigation strategies and</li> </ul>

	<p>cancer treatment modification by treating physician</p> <ul style="list-style-type: none"> <li>• Therapy surveillance by phone with a structured interview (week 1, 2, 3, 4, 5 during first 2 cycles; week 2 and 4 in subsequent cycles)</li> <li>• Availability of coach for unscheduled contacts by phone (during normal business hours)</li> </ul> <p style="text-align: center;"><b>PREPARE</b></p>
<p>Criteria for tumor evaluation</p>	<p>RECIST 1.1</p>
<p>Rationale</p>	<p>Clinical outcome has improved since the introduction of targeted therapies in the field of metastatic renal cell carcinoma (mRCC). Agents inhibiting the vascular endothelial growth factor receptor (VEGFR) are a key element in the treatment of mRCC and are associated with a response rate of approx. 30% (Motzer et al., 2013). However, 10-20% of patients are not able to tolerate treatment and stop early because of treatment-related toxicity (Motzer et al., 2013; 2007). For patients dropping-off therapy for intolerance, clinical outcome remains poor (Grünwald et al., 2013). Proactive treatment has been shown to impact time to event and severity of adverse events (AE) in cancer patients (Lacouture et al., 2010), justifying a structured approach to manage treatment-emergent adverse events (TEAEs) proactively.</p> <p>The goal of our study is to define the benefit of proactive coaching in mRCC, when compared to a reactive approach, which is considered the standard of care.</p> <p>It's hypothesized that intensified proactive coaching during the first 24 weeks of treatment improves patients' health related quality of life (HR-QoL), which may improve patients' adherence to treatment and ultimately clinical outcome.</p>

## Arbeitsgruppe Ösophagus-/ Magen-Karzinom

### Stadium II/III Adenokarzinom des Magens oder gastroösophagealen Übergangs – neoadjuvante/ perioperative Therapie

**AIO-STO-0315/ass: Perioperative RAMucirumab in combination with FLOT versus FLOT alone for reSEctable eSophagogastric adenocarcinoma – RAMSES – A phase II/III trial of the AIO**

#### AIO-assozierte Studie

Studiennummer/-Code: AIO-STO-0315/ass | RAMSES | FLOT7

Status: in Rekrutierung

Rekrutierungszeitraum 2016 - 2018

Weitere Zentren: Nicht benötigt

Letzte Aktualisierung April 2018

Study type	Multicenter, randomized, open label phase II/III study
Investigational and control drugs	Ramucirumab FLOT (backbone therapy)
Sponsor	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Contact: Prof. Dr. Salah-Eddin Al-Batran, Dr. Claudia Pauligk, Ulli Simone Bankstahl, Dr. Gerrit zur Hausen
Objectives	<p>Phase II:</p> <ul style="list-style-type: none"> <li>To compare rate of pathological complete or subtotal responses (pCR/SR) in patients treated with ramucirumab plus FLOT versus patients treated with FLOT alone.</li> <li>To determine R0 resection rates, progression-free survival (PFS), overall survival (OS)</li> </ul> <p>Phase III:</p> <ul style="list-style-type: none"> <li>To compare OS in both trial arms</li> <li>To determine R0 resection rates, pathological response rates, PFS and OS rates at 3 and 5 years and PFS.</li> </ul> <p>Safety Objectives (phase II and III)</p> <ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of the ramucirumab plus FLOT compared with FLOT in patients with adenocarcinoma of the stomach and GEJ, focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade <math>\geq 3</math> adverse events, and Grade <math>\geq 3</math> laboratory toxicities</li> <li>To evaluate the perioperative morbidity and mortality of the regimens described above</li> </ul>
Study design	<p>This is a multicenter, randomized, controlled, open-label study including patients with locally advanced adenocarcinoma of the stomach and GEJ scheduled to receive perioperative chemotherapy.</p> <p>The scope of the phase II portion of the trial is to evaluate pathological response rates of either regimen assessed by a centralized pathology and evaluate safety and tolerability.</p> <p>Patients with locally advanced esophagogastric adenocarcinoma (i.e. cT2 any N or any T N-positive) with exclusion of distant metastases will be included in this trial.</p> <p>Patients will be centrally reviewed and then stratified by tumor site (GEJ vs. gastric), histological type (intestinal vs. diffuse/mixed or unknown) and clinical stage (T1/2 vs. T3/4 and/or N+) and randomized 1:1 to receive either FLOT (Arm A) or FLOT/ramucirumab (Arm B).</p>

**Arm A (FLOT)**

Patients randomized to Arm A will receive 4 pre-operative cycles (8 weeks) of biweekly FLOT (Docetaxel 50 mg/m<sup>2</sup> in 250 ml NaCl 0.9%, iv over 1 h; Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2h; Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0.9%, iv over 30 min; 5-FU 2600 mg/m<sup>2</sup>, iv over 24 h, q2wk) of the preoperative treatment phase. Surgery in Arm A is planned to occur 4 to 6 weeks after d1 of last FLOT. Patients will receive 4 additional post-operative cycles (8 weeks) of FLOT in the post-operative treatment phase. Post-operative treatment should start 6 to 8 weeks, but at maximum 12 weeks after surgery.

**Arm B (FLOT/ramucirumab)**

Patients randomized to Arm B will receive ramucirumab 8mg/kg i.v. over 60 min in combination with the FLOT regimen, which is administered identical to Arm A as described above. Surgery in Arm B is planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients will receive 4 additional post-operative cycles (8 weeks) of FLOT/ramucirumab in the post-operative treatment phase followed by a total of 16 cycles of ramucirumab as a monotherapy (q2wk), starting 2 weeks after d1 of the last cycle of FLOT/ramucirumab.

In both of the arms, tumor assessments (CT or MRI) are performed before randomization and prior to surgery, and then every 3 months thereafter until progression/relapse, death or end of follow-up. A change from CT into MRI in the follow up period is possible at any time.

During treatment, clinical visits (blood cell counts, detection of toxicity) occur prior to every treatment dose. Safety of FLOT/ramucirumab will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.

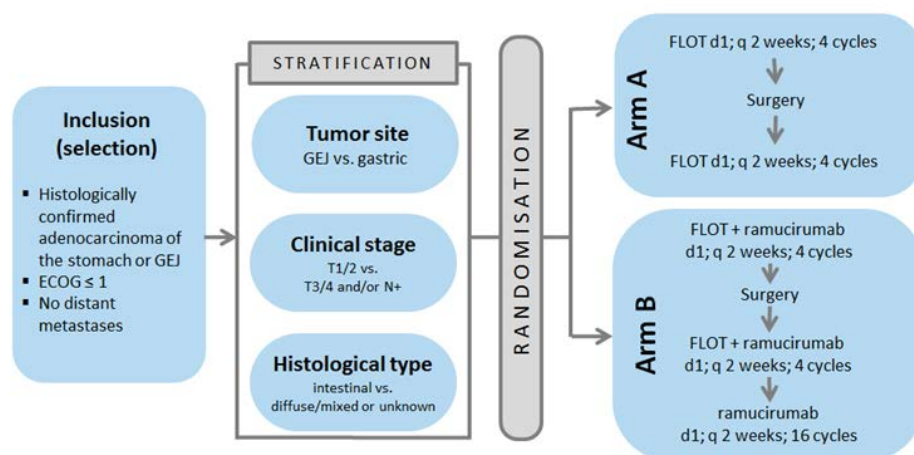


Figure 1: Study Flow Chart.

When the recruitment of the phase II portion is completed, the primary end point of the phase II portion will be analyzed, along with all relevant safety outcome measures. A continuation to phase III will be recommended if the phase II portion observes a positive efficacy signal in terms of pCR/pSR rates, and if FLOT/ramucirumab is shown to be feasible and is not associated with relevant increase in postsurgical morbidity or mortality (for further information s. protocol).

If decided to continue the trial into phase III and this is confirmed and accepted by Lilly Deutschland GmbH, further efficacy endpoints will not be analyzed at this time. The transition into phase III will be performed via an amendment of the study protocol, considering a new sample size calculation taking into account the results of the FLOT4. For the phase III part, additional centers in representative parts of the world will be recruited. The phase II/III design is not alpha-spending. In case of continuation, only pathologic response and safety will be analyzed at the end of the phase II portion. All other efficacy parameters such as OS, PFS etc. will not be analyzed. Therefore, alpha level for the primary endpoint of phase III which is OS will not be affected by the phase II/III

	design and is at $p=0.05$ .
Rationale	FLOT is regarded a standard chemotherapy regimen in Germany according to German S3 guidelines. The use of FLOT in the perioperative setting has become German wide practice. Within the framework of the AIO FLOT4 study, the FLOT regimen is currently compared against another standard for perioperative treatment, ECF. Interim results showed that FLOT is safe. More patients undergo postoperative chemotherapy with FLOT (ASCO 2012). Interim results from the phase II part of the FLOT4 trial also show that FLOT was associated with significantly more pathologic complete and subtotal response.
Chemotherapy schedule	<p><b>FLOT</b></p> <ul style="list-style-type: none"> <li>· Docetaxel 50 mg/m<sup>2</sup>, iv over 1 h, d1</li> <li>· Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2h, d1</li> <li>· Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0,9%, iv over 1 h, d1</li> <li>· 5-FU 2600 mg/m<sup>2</sup>, iv over 24 h, d1</li> </ul> <p>(= 1 cycle) Start of next cycle on day 15 (d15)</p> <p>Patients in arm B (ramucirumab/FLOT parallel group) will receive ramucirumab 8mg/kg iv over 60 min in combination with FLOT on d1 (i.e. parallel to the 4 cycles of FLOT scheduled pre- and postoperatively) followed by a total of 16 cycles as monotherapy every 2 weeks, starting 2 weeks after the last cycle of FLOT.</p>
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Histologically confirmed, resectable adenocarcinoma of the gastroesophageal junction (AEG/GEJ-type II-III) or the stomach (uT2, uT3, uT4, any N category, M0), or any T N+ M0 patient, with the following specifications: <ol style="list-style-type: none"> <li>a. Medical and technical operability, according to the techniques described in Chapter 12 Surgical Therapy that are subtotal, total or transhiatal extended gastrectomy (patients planned to receive transthoracic esophagectomy are not eligible for the study)</li> <li>b. Participating sites in PETRARCA study: Negative HER-2 detection (score IHC HER-2 0 or IHC HER-2 1+ ); IHC HER-2 2+ and negative by FISH, SISH or CISH1</li> </ol> </li> <li>2. No preceding cytotoxic or targeted therapy</li> <li>3. No prior partial or complete tumor resection</li> <li>4. Female and male patients <math>\geq 18</math> and <math>\leq 70</math> years. Patients in reproductive age must be willing to use adequate contraception during the study and for 7 months after the end of ramucirumab treatment (Appropriate contraception is defined as surgical sterilization (e.g., bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)). Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start.<sup>2</sup></li> <li>5. ECOG <math>\leq 1</math></li> <li>6. Exclusion of distant metastasis by CT of thorax and abdomen, bone scan or MRI (if osseous lesions are suspected due to clinical signs). Exclusion of the infiltration of any adjacent organs or structures by CT or MRI.</li> <li>7. Laparoscopic exclusion of peritoneal carcinomatosis, if suspected clinically</li> <li>8. Adequate haematological, hepatic and renal function parameters:</li> </ol>

<sup>1</sup> HER-2 positive patients are recruited in the German PETRARCA study (EudraCT: 2014-002695-86) sponsored by the IKF. So this study is restricted for HER-2 negative patients at sites where PETRARCA is recruiting.

<sup>2</sup> There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.



	<ol style="list-style-type: none"> <li>a. Leukocytes <math>\geq 3000/\text{mm}^3</math>, platelets <math>\geq 100,000/\text{mm}^3</math>, neutrophil count (ANC) <math>\geq 1000/\mu\text{L}</math>, hemoglobin <math>\geq 9 \text{ g/dL}</math> (5.58 mmol/L),</li> <li>b. Adequate coagulation function as defined by International Normalized Ratio (INR) <math>\leq 1.5</math>, and a partial thromboplastin time (PTT) <math>\leq 5</math> seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to randomization.</li> <li>c. Serum creatinine <math>\leq 1.5 \times</math> upper limit of normal</li> <li>d. Urinary protein <math>\leq 1+</math> on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is <math>\geq 2+</math>, a 24-hour urine collection for protein must demonstrate <math>&lt; 1000 \text{ mg}</math> of protein in 24 hours to allow participation in this protocol).</li> <li>e. Bilirubin <math>\leq 1.5 \times</math> upper limit of normal, AST and ALT <math>\leq 3.0 \times</math> upper limit of normal, alkaline phosphatase <math>\leq 6 \times</math> upper limit of normal</li> </ol> <p>9. Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures</p>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Known hypersensitivity against ramucirumab, 5-FU, leucovorin, oxaliplatin, or docetaxel</li> <li>2. Other known contraindications against ramucirumab, 5-FU, leucovorin, oxaliplatin, or docetaxel</li> <li>3. Patients with esophageal cancer and those with adenocarcinoma of GEJ type I and all patients who are planned to have transthoracic esophagectomy.</li> <li>4. Clinically significant active coronary heart disease, clinically active cardiomyopathy or congestive heart failure, peripheral artery occlusive disease (PAOD, German pAVK), or any history of aortic aneurysm</li> <li>5. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina</li> <li>6. Uncontrolled or poorly-controlled hypertension (<math>&gt; 160 \text{ mmHg}</math> systolic or <math>&gt; 100 \text{ mmHg}</math> diastolic for <math>&gt; 4</math> weeks) despite standard medical management.</li> <li>7. Clinically significant valvular defect</li> <li>8. Past or current history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix</li> <li>9. Radiologically documented evidence of major blood vessel invasion or encasement by cancer.</li> <li>10. Patients with involved retroperitoneal (e.g. para-aortal, paracaval or interaortocaval lymph nodes) or mesenterial lymph nodes (distant metastasis!)</li> <li>11. Known brain metastases</li> <li>12. Other severe internal disease or acute infection</li> <li>13. Peripheral polyneuropathy <math>\geq</math> NCI Grade II</li> <li>14. Chronic inflammatory bowel disease</li> <li>15. Grade 3-4 GI bleeding within 3 months prior to enrollment.</li> <li>16. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment.</li> <li>17. The patient has undergone major surgery within 28 days prior to enrollment.</li> <li>18. Receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.</li> <li>19. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to randomization.</li> <li>20. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.</li> </ol>

	<p>21. On-treatment participation in another clinical study in the period 30 days prior to inclusion and during the study</p> <p>22. Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.</p> <p>23. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)</p> <p>24. Any other concurrent antineoplastic treatment including irradiation</p> <p>25. Current chronic alcohol, nicotine or drug abuse or history of chronic alcohol abuse during last 12 months. Nicotine abuse is defined as <math>\geq 25</math> pack-years (Willigendael et al., 2004).</p>
Sample size	<p>Phase II portion: n = 150 (75 per Arm)</p> <p>Phase III portion: n = 758 patients (379 per Arm)</p>
Duration of the study (planned)	<p>Recruitment duration will be 1 year for phase II and 2.5 years for phase III = recruitment duration for phase II/III is 3.5 years</p> <p>The follow-up time for the phase III is 2 year after last patients in, resulting in a total study duration of 5.5 years (3.5+2) for phase II/III study</p> <p>Note: If the phase II study part continues to phase III, there are no specific follow-up times for the phase II part. If continuation is not proposed, at least a two years follow-up (counted from last patient in) will be applicable. So the length of the phase II study will be 3 years.</p>
Teilnehmende Zentren	51
Anzahl eingeschl. Pat.	129 (Stand 06.04.2018)

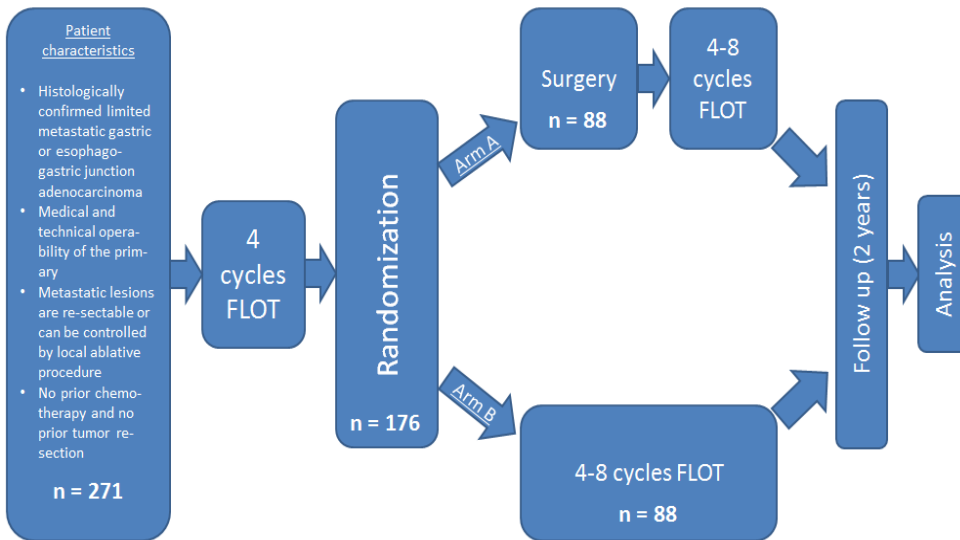
**AIO-STO-0215: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction – a phase III trial of AIO/CAO-V/CAOGI (RENAISSANCE / FLOT5)**

### AIO-Studie

Studiennummer/-Code:	AIO-STO-0215 - RENAISSANCE / FLOT5
Status:	in Rekrutierung
Rekrutierungszeitraum	2016 - 2020
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	09.04.2018

Trial type	Prospective, randomized, multicentre, open label, phase III trial
Coordinating investigators	<p>Prof. Dr. med. Salah-Eddin Al-Batran (LKP)          Institut für Klinisch-Onkologische Forschung (IKF)          Krankenhaus Nordwest          UCT – Universitäres Centrum für Tumorerkrankungen Frankfurt          Steinbacher Hohl 2-26, 60488 Frankfurt          Tel. 069/7601-4420, Fax 069/7601-3655, albatran.salah@khnw.de</p> <p>Prof. Dr. med. Stefan P. Mönig          Hôpitaux Universitaires de Genève, Service de Chirurgie viscéral          stefan.moenig@unige.ch</p>
Medical condition	Limited metastatic adenocarcinoma of the stomach or esophagogastric junction (modified Flot3 arm B trial population)
Objective(s)	The aim of the study is to investigate whether induction chemotherapy followed by resection of the primary tumor (and eventually the metastases)

	prolongs overall survival with maintained quality of life compared to chemotherapy alone (the current standard) in previously untreated patients with synchronously limited metastatic esophagogastric adenocarcinoma. The primary endpoint is overall survival.
Intervention(s)	<p><u>Experimental intervention/index test:</u>  Arm A: Four cycles of FLOT (Docetaxel 50 mg/m<sup>2</sup>, iv over 2 h, d1; Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2h, d1; Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0,9%, iv over 1 h, d1; 5-FU 2600 mg/m<sup>2</sup>, iv over 24 h, d1 (= 1 cycle); Start of next cycle on day 15 (every two weeks)) followed by surgery. Target of surgery: Complete (R0 and at least D2) resection of the primary tumor and, whenever technically possible, complete (R0) resection or complete macroscopic cytoreduction of the metastases. After surgery, 4 to 8 additional cycles will be applied.</p> <p><u>Control intervention/reference test:</u>  Arm B: Patients will receive 8 to 12 cycles of FLOT for palliation (current standard).</p> <p><u>Follow-up per patient:</u>  Survival status will be assessed every 3 months for up to 5 years after randomization.</p> <p><u>Duration of intervention per patient:</u>  Basically, a total treatment of 8-12 cycles FLOT (16 to 24 weeks) will be administered.</p> <p><u>Experimental and/or control off-label or on-label in Germany:</u>  not applicable</p>
Key inclusion and exclusion criteria	<p><u>Key inclusion criteria:</u></p> <ul style="list-style-type: none"> <li>- Histologically confirmed limited metastatic gastric or esophagogastric junction adenocarcinoma.</li> <li>- Medical and technical operability of the primary (central evaluation).</li> <li>- Metastatic lesions are resectable or can be controlled by local ablative procedure (central evaluation). This criterion does not apply for the patients with distant lymph node metastases.</li> <li>- No prior chemotherapy and no prior tumor resection.</li> </ul> <p><u>Key exclusion criteria:</u></p> <ul style="list-style-type: none"> <li>- Medical inoperability.</li> <li>- Inability to understand the study and/or comply with the protocol procedures.</li> <li>- Extensive metastatic status or cM0.</li> <li>- Secondary malignancy &lt; 3 years ago.</li> </ul>
Outcome(s)	<p><u>Primary efficacy endpoint:</u> Overall survival (OS)</p> <p><u>Key secondary endpoint(s):</u> Quality of life (QoL) adjusted OS, QoL-response, QoL mean scores, OS in pts with lymph node metastases only, Progression free survival (PFS); perioperative morbidity and mortality, toxicity</p> <p><u>Assessment of safety:</u> 30 days and 90 days mortality/morbidity, toxic effects are graded using CTC adverse events criteria ver. 4.0</p>
Sample size	176 (88 per Arm)
Trial duration	<p>First patient in to last patient out (months): 72</p> <p>Duration of the entire trial (months): 72</p> <p>Recruitment period (months): 48</p>
Anzahl eingeschl. Pat.	72 (Stand 09.04.2018)

**Study-Design: FLOT5**

**AIO-STO-0115/ass: FLOT vs. FLOT/Herceptin/Perjeta for perioperative therapy of adenocarcinoma of the stomach and gastroesophageal junction expressing HER-2, a phase II/III trial of the AIO (PETRARCA-Trial)**

**AIO-assozierte Studie**

Studiennummer/-Code:	AIO-STO-0115/ass   PETRARCA-Trial
Status:	in Rekrutierung
Rekrutierungszeitraum	2016 - 2018
Weitere Zentren:	Nicht benötigt
Letzte Aktualisierung	April 2018

Investigational and control drugs	Pertuzumab (Perjeta) Herceptin FLOT (backbone therapy)
Study type	Randomized, open, phase II/III
Coordinating Investigator (LKP according to AMG)	Prof. Dr. Ralf-Dieter Hofheinz TagesTherapieZentrum am Interdisziplinären Tumorzentrum Universitätsmedizin Mannheim der Universität Heidelberg Theodor-Kutzer Ufer 1-3, Haus 9, 68167 Mannheim e-mail: ralf.hofheinz@umm.de
Sponsor	IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt/Main Contact: Prof. Salah-E. Al-Batran, Dr. Claudia Pauligk, Ulli S. Bankstahl, Dr. Gerrit zur Hausen
Objectives / Endpoints (efficacy, safety)	<p>Phase II: To compare rate of pathological complete response in patients treated with pertuzumab (Perjeta®) in addition to trastuzumab (Herceptin®) plus FLOT (5-FU, Leucovorin, Oxaliplatin and Taxotere (Docetaxel)) versus patients treated with FLOT alone. To determine R0 resection rates, median disease-free survival (DFS), median overall survival (OS) and to analyze the predictive effect of molecular alterations (exploratory) and pharmacokinetics (in selected centers)* *Only in case the study does not continue into phase III</p> <p>Phase III: To compare median DFS in both trial arms To determine R0 resection rates, pathological response rates, DFS and OS rates at 3 and 5 years and median OS. To analyze the predictive effect of molecular alterations (exploratory)</p> <p>Safety Objectives (phase II and III) To evaluate the safety and tolerability of Perjeta / Herceptin plus FLOT compared with FLOT in patients with adenocarcinoma of the stomach and GEJ (gastroesophageal junction), focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade <math>\geq</math> 3 adverse events, and Grade <math>\geq</math> 3 laboratory toxicities To evaluate the perioperative morbidity and mortality of the regimens described above</p> <p>Primary efficacy endpoint (phase II)</p> <ul style="list-style-type: none"> <li>• Rate of pathological complete response</li> </ul> <p>Secondary efficacy endpoints (phase II)</p> <ul style="list-style-type: none"> <li>• R0 resection rate</li> </ul>

	<ul style="list-style-type: none"> <li>• Median disease-free survival (DFS)*</li> <li>• Median overall survival (OS)*</li> <li>• PK Analysis (in selected centers)</li> <li>• Subgroup analyses: pathological response according to HER-2 status HER-2 IHC 3+ vs. other cases</li> <li>• Subgroup analyses: DFS and OS according to HER-2 status HER-2 IHC 3+ vs. other cases*</li> </ul> <p>* Only in case the study does not continue into phase III</p> <p>Primary efficacy endpoint (phase III)</p> <ul style="list-style-type: none"> <li>• Median DFS</li> </ul> <p>Secondary efficacy endpoints (phase III)</p> <ul style="list-style-type: none"> <li>• R0 resection rate</li> <li>• Pathological response rates</li> <li>• DFS rates at 3 and 5 years</li> <li>• OS rates at 3 and 5 years</li> <li>• Median OS</li> <li>• Subgroup analyses: pathological response, DFS, and OS according to HER-2 status HER-2 IHC 3+ vs. other cases</li> </ul>
Background / Rationale	<p>The outcome of patients with advanced gastric or GEJ cancer remains unsatisfactory. The 5-year survival rate with perioperative Epirubicin, Cisplatin and 5-FU (ECF) or Cisplatin and 5-FU (CF) is below 40 %. It is clear that considerable investigation is still required to improve perioperative protocols and their efficacy.</p> <p>FLOT is one of the most intensively evaluated regimen for gastric and GEJ cancer and one of the standard chemotherapy regimen for first-line treatment of gastric cancer, according to German S3 guidelines. Within the framework of the AIO FLOT 4 phase II/III study, the FLOT regimen is currently compared against another standard for perioperative treatment, ECF/ECX. An unpublished interim analysis of this phase III trial showed significantly improved pathological response rates for FLOT against ECF/ECX. A published safety analysis confirmed feasibility and tolerability of FLOT as compared with ECF/ECX. For patients with HER-2 positive tumors, the HER-FLOT trial has been conducted within the AIO network including n = 58 patients. The tolerability of FLOT / Herceptin was good and results showed a comparatively high rate of pCR (23 % among the first n = 53 analysed patients; were presented at ASCO 2014). Thus, FLOT / Herceptin constitutes a safe and presumably very active regimen for patients with gastric and GEJ tumors and HER-2 overexpression that deserves further evaluation in randomized trials.</p>

Study design	<p>This is a multicenter, randomized, controlled, open-label study including patients with locally advanced adenocarcinoma of the stomach and GEJ scheduled to receive perioperative chemotherapy. According to centrally assessed HER-2 status: Patients with HER-2 positive tumors will receive FLOT +/- Herceptin / Perjeta.</p> <p>The scope of the phase II portion of the trial is to evaluate pathological response rates of either regimen assessed by a centralized pathology and evaluate safety and tolerability.</p> <p>Patients with locally advanced esophagogastric adenocarcinoma (i.e. cT2 any N or any T N-positive) with exclusion of distant metastases will be included in this trial.</p> <p>Patients will be stratified by age (18-69 vs. <math>\geq 70</math>), tumor site (GEJ vs. gastric) and clinical stage (T1/2 vs. 3/4 and N- vs. N+) and randomized 1:1 to receive either FLOT (Arm A) or FLOT/Herceptin/Perjeta (Arm B).</p> <p><u>Arm A (FLOT)</u></p> <p>Patients randomized to Arm A will receive 4 pre-operative treatments of FLOT (Docetaxel 50 mg/m<sup>2</sup>, iv over 1 h; Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2 h; Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0.9 %, iv over 30 min; 5-FU 2600 mg/m<sup>2</sup>, iv over 24 h) on d1, d15, d29, d43 of the preoperative treatment phase. Surgery is recommended to occur 4 weeks after last FLOT (4 weeks after d43 = day 71). Patients will receive 4 additional post-operative treatments of FLOT on d1, d15, d29, and d43 of the post-operative treatment phase. Post-operative treatment should start 6 to 8 weeks, but at maximum 12 weeks after surgery.</p> <p><u>Arm B (FLOT/Herceptin/Perjeta)</u></p> <p>Patients randomized to Arm B will receive the FLOT regimen identical to Arm A as described above in conjunction with three-weekly Herceptin at 8mg/kg initial dose (Day 1, loading dose) followed by subsequent doses of Herceptin at 6mg/kg on d22 and d43 and Perjeta at 840mg on d1, d22, and d43. Surgery is recommended to occur 4 weeks after last FLOT/Herceptin/Perjeta dose (4 weeks after d43 = day 71). Patients will receive 3 additional doses of Herceptin and Perjeta on d1, d22, and d43 of the post-operative treatment phase, together with the postoperative chemotherapy. Moreover, patients will receive 9 additional doses of Herceptin and Perjeta after the end of post-operative FLOT (see overview in Figure 2).</p> <p>In both of the arms, tumor assessments (CT or MRI) are performed before randomization and prior to surgery and then every 3 months thereafter until progression/relapse, death or end of follow-up.</p> <p>During treatment, clinical visits (blood cell counts, detection of toxicity) occur prior to every treatment dose. Safety of FLOT/Herceptin/Perjeta will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.</p>
Population	Adult patients with HER2-positive, locally advanced EGA scheduled to receive perioperative chemotherapy.
Inclusion/exclusion criteria	<p><b>Inclusion</b></p> <ul style="list-style-type: none"> <li>• Histologically confirmed adenocarcinoma of the GEJ (type I-III) or the stomach (uT2, uT3, uT4, any N category, M0), or any T N+ M0 patient, with the following specifications: <ul style="list-style-type: none"> <li>- Medical and technical operability</li> <li>- Centralized detection of either an adenocarcinoma with HER-2 3+ (IHC) or HER-2 2+ (IHC) with amplification proven by FISH, SISH or CISH</li> </ul> </li> <li>• No preceding cytotoxic or targeted therapy</li> <li>• No prior partial or complete tumor resection</li> <li>• Exclusion of the infiltration of any adjacent organs or structures by CT or MRI</li> <li>• Exclusion of distant metastasis by CT or MRI of thorax and abdomen, and bone scan (if osseous lesions are suspected due to clinical signs)</li> <li>• Female and male patients <math>\geq 18</math> years. Patients in reproductive age must be willing to use adequate contraception during the study and for 7</li> </ul>

	<p>months after the end of pertuzumab and Herceptin treatment (Appropriate contraception is defined as surgical sterilization (e.g., bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)). Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start.</p> <ul style="list-style-type: none"> <li>• ECOG <math>\leq</math> 2</li> <li>• Laparoscopic exclusion of peritoneal carcinomatosis, if suspected clinically</li> <li>• Adequate haematological, hepatic and renal function parameters: <ul style="list-style-type: none"> <li>- Leukocytes <math>\geq</math> 3.000/mm<sup>3</sup>, platelets <math>\geq</math> 100.000/mm<sup>3</sup></li> <li>- Serum creatinine <math>\leq</math> 1.5 x upper limit of normal, or GFR &gt; 40 ml/min</li> <li>- Bilirubin <math>\leq</math> 1.5 x upper limit of normal, AST and ALT <math>\leq</math> 3.5 x upper limit of normal, alkaline phosphatase <math>\leq</math> 6 x upper limit of normal</li> </ul> </li> <li>• LVEF value <math>\geq</math> 55 %, as assessed by echocardiography</li> <li>• Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures</li> </ul> <p>Exclusion</p> <ul style="list-style-type: none"> <li>• Patients with involved retroperitoneal (e.g. para-aortal, paracaval or interaortocaval lymph nodes) or mesenterial lymph nodes (distant metastasis!)</li> <li>• Known hypersensitivity against Herceptin, pertuzumab, 5-FU, leucovorin, oxaliplatin, or docetaxel</li> <li>• Other known contraindications against Herceptin, pertuzumab, 5-FU, leucovorin, oxaliplatin, or docetaxel</li> <li>• Documented history of congestive heart failure of any NYHA, myocardial infarction within the past 6 months before the first dose of study treatment</li> <li>• Clinically significant valvular defect, history of poorly controlled arterial hypertension (systolic blood pressure &gt; 180 mmHG or diastolic blood pressure &gt; 100 mmHg) or uncontrollable high-risk cardiac arrhythmia (i.e tachycardia with a heart rate &gt; 100/min at rest), significant ventricular arrhythmia (ventricular tachycardia) or higher grade atrioventricular-block (second degree AV-block Type 2 (Mobitz2) or third degree AV-block)</li> <li>• Past or current history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix</li> <li>• Known brain metastases</li> <li>• Other severe internal disease or acute infection</li> <li>• Peripheral polyneuropathy <math>\geq</math> NCI Grade II</li> <li>• Chronic inflammatory bowel disease</li> <li>• Clinically significant active GI bleeding</li> <li>• On-treatment participation in another clinical study in the period 30 days prior to inclusion and during the study</li> <li>• Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.</li> <li>• Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)</li> <li>• Any other concurrent antineoplastic treatment including irradiation</li> </ul>
Dose, regimen, treatment cycle	<p>Arm A (FLOT):</p> <p>Pre-operative therapy:  Docetaxel 50 mg/m<sup>2</sup>, iv over 2 h, d1, d15, d29, d43  Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2h, d1, d15, d29, d43  Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0.9 %, iv over 1 h, d1, d15, d29, d43 *</p>



	<p>5-FU 2600 mg/m<sup>2</sup>, iv over 24 h, d1, d15, d29, d43</p> <p>Surgery is recommended to be scheduled 4 weeks after d43.</p> <p>Post-operative therapy (start 6 to 8 weeks after surgery):  Docetaxel 50 mg/m<sup>2</sup>, iv over 2 h, d1, d15, d29, d43  Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2h, d1, d15, d29, d43  Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0.9 %, iv over 1 h, d1, d15, d29, d43 *</p> <p>5-FU 2600 mg/m<sup>2</sup>, iv over 24 h, d1, d15, d29, d43</p> <p>Arm B (FLOT/Herceptin/Perjeta)</p> <p>Pre-operative therapy:  Herceptin 8/6 mg/kg 250 ml of 0.9 % NaCl, d1, d22, d43 **  Perjeta 840 mg in 250 ml NaCl 0.9 %, d1, d22, d43  Docetaxel 50 mg/m<sup>2</sup>, iv over 1 h, d1, d15, d29, d43  Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2 h, d1, d15, d29, d43  Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0.9 %, iv over 30 min, d1, d15, d29, d43 *</p> <p>5-FU 2600 mg/m<sup>2</sup>, iv over 24 h, d1, d15, d29, d43</p> <p>Surgery is recommended to be scheduled 4 weeks after d43.</p> <p>Post-operative therapy (start 6 to 8 weeks after surgery):  Herceptin 8/6 mg/kg in 250 ml NaCl 0.9 %, d1, d22, d43 **  Perjeta 840 mg in 250 ml NaCl 0.9 %, d1, d22, d43  Docetaxel 50 mg/m<sup>2</sup>, iv over 1 h, d1, d15, d29, d43  Oxaliplatin 85 mg/m<sup>2</sup> in 500 ml G5%, iv over 2 h, d1, d15, d29, d43  Leucovorin 200 mg/m<sup>2</sup> in 250 ml NaCl 0,9 %, iv over 30 min, d1, d15, d29, d43 *</p> <p>5-FU 2600 mg/m<sup>2</sup>, iv over 24 h, d1, d15, d29, d43.</p> <p>(*) Note: Leucovorin can be replaced by sodium folinate that is given according to local guideline. The infusion durations and solution volumes described above are recommendations. Investigators can use their local protocols.</p> <p>9 additional doses of Herceptin and Perjeta follow after the end of post-operative FLOT.</p>
Key dates	Recruitment duration: 1 year for phase II Follow-up: at least 2 years
Number of patients, centers and location	Total number of patients: n = 100 patients with EGA overexpression of HER-2 will be included in the phase II portion of the study Number of sites: 60 Location of sites: Germany
No. patients included	65 (Stand 06.04.2018)

**AIO-STO-0317: A randomized, open-label Phase II efficacy and safety study of Atezolizumab in combination with FLOT versus FLOT alone in patients with gastric cancer and adenocarcinoma of the oesophago-gastric junction (MO30039) – The DANTE Trial**

### AIO-Studie

Studiennummer/-Code:	AIO-STO-0317 - DANTE-Trial
Status:	in Vorbereitung
Rekrutierungszeitraum	2018-2020 (geplant)
Weitere Zentren:	nein
Letzte Aktualisierung	April 2018

Study type	Multicenter, randomized, open label phase II study
Protocol Code	MO30039 / DANTE
Investigational and control drugs	Atezolizumab FLOT (backbone therapy)
Objectives	<p><u>Primary Efficacy Objective</u></p> <ul style="list-style-type: none"> <li>to compare progression/disease-free survival (PFS/DFS) in patients with locally advanced, operable esophagogastric adenocarcinoma receiving perioperative FLOT with atezolizumab versus FLOT alone in the intent to treat population (ITT) and where PFS/DFS is defined as the time from randomization to disease progression or relapse after surgery or death from any cause</li> </ul> <p><u>Secondary Efficacy Objectives</u></p> <ul style="list-style-type: none"> <li>Pathological complete regression (pCR, TRG 1a by Becker) rate where pCR is defined as the absence of residual tumor based on evaluation of the resected esophagogastric specimen in the primary by a central reference pathologist</li> <li>Pathological complete and subtotal regression (TRG1a/b by Becker). TRG1a/b is defined as &lt; 10% residual tumor per tumor bed based on evaluation of the resected esophagogastric specimen in the primary by a central reference pathologist.</li> <li>TRG1a and TRG1a/b in the sampled regional lymph nodes.</li> <li>R0 resection rate where R0 resection is defined as a microscopically margin negative resection with no gross or microscopic tumor remains in the areas of the primary tumor and/or sampled regional lymph nodes based on evaluation by the local pathologist.</li> <li>Overall survival (OS) where OS is defined as the time from randomization to death from any cause</li> <li>The immune cell infiltration rate determined by comparing the density of CD8-positive cells in tumor biopsies obtained from the same tumor location at baseline and after two and four cycles of study treatment..</li> </ul> <p><u>Safety Objectives</u></p> <ul style="list-style-type: none"> <li>Incidence, frequency, severity, and timing of adverse events (AEs)</li> <li>Changes in vital signs, physical findings, and clinical laboratory results</li> <li>Perioperative morbidity and mortality</li> </ul>
Study design	<p>This is a multicenter, randomized, controlled, open-label study comparing perioperative atezolizumab with FLOT chemotherapy versus FLOT alone in patients with locally advanced, operable adenocarcinoma of the stomach or GEJ.</p> <p>The study will evaluate the safety and efficacy of the study treatment regimens. The study includes an evaluation of rate of immune cell infiltration into the esophagogastric tumor tissue following two and four cycles of neoadjuvant therapy.</p> <p>Potential study participants will be assessed for eligibility during a 28-day screening period that includes central verification of clinical stage and</p>

eligibility. Eligible patients will be enrolled and randomized to perioperative treatment with either atezolizumab with FLOT (Arm A) or FLOT alone (Arm B). Randomization will occur in a 1:1 ratio with stratification by clinical nodal stage (N+ vs. N-), location of the primary (GEJ type I vs. GEJ type II/II vs. stomach), and MSI-status (MSI-high vs. MSI-low/MSI-stable). Quantitative PDL-1 mRNA expression [high vs. intermediate vs. low] will be performed but not used as stratification factor.

Following randomization, study patients will enter the study treatment period which will last approximately 22 to 52 weeks depending on treatment arm and timing of surgery.

**Arm A: Atezolizumab with FLOT:**

Patients randomized to treatment Arm A will receive atezolizumab + FLOT in four 2-week treatment cycles as described below prior to undergoing surgery. Following surgery, patients will receive four further 2-week cycles of atezolizumab + FLOT followed by 8 additional 3-week treatment cycles with atezolizumab alone (maintenance setting: 1,200 mg q3w). FLOT can be deescalated to FLO, FLT or FL in case of chemo-related toxicity at any time and at the discretion of investigator.

**Arm B: FLOT alone:** Patients randomized to Arm B will receive FLOT alone for four 2-week treatment cycles prior to surgery. Following surgery, patients will receive four further 2-week cycles of chemotherapy alone. FLOT can be deescalated to FLO, FLT or FL in case of chemo-related toxicity at any time and at the discretion of investigator.

In both study arms, surgery is recommended to occur 4 weeks after the last administration of pre-operative study therapy. Post-operative treatment is recommended to start 6 to 8 weeks (to a maximum of 12 weeks) after surgery. Study specifications for surgical resection are consistent with national guidelines. Surgical approaches will be tailored to the individual patient according to local standards with the goal of achieving R0-resection of the primary tumor. All resection samples will be submitted for central evaluation of histopathological regression.

During the treatment period, safety assessments conducted with results reviewed prior to each study treatment include hematology, serum chemistry, physical exam, and recording of concomitant medications and AEs. AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. Disease assessments will be conducted at screening, prior to surgery and every 3 months thereafter, until disease progression, relapse or death or end of the study. Assessments will include CT or MRI of the chest and abdomen. Disease assessment at screening will also include laparoscopy as clinically indicated (i.e. T3 or T4 tumors of diffuse type histology in the stomach or upon request of the central review) to confirm eligibility. There will be central review of the patient records including the reports of endoscopy, endoscopic ultrasound (if applicable), histology, CT and/MRI, and laparoscopy (if applicable) prior to randomization. The review is conducted by an oncologist and a surgeon. Additional assessments may be conducted as clinically indicated in accordance with local standards of care.

Following a study visit, approximately 28 days after completion of study treatment, patients will enter the follow-up period. During this period, they will be followed every 3 months for disease status until first relapse or progression, and survival.

Note: there will be a Safety Run-in Phase comprising the first 10 patients enrolled into the experimental study arm A and completed neoadjuvant treatment, but before surgery. Data of the first 10 patients in Arm A will be reviewed by the lead investigators and by the independent data monitoring committee (IDMC).

Once approximately 40 patients (20/treatment arm) have completed neoadjuvant treatment cycles and surgery, the IDMC will review all available safety data (including perioperative morbidity and mortality) before providing a recommendation whether to continue, modify or terminate the study.

	Enrollment will be halted for this review. The IDMC will be responsible for continued safety review over the remainder of the study period.
Therapy schedule	<p><b><u>Arm A: Atezolizumab with FLOT</u></b></p> <p><u>Atezolizumab</u> Day 1 q2w: 840 mg/m<sup>2</sup> IV over 1 hour combined with: <u>FLOT</u> docetaxel Day 1 q2w: 50 mg/m<sup>2</sup> IV over 2 hours oxaliplatin Day 1 q2w: 85 mg/m<sup>2</sup> IV over 2 hours leucovorin Day 1 q2wk: 200 mg/m<sup>2</sup> IV over 1 hour 5-FU Day 1 q2wk: 2600 mg/m<sup>2</sup> IV over 24 hours</p> <p>pre-operative: four cycles; post-operative four cycles</p> <p><u>Atezolizumab alone</u> (8 cycles following completion of post-operative atezolizumab/chemotherapy) Atezolizumab Day 1 q3w: 1,200 mg/m<sup>2</sup> IV over 1 hour</p> <p><b><u>Arm B: FLOT alone</u></b></p> <p>FLOT as described in Arm A. pre-operative: four cycles; post-operative four cycles</p>
Inclusion criteria	<p>Patients must meet the following criteria to be eligible for the study:</p> <ul style="list-style-type: none"> <li>• Have provided written informed consent</li> <li>• In the investigator's judgement, is willing and able to comply with the study protocol including the planned surgical treatment</li> <li>• Female and male patients* ≥ 18 years of age</li> <li>• Diagnosed with histologically confirmed adenocarcinoma of the GEJ (Type I-III) or the stomach (cT2, cT3, cT4, any N category, M0), or (any T, N+, M0) that: <ol style="list-style-type: none"> <li>1. is not infiltrating any adjacent organs or structures by CT or MRI evaluation</li> <li>2. does not involve peritoneal carcinomatosis</li> <li>3. is considered medically and technically resectable</li> </ol> <p><u>Note:</u> the absence of distant metastases must be confirmed by CT or MRI of the thorax and abdomen, and, if there is clinical suspicion of osseous lesions, a bone scan. If peritoneal carcinomatosis is suspected clinically, its absence must be confirmed by laparoscopy. Diagnostic laparoscopy is mandatory in patients with T3 or T4 tumors of the diffuse type histology in the stomach.</p> </li> <li>• No prior cytotoxic or targeted therapy</li> <li>• No prior partial or complete esophagogastric tumor resection</li> <li>• ECOG ≤ 1</li> <li>• Availability of a representative tumor specimen that is suitable for determination of PD-L1 and MSI status via central testing; PD-L1 and MSI assessment will be performed prior to randomization. The analysis requires paraffin embedded biopsy samples. Patients are included in the trial upon available results only.</li> <li>• Females of childbearing potential must agree to remain abstinent</li> </ul>

	<p>(refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of &lt;1% per year during the treatment period and for at least 5 months after the last study treatment. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (has not had <math>\geq 12</math> continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of &lt; 1% per year include bilateral tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.</p> <ul style="list-style-type: none"> <li>• Males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:       <ol style="list-style-type: none"> <li>1. With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of 1% per year during the treatment period and for at least 3 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Men with a pregnant partner must agree to remain abstinent or to use a condom for the duration of the pregnancy.</li> </ol> </li> <li>• Adequate hematological, hepatic and renal function as indicated by the following parameters:       <ol style="list-style-type: none"> <li>1. Leukocytes <math>\geq 3.000/\text{mm}^3</math>, platelets <math>\geq 100.000/\text{mm}^3</math> without transfusion, absolute neutrophil count (ANC) <math>\geq 1500/\text{mm}^3</math> without granulocyte colony-stimulating factor support, Hemoglobin <math>\geq 90</math> g/L (9 g/dL) - Patients may be transfused to meet this criterion.</li> <li>2. Bilirubin <math>\leq 1.5</math> x upper limit of normal, aspartate transaminase and alanine transaminase <math>\leq 2.5</math> x upper limit of normal, alkaline phosphatase <math>\leq 2.5</math> x upper limit of normal</li> <li>3. Serum creatinine <math>\leq 1.5</math> x upper limit of normal, or glomerular filtration rate <math>&gt; 45</math> ml/min</li> <li>4. Serum albumin <math>\geq 25</math> g/L (2.5 g/dL)</li> <li>5. For patients not receiving therapeutic anticoagulation: INR or aPTT <math>\leq 1.5</math> x ULN; for patients receiving therapeutic anticoagulation: stable anticoagulant regimen</li> </ol> </li> </ul> <p>* There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.</p>
Exclusion criteria	<p>26. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion protein; Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation</p> <p>27. Any known contraindication (including hypersensitivity) to docetaxel, 5-</p>

	<p>FU, leucovorin, or oxaliplatin.</p> <p>28. History of autoimmune disease including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.</p> <p><u>Note:</u> History of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone, or controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible based on consultation with the sponsor's medical monitor. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:</p> <ul style="list-style-type: none"> <li>• Rash must cover &lt; 10% of body surface area</li> <li>• Disease is well controlled at baseline and requires only low-potency topical corticosteroids</li> <li>• No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months</li> </ul> <p>29. Prior allogeneic bone marrow transplantation or prior solid organ transplantation</p> <p>30. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, idiopathic pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan.</p> <p><u>Note:</u> History of radiation pneumonitis within the radiation field (fibrosis) is permitted.</p> <p>31. Positive test for human immunodeficiency virus (HIV)</p> <p>32. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C</p> <p><u>Note:</u> Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction testing is negative for HCV ribonucleic acid (RNA).</p> <p>33. Active tuberculosis</p> <p>34. Uncontrolled tumor-related pain; Patients requiring pain medication must be on a stable regimen at study entry</p> <p>35. Administration of a live, attenuated vaccine within four weeks prior to start of enrollment, or anticipation that such a live attenuated vaccine will be required during the study or within 5 months after the last dose of atezolizumab</p> <p>36. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibodies</p> <p>37. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within four weeks or five half-lives of the drug, whichever is longer, prior to study enrollment</p> <p>38. Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to study enrollment. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.</p> <p>39. Requirement for use of denosumab during the study. Patients who are receiving denosumab for any reason (including hypercalcemia) must be willing and eligible to receive a bisphosphonate instead while in the study.</p> <p>40. Significant cardiovascular disease, such as cardiac disease (New York Heart Association Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study</p>
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	<p>treatment, unstable arrhythmias, or unstable angina.</p> <p>41. Clinically significant valvular defect</p> <p>42. History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer</p> <p>43. Known central nervous system metastases</p> <p>44. Peripheral polyneuropathy <math>\geq</math> NCI CTCAE grade 2</p> <p>45. Serum albumin <math>&lt;</math> 2.5 g/dL.</p> <p>46. Uncontrolled or symptomatic hypercalcemia (ionized calcium <math>&gt;</math> 1.5 mmol/L, calcium <math>&gt;</math> 12 mg/dL or corrected serum calcium <math>&gt;</math> ULN)</p> <p>47. Serious infection requiring oral or IV antibiotics within 14 days prior to study enrollment</p> <p>48. Chronic inflammatory bowel disease</p> <p>49. Clinically significant active gastrointestinal bleeding</p> <p>50. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment</p> <p>51. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results</p> <p>52. Participation in another interventional clinical study <math>\leq</math> 30 days prior to study enrollment or planned participation in such a study at the same time as this study</p> <p>53. Receipt of an investigational drug within 28 days prior to initiation of study drug</p> <p>54. Pregnancy or breast feeding, or planning to become pregnant within 5 months after the end of treatment. Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.</p>
Sample size	295 patients will be randomized into the study at a 1:1 ratio.
Anzahl eingeschl. Pat.	0

Locally advanced, resectable adenocarcinoma of the esophagogastric junction

**AIO-STO-0118: Neoadjuvant Radiochemotherapy versus Chemotherapy for Patients with Locally Advanced, Potentially Resectable Adenocarcinoma of the Gastroesophageal Junction (GEJ) - A randomized phase III joint study of the AIO, ARO and DGAV (RACE-trial)**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-STO-0118   RACE-Trial
Status:	in Vorbereitung Förderantrag bei der Deutschen Krebshilfe wurde 2018 bewilligt.
Rekrutierungszeitraum:	Studienstart noch offen
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	06.04.2018

STUDY TYPE	Multicenter randomized phase III
PRINCIPAL INVESTIGATOR	Prof. Dr. Ralf-Dieter Hofheinz TagesTherapieZentrum am Interdisziplinären Tumorzentrum Universitätsmedizin Mannheim der Universität Heidelberg Theodor-Kutzer Ufer 1-3, Haus 9 68167 Mannheim

TRIAL OFFICE	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt/Main
SPONSOR	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt/Main
CONDITION	Locally Advanced, Potentially Resectable Adenocarcinoma of the Gastroesophageal Junction (GEJ)
DESIGN	A multicentre, prospective, randomized stratified phase III trial with a 1:1 allocation into two treatment arms
INDICATION	Adenocarcinoma of the Gastroesophageal Junction (AEG type I-III)
OBJECTIVE(S)	Primary Objective: To determine if adding radiochemotherapy to neoadjuvant chemotherapy before undergoing oncologically adequate resection improves progression free survival of patients with resectable GEJ adenocarcinoma
INTERVENTION(S)	<p>Arm A (experimental arm)</p> <p>Two cycles of neoadjuvant induction chemotherapy with FLOT (5-FU 2600 mg/m<sup>2</sup> d1, leucovorin 200 mg/m<sup>2</sup> d1, oxaliplatin 85 mg/m<sup>2</sup> d1, docetaxel 50 mg/m<sup>2</sup> d1) every two weeks (4 weeks of therapy) followed by radiochemotherapy beginning at day 21 after day one of the last cycle of chemotherapy. Radiochemotherapy consists of oxaliplatin 45 mg/m<sup>2</sup> weekly (d1, 8, 15, 22, 29) and continuous infusional 5-FU 225 mg/m<sup>2</sup> plus concurrent radiotherapy given in 5/week fractions with 1.8 Gy to a dose of 45 Gy on 5 weeks. Resection is performed 4-8 weeks after the end of neoadjuvant treatment. Adjuvant treatment starts 6-12 weeks after surgery and consists of 4 cycles of FLOT (total treatment period of 26 – 33 weeks)</p> <p>Arm B (control arm)</p> <p>Four cycles of neoadjuvant chemotherapy with FLOT every two weeks (doses as above) followed by surgical resection 4-8 weeks after end of neoadjuvant therapy. 6-12 weeks after surgery adjuvant chemotherapy starts with 4 cycles of FLOT (total treatment period 25-32 weeks)</p>
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	na
BACKGROUND/RATIONALE	<p>The current prognosis of patients with locoregionally advanced adenocarcinoma of the gastroesophageal junction is still comparatively poor, with clearly less than half of the patients cured despite perioperative chemotherapy or radiochemotherapy. Thus, there is a need to use modern chemotherapy combinations in clinical trials with and without radiation and for research into assessing methods for predicting outcomes from neoadjuvant treatment as part of the paradigm of therapy for this disease.</p> <p>FLOT is established as a highly active and well tolerated regimen in the treatment of advanced cancer of the gastroesophageal junction or the stomach. The favourable toxicity in comparison to other established chemotherapy triplets led to a good acceptance even in elderly patients. Its tolerability and efficacy has likewise been shown in the neoadjuvant setting (data on file). Within the framework of the AIO FLOT 4 study, the FLOT regimen is currently compared against the present standard for perioperative treatment, ECF. The primary objective of AIO FLOT 4 is disease-free survival. Secondary criteria include overall survival and the rate of complete pathological responses (pCR).</p> <p>The RACE trial seeks to demonstrate superiority of preoperative FLOT induction chemotherapy followed by preoperative radiochemotherapy and postoperative completion FLOT chemotherapy over perioperative FLOT chemotherapy without radiotherapy in patients with adenocarcinoma of the gastroesophageal junction undergoing adequate oncological surgery (D2</p>



	<p>dissection). The primary outcome of the trial will be progression-free survival, which is regarded a valid surrogate parameter for overall survival in patients with GEJ adenocarcinoma in the adjuvant and metastatic setting [43, 44] Several other clinically relevant parameters will be used as secondary outcomes.</p> <p>In addition to addressing clinical questions, companion studies are foreseen: The study also aims at collecting tissue and liquid biopsies including circulating tumor cells, for translational research. Additional substudies will address questions of biomarker use and genomic alterations complimenting the well annotated clinical information and follow up data from the clinical trial. This could be a first step towards finding molecular predictors of response to different neoadjuvant therapies and potentially offer a molecular method of stratifying which patients will benefit the most from specific neoadjuvant therapies.</p>
KEY EXCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Evidence of metastatic disease on CT of thorax and abdomen, bone scan or MRI (the latter two to be performed only if osseous lesions are suspected due to clinical signs)</li> <li>• Known hypersensitivity /contraindications against 5-FU, leucovorin, oxaliplatin or docetaxel</li> <li>• Clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV</li> <li>• Clinically significant valvular defect</li> <li>• Past or current history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix</li> <li>• Other severe disease or acute infection</li> <li>• Peripheral polyneuropathy &gt; NCI Grade II according to CTCAE version 4.0</li> <li>• Participation in another clinical trial in the period 30 days prior to inclusion and during the study</li> <li>• Subject pregnant or breast feeding</li> <li>• Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)</li> <li>• Any other concurrent antineoplastic treatment including irradiation</li> </ul>
KEY INCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Patients with new diagnosis of a histopathologically confirmed adenocarcinoma of the GEJ (Siewert I, II, III), locally advanced (cT3-4), any cN, M0, surgically resectable as judged by treating surgeon</li> <li>• Staging according to TNM classification assessed by endoscopic ultrasound, spiral computed tomography of the chest and abdomen</li> <li>• Patients must be surgical candidates as determined by the treating surgeon</li> <li>• ECOG performance status 0-1</li> <li>• Age 18 years and above</li> <li>• Adequate hematologic and liver and renal function</li> <li>• Consent to biomarker analyses on tumor tissue and blood</li> </ul>
OUTCOME(S)	<p>Progression-free survival</p> <p>Overall survival including survival rates after 1, 3 and 5 years</p> <p>R0 resection rate</p> <p>Number of harvested lymph nodes</p> <p>Site of tumor relapse.</p> <p>Perioperative complication and mortality rate</p> <p>Safety/toxicity as assessed by NCI CTC criteria</p> <p>Quality of life (QoL) by using the EORTC QLQ- C30 and the esophagogastric module Oes24</p>

STATISTICAL ANALYSIS	<p>Efficacy/test accuracy The primary aim is to compare PFS between both study groups. Description of the primary efficacy/test accuracy analysis and population PFS will be compared between both study groups using a logrank test stratified for tumor site on a two-sided level of significance of 5% following the intention-to-treat principle. Kaplan-Meier curves will be shown and the hazard ratio will be calculated.</p> <p>Safety Absolute and relative frequencies of adverse events will be presented for both treatment groups and for relevant subgroups. Estimation of confidence intervals for event probabilities; Fisher's exact test for group comparisons.</p> <p>Secondary endpoints Descriptive statistics; 95% confidence intervals for relevant quantities and effect sizes; analysis of overall survival as described for PFS; stratified Chi-squared tests for comparison of categorical measures (response rate, R0 resection rate); linear regression for comparison of continuous outcomes (QoL scores)</p>
SAMPLE SIZE	340 patients
TRIAL DURATION	4 years
PARTICIPATING CENTERS	40 (anticipated)
FURTHER CENTERS DESIRED?	yes
NUMBER of PATIENTS	340 (planned)
CURRENT NUMBER of PATIENTS	Recruitment not open

Lokal fortgeschrittenes oder metastasiertes Adenokarzinom des Magens oder gastroösophagealen Übergangs – palliative Therapie, 1st-line

**AIO-YMO-0111/STO: Randomized controlled trial of S-1 maintenance therapy in metastatic esophagogastric cancer (MATEO = maintenance Teysuno in esophagogastric carcinoma)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO-0111 - MATEO
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany Tel: +49-30 – 814534435, FAX: +49-30 – 322932926
Coordinating Investigator	Dr. Georg Martin Haag NCT-Med. Onkologie, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany Tel: +49-6221 – 564801, FAX: +49-6221 - 5633853 E-Mail: GeorgMartin.Haag@med.uni-heidelberg.de
Study design	Open-label, multi-center, controlled, randomized, parallel-group, phase II non-inferiority trial in patients with metastatic esophagogastric cancer having received induction chemotherapy. Eligible patients having completed the preplanned induction therapy without

	<p>tumor progression (CR, PR, SD, non-CR/non-PD according to RECIST 1.1 Criteria) at week 12, being able to swallow capsules and having ECOG performance score of 0-1 will be randomized in a 2:1 ratio into Arm A and B.</p> <ul style="list-style-type: none"> <li>Patients in Arm A will continue with S-1 de-escalation phase starting at week 13 until disease progression, toxicities requiring discontinuation, withdrawal of consent, pregnancy, death or lost to follow up whichever occurs first. In patients with drug-related severe toxicity S-1 dose will be adjusted or study treatment will be terminated.</li> <li>Patients in Arm B will continue to receive the same polychemotherapy as during induction therapy until tumor progression, toxicities requiring discontinuation, withdrawal of consent, pregnancy, death or loss to follow up whichever occurs first.</li> </ul>
	<pre> graph TD     Reg1[registration] --&gt; Induction[Induction phase polychemotherapy Investigator's choice (12 weeks)]     Induction -- CR, PR, SD --&gt; R((R 2:1))     Induction -- PD lim. toxicity --&gt; OffStudy[Off Study]     R --&gt; ArmA[Arm A]     R --&gt; ArmB[Arm B]     ArmA --&gt; Maintenance[Maintenance therapy: S-1]     ArmB --&gt; Continuation[Continuation of polychemotherapy Investigator's choice]     Reg2[registration] --&gt; R   </pre>
Indication	Metastatic esophagogastric adenocarcinoma
Proposed countries / Total number of sites	Approximately 50 sites in 6 European countries (Austria, Belgium, France, Germany, Spain, Sweden)
Status	<ul style="list-style-type: none"> <li>193 patients registered, 123 randomized</li> <li>30 Study Sites initiated in Germany</li> <li>18 Study Sites initiated in Austria, Sweden, Spain, Belgium, France</li> </ul>
Study Participation	Currently no further sites are needed
Primary objective	To assess the relative efficacy of S-1 de-escalation therapy vs. continuation of chemotherapy after induction therapy in patients with metastatic esophagogastric cancer in terms of overall survival
Secondary objectives	<p>To compare S-1 de-escalation vs. continuation of chemotherapy after induction therapy with respect to</p> <ul style="list-style-type: none"> <li>Safety/toxicity</li> <li>Progression-free-survival</li> <li>Quality of life</li> </ul>
Tertiary objectives	<ul style="list-style-type: none"> <li>Assessment of malnutrition</li> <li>Overall Survival of non-randomized patients</li> <li>Validation of biomarkers associated with the fluoropyrimidine pharmacodynamics and pharmacokinetics</li> <li>Exploration of new promising biomarkers for chemotherapy sensitivity / toxicity</li> </ul>
Planned sample size	A total of 297 patients will be randomized
Inclusion Criteria	<ol style="list-style-type: none"> <li>Signed written informed consent incl. participation in translational research</li> <li>Male or female patient 18 years or older</li> <li>Histologically confirmed metastatic or locally advanced unresectable gastric adenocarcinoma or adenocarcinoma of the esophagus or the esophagogastric junction (Her-2/neu negative or with unknown Her-2/neu status)</li> </ol>

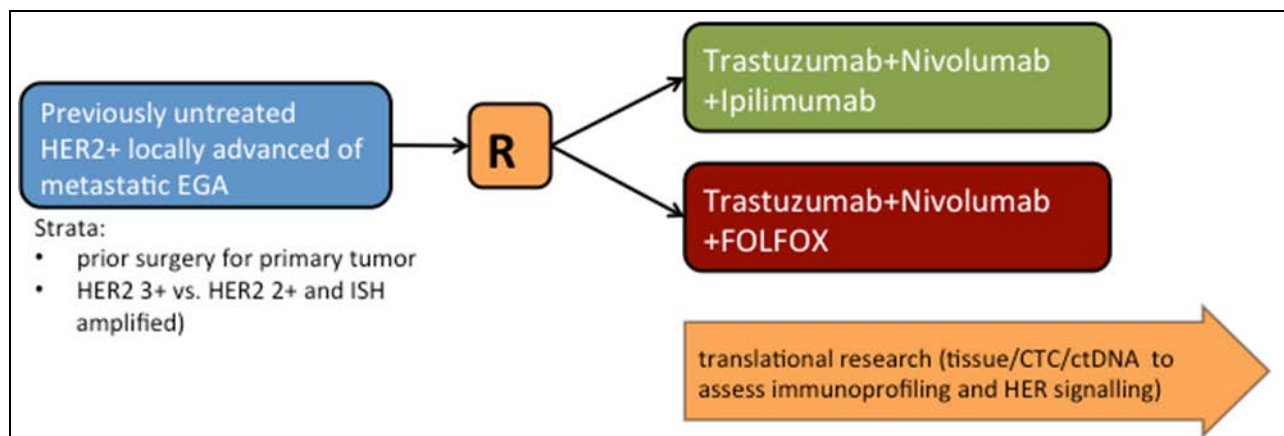
	<ol style="list-style-type: none"> <li>4. Adjuvant/neoadjuvant or perioperative chemotherapy or (chemo-)radiotherapy must have been finished at least 6 months before start of the induction therapy</li> <li>5. For patients enrolled before induction therapy: No previous systemic treatment (i.e. chemotherapy) for metastatic disease</li> <li>6. For patients enrolled after induction therapy: Having finished a three-months induction therapy (6 cycles of a bi-weekly regimen, 4 cycles of a three-weekly regimens or 3 cycles of a four-weekly regimen) without tumor progression or limiting toxicity</li> <li>7. ECOG Performance Score 0-1 (Karnofsky Performance status <math>\geq</math> 80%)</li> <li>8. Ability for oral intake of the study drug, patients with tumor-related problems with oral intake might be registered if the symptom is expected to be improved during induction therapy (e.g. due to a tumor stenosis)</li> <li>9. Female patient of childbearing potential (i.e. did not undergo surgical sterilization – hysterectomy, bilateral tubal ligation, or bilateral oophorectomy - and is not post-menopausal for at least 24 consecutive months) with a negative pregnancy test</li> <li>10. Hematology and biochemistry laboratory results within the limits normally expected for the patient population, defined by the following: <ul style="list-style-type: none"> <li>• Absolute neutrophil count <math>\geq</math> 1500/<math>\mu</math>l</li> <li>• Platelet count <math>\geq</math> 100000/<math>\mu</math>l</li> <li>• Leukocyte count <math>&gt;</math> 3000/<math>\mu</math>l</li> <li>• Hemoglobin <math>\geq</math> 9 g/dL or 5.59 mmol/l, previous transfusions (<math>&gt;</math>3 days) of erythrocytes are allowed</li> <li>• Total bilirubin <math>\leq</math> 1.5 times the upper limit of normal (ULN), in patients with known Meulengracht syndrom <math>\leq</math> 3 x ULN</li> <li>• AST <math>\leq</math> 3xULN in absence of liver metastases, or <math>\leq</math>5xULN in presence of liver metastases</li> <li>• ALT <math>\leq</math> 3xULN in absence of liver metastases, or <math>\leq</math>5xULN in presence of liver metastases</li> <li>• Creatinine clearance <math>\geq</math>30 mL/min according to Cockcroft-Gault formula</li> </ul> </li> </ol>
Exclusion Criteria	<ol style="list-style-type: none"> <li>1. Previous major surgery within the last 28 days before the start of the induction treatment. The implantation of a central venous access (e.g. porth-a cath system) is allowed.</li> <li>2. History of other malignant tumors within the last 5 years before start of induction treatment, except basal cell carcinoma or curatively excised cervical carcinoma in situ</li> <li>3. Known brain metastases</li> <li>4. Concurrent radiotherapy involving target lesions used for this study. Concurrent palliative radiation for non-target lesions is allowed if other target lesions are available outside the involved field; previous radiotherapy including target lesions must have been finished at least 28 days before start of induction treatment.</li> <li>5. For patients enrolled before the induction therapy: Previous systemic treatment (i.e. chemotherapy) for metastatic disease</li> <li>6. Known active HBV, HCV infection or documented HIV infection</li> <li>7. Serious concomitant disease or medical condition that by judgment of the Investigator renders the patient at high risk of treatment complications</li> <li>8. Clinically relevant coronary artery disease (NYHA functional angina classification III/IV), congestive heart failure (NYHA III/IV), clinically relevant cardiomyopathy, history of myocardial infarction in the last 3 months, or high risk of uncontrolled arrhythmia</li> <li>9. Female patient pregnant or breast feeding</li> <li>10. Female patient of childbearing potential (i.e. did not undergo surgical sterilization – hysterectomy, bilateral tubal ligation, or bilateral oophorectomy - and is not post-menopausal for at least 24 consecutive months) not willing to use an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the end of treatment. Male patient not willing to use an adequate method of contraception to avoid conception throughout the study and for up to 26</li> </ol>

	<p>weeks after the end of treatment in such a manner that the risk of pregnancy is minimized.</p> <ol style="list-style-type: none"> <li>11. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 60 days prior to start of induction (e.g. one of the allowed standard chemotherapies (see above) with or without additional placebo within a clinical trial is allowed)</li> <li>12. Chronic diarrhea or short bowel syndrome</li> <li>13. Known hypersensitivity to S-1, other fluoropyrimidines or platinum compounds. Contraindication to receive S-1 or the polychemotherapy (induction &amp; arm B) chosen for this patient as per current Summary of Product Characteristics. Known DPD deficiency</li> <li>14. For patients enrolled before the induction therapy: Grade <math>\geq</math> 2 peripheral neuropathy</li> <li>15. Known drug abuse/alcohol abuse</li> </ol>
Investigational Agent	S-1, an oral fluoropyrimidine (tegafur, gimeracil, oteracil) Components of polychemotherapy (comparative arm) (Oxaliplatin, Cisplatin, 5-FU, Capecitabine, Docetaxel, Epirubicin, Leucovorin)
Induction therapy	Induction chemotherapy by choice of Investigator, including a platinum compound, fluoropyrimidine and optional a taxane or anthracycline compound, i.e. the following regimens are allowed: FLO/mod. Folfox-6, Cisplatin/5-FU, Cisplatin/S-1, FLOT, EOX/EOF, XP
Maintenance schedule	<p><b>Arm A: De-escalation therapy (S-1):</b> S-1 30 mg/m<sup>2</sup> bid d1-14 q21d</p> <p><b>Arm B: Chemotherapy by Investigator's choice</b> Continuation of polychemotherapy administered during induction therapy (i.e. Cisplatin/5-FU, FLO/mod. Folfox-6, Cisplatin/S-1, EOF/EOX, FLOT, XP)</p>
Primary endpoint	<ul style="list-style-type: none"> <li>• Overall survival defined as the time from randomization until death from any cause</li> </ul>
Secondary endpoints	<ul style="list-style-type: none"> <li>• Adverse Events according to the CTCAE Criteria (Version 4.03)</li> <li>• Progression-free-survival defined as the time from randomization until disease progression or death from any cause</li> <li>• Quality of life according to the EORTC QLQ-C30 and QLQ-STO22</li> </ul>
Tertiary endpoints	<ul style="list-style-type: none"> <li>• Nutritional status according to the NRS Nutritional Risk Screening questionnaire</li> <li>• Overall survival of non-randomized patients</li> <li>• Identification of molecularly defined subgroups with benefit from S-1 maintenance therapy</li> </ul>
Randomization procedure	<p>Patients with CR, PR, SD or non-PD/non-CR (in case of non-measurable lesions only) after 12 weeks of induction treatment, being able to swallow capsules and having ECOG performance score of 0-1 will be randomized in a 2:1 ratio to receive either Arm A or Arm B until tumor progression. Stratified permuted block randomization will be applied to guarantee balanced group numbers. Stratification parameters will be</p> <ul style="list-style-type: none"> <li>• Response to induction therapy at time of randomization (CR SD or PR vs. SD or non-CR/non-PD (in case of non-measurable lesions only))</li> <li>• Polychemotherapy (two-drug vs. three-drug combinations)</li> <li>• Enrollment before vs. after the induction chemotherapy</li> </ul>
Rationale for study design and sample size	Sample size estimation of this phase II trial is based on the statistical goal to allow for a first formal within-study comparison of efficacy and to exclude any increase of risk of death due to de-escalation with S-1 by more than 33% compared to continuation of polychemotherapy using a non-inferiority testing approach on a 10% significance level. With a power of 80% under the alternative hypothesis that both treatment arms are in fact associated with the

	<p>same underlying hazard rates, a total of 250 deaths are required for statistical analysis. Assuming that 10 patients can be randomized per months, with 297 patients the total study duration (accrual plus follow-up) can be bounded at 39 months.</p>
Interim / partial analyses required	<p>No confirmatory interim analyses with the aim to prematurely stop the trial are planned.</p>
Translational analyses	<p>The translational part of this trial aims to identify a subgroup of patients with a sustained, beneficial response to chemotherapy, especially to S-1 based maintenance therapy. Blood samples will be analysed for DNA polymorphisms of the fluoropyrimidine pathway, cytokine patterns and microRNA levels. Tumor tissue will be analysed using Gene Expression Profiling and Whole Genome Methylation Analyses.</p>
Study plan	<p>First Patient In (FPI): Feb/2015 Last Patient In (LPI): Mar/2019 Last Patient Off Treatment: Sep/2019 Last Patient Last Visit (LPLV): Dec/2019</p>

**AIO-STO-0217: Ipilimumab or FOLFOX in combination with Nivolumab and Trastuzumab in previously untreated HER2 positive locally advanced or metastatic EsophagoGastric Adenocarcinoma. The randomized phase 2 INTEGA trial.**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-STO-0217 - INTEGA-trial
Status:	in Rekrutierung
Rekrutierungszeitraum	2018 – 2020
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	April 2018
<b>National Coordinating Investigator (LKP)</b>	PD Dr. Alexander Stein Universitätsklinikum Hamburg-Eppendorf, II. Medizinische Klinik und Poliklinik (Onkologie, Hämatologie, KMT mit Sektion Pneumologie) Hubertus Wald Tumorzentrum – UCCH Martinistr. 52, Gebäude Ost 24 20246 Hamburg
<b>Sponsor</b>	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin
<b>Design</b>	Randomized, open labelled, multicenter phase II trial
<b>Indication</b>	Patients with previously untreated metastatic HER2 positive esophagogastric adenocarcinoma
<b>Recruitment status</b>	97 patients planned, 5 patients enrolled
<b>Total number of sites</b>	40 planned, 37 recruited, 23 initiated
<b>Study Duration</b>	Duration of recruitment: 24 months at a rate of 4 patients/month (counted from at least 50% of sites activated). Follow-up from last patient in to primary endpoint or end of safety follow up 3 months after last administration of up to 12 months of nivolumab +/- ipilimumab (up to 15 months). Further follow-up for survival until trial termination 48 months after first patient in. Expected total trial duration 4 years.
<b>Endpoints</b>	<u>Primary endpoint:</u> <ul style="list-style-type: none"> <li>• Overall Survival including milestone rate @ 12 months</li> </ul> <u>Secondary endpoints:</u> <ul style="list-style-type: none"> <li>• Safety and tolerability (acc. to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters and feasibility of the regimen)</li> <li>• Progression Free Survival (PFS) according to RECIST v1.1</li> <li>• Response Rate (RR) according to RECIST v1.1</li> <li>• Quality of life (EORTC QLQ-C30 and STO-22)</li> <li>• Translational research (correlation of immune response signatures, changes in HER2 and PD-L1 and HER signaling status in tissue, CTC and ctDNA with efficacy)</li> <li>• central imaging review and determination of ORR and PFS according to modified RECIST)</li> </ul>
<b>Trial Overview</b>	



### Inclusion Criteria

- All subjects must have inoperable, advanced or metastatic GC or GEJ carcinoma and have histologically confirmed predominant adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging.
- Subjects must have HER2-positive disease defined as either IHC 3+ or IHC 2+, the latter in combination with ISH+, as assessed locally on a primary or metastatic tumour (*Note: Availability of formalin-fixed paraffin-embedded (FFPE) representative tumor tissue for central confirmation of HER2 is mandatory (Preferably fresh biopsy)*)
- Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease.
- Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization.
- Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D).
- ECOG performance status score of 0 or 1 (Appendix B).
- Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03 ):
  - WBC  $\geq$  2000/uL
  - Neutrophils  $\geq$  1500/ $\mu$ L
  - Platelets  $\geq$  100x10<sup>3</sup>/ $\mu$ L
  - Hemoglobin  $\geq$  9.0 g/dL
  - eGFR  $\geq$  30ml/min
  - AST  $\leq$  3.0 x ULN (or  $\leq$  5.0X ULN if liver metastases are present)
  - ALT  $\leq$  3.0 x ULN (or  $\leq$  5.0X ULN if liver metastases are present)
  - Total Bilirubin  $\leq$  1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of  $<$  3.0 x ULN)
- Males and Females,  $\geq$  18 years of age
- Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
- Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Women must not be breastfeeding.
- WOCBP must use a highly effective method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-



	<p>lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. WOCBP should use an adequate method to avoid pregnancy for approximately 5 months (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug.</p> <p>18. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. Males who are sexually active with WOCBP must continue contraception for approximately 7 months (90 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. In addition, male subjects must be willing to refrain from sperm donation during this time.</p>
<p><b>Exclusion Criteria</b></p>	<ol style="list-style-type: none"> <li>1. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS &gt; 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)</li> <li>2. Subjects with untreated known CNS metastases. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of &lt; 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.</li> <li>3. History of exposure to the following cumulative doses of anthracyclines (epirubicin &gt; 720 mg/m<sup>2</sup>, doxorubicin or liposomal doxorubicin &gt; 360 mg/m<sup>2</sup>, mitoxantrone &gt; 120 mg/m<sup>2</sup> and idarubicin &gt; 90 mg/m<sup>2</sup>, other (other anthracycline greater than the equivalent of 360 mg/m<sup>2</sup> of doxorubicin). If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m<sup>2</sup> of doxorubicin</li> <li>4. Baseline LVEF value &lt; 55%, assessed by echocardiogram, multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) scan</li> <li>5. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the medical monitor be consulted prior to signing informed consent.</li> <li>6. Subjects with a condition requiring systemic treatment with either corticosteroids (&gt; 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses &gt; 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.</li> <li>7. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.</li> <li>8. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade &gt; 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.</li> <li>9. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug.</li> </ol>

	<p>10. Significant acute or chronic infections including, among others:</p> <ol style="list-style-type: none"> <li>a. Any positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)</li> <li>b. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.</li> </ol> <p>11. History of allergy or hypersensitivity to study drugs or any constituent of the products</p> <p>12. History of allogeneic tissue/solid organ transplant</p> <p>13. Participation in another clinical study with an investigational product during the last 30 days before inclusion</p> <p>14. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>15. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p>
<p><b>Treatment, Dosage and Administration</b></p>	<p>All eligible patients will be randomized, stratified for prior surgery of primary tumour and HER2 positivity status to</p> <p><b>Arm A</b>  <b>Week 1-12</b>  Trastuzumab 6mg/kg d1 every 3 weeks (loading dose 8mg/kg)  Nivolumab 1mg/kg i.v. d1 every 3 weeks  Ipilimumab 3mg/kg i.v. d1 every 3 weeks</p> <p><b>Week 13 till EOT</b>  Trastuzumab 4mg/kg d1 every 2 weeks  Nivolumab 240mg i.v. d1 every 2 weeks</p> <p><b>Arm B</b>  Trastuzumab 4mg/kg d1 every 2 weeks (loading dose 6mg/kg)  Nivolumab 240mg i.v. d1 every 2 weeks  mFOLFOX6 every 2 weeks  Oxaliplatin at a dose of 85 mg/m<sup>2</sup> IV over two hours (day 1)  5-FU 400 mg/m<sup>2</sup> IV bolus (day 1)  LV at a dose of 400 mg/m<sup>2</sup> iv over two hours (day 1)  5-FU at a dose of 2400 mg/m<sup>2</sup> IV over 46 hours (day 1-3)</p> <p><b>Duration of treatment</b></p> <p>Treatment with trastuzumab, nivolumab and ipilimumab or FOLFOX will be administered until progression (according to RECIST v1.1), intolerable toxicity, withdrawal of consent or secondary resection. The treatment with nivolumab will be limited to a maximum of 12 months (24 applications of nivolumab). Ipilimumab will only be applied in weeks 1, 4, 7, and 10.</p>
<p><b>Assessments</b></p>	<p><b>Baseline (within 4 weeks before treatment start)</b></p> <ul style="list-style-type: none"> <li>• Review of inclusion and exclusion criteria</li> <li>• Medical and medication history, physical examination including height, weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), oxygen saturation, ECOG-performance status</li> <li>• Laboratory Tests</li> <li>• Blood draw for translational research</li> <li>• Obtain paraffin-embedded tumor-tissue for translational research</li> <li>• Echocardiography and ECG</li> <li>• Quality of life assessment (EORTC QLQ-C30 and STO-22)</li> <li>• Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan)</li> </ul> <p><b>During treatment (at start of treatment and every 2 or 3 weeks, +3/-2 days previous to any new cycle) (safety-relevant assessments, including</b></p>

	<p>pregnancy test have to be completed before dosing)</p> <ul style="list-style-type: none"> <li>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication</li> <li>• Laboratory tests (hematology and chemistry panel), including</li> <li>• Free T3/T4 and TSH (every 6 weeks)</li> <li>• Pregnancy test for women of childbearing potential (every 4 weeks)</li> <li>• Quality of life assessment (EORTC QLQ-C30 and STO-22) every 2 months (together with imaging)</li> <li>• Blood draw for translational research (cycle 2,5 and end of treatment)</li> <li>• Echocardiography every 3 months</li> </ul> <p><b>Additional assessments during treatment with nivolumab, ipilimumab and trastuzumab in arm A until week 13 on day 12 of every cycle (+/-3 days)</b></p> <ul style="list-style-type: none"> <li>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication</li> <li>• Laboratory tests (hematology and chemistry panel)</li> </ul> <p><b>Final staging</b></p> <p>When any subject discontinues dosing of all study treatment, the following assessments should be made:</p> <ul style="list-style-type: none"> <li>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication</li> <li>• Laboratory tests (baseline panel), including free T4 and TSH and pregnancy test for women of childbearing potential</li> <li>• Echocardiography and ECG</li> <li>• Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan)</li> </ul> <p><b>30 and 100 days safety follow-up (±7 days)</b></p> <ul style="list-style-type: none"> <li>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication</li> <li>• Laboratory tests (hematology and chemistry panel), including free T3/T4 and TSH and pregnancy test for women of childbearing potential</li> </ul> <p><b>Extended safety follow-up</b></p> <p>Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed every 30 days up to 100 days after the last dose of nivolumab+/- ipilimumab.</p> <p>The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.</p> <p><b>Follow-up</b></p> <p>All subjects will be followed every 3 months ± 28 days for up to 4 years after start of recruitment.</p> <p>In case of progressive disease after study treatment only:</p> <ul style="list-style-type: none"> <li>• Survival, disease status, protracted toxicity, further treatment</li> </ul> <p>In any other case additionally:</p> <ul style="list-style-type: none"> <li>• Disease assessment, physical examination including weight, ECOG-performance status</li> </ul> <p><b>Tumor Response Assessment</b></p> <p>During treatment tumor response will be assessed every 8 weeks (±7 days) for up to 12 months and afterwards 3 monthly by the investigator according to RECIST v1.1 (Radiological imaging by CT and/or MRI of the chest, abdomen, pelvis and all other sites of disease). After treatment discontinuation for other than progressive disease imaging will be performed according to standard of</p>
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	<p>care until progression or death. CT and/or MRI scans will be independently reviewed, thus blinded data will be collected.</p> <p><b>Safety</b></p> <p>Safety assessments will include physical examinations with vital signs (blood pressure, heart rate, respiratory rate, ioxygen saturation and body temperature), performance status (ECOG), clinical laboratory profile and adverse events.</p> <p>All observed toxicities and side effects will be graded according to NCI CTCAE v4.03 for all patients and the degree of association of each with the procedure assessed and summarized.</p> <p>Treatment related serious adverse events rate (SAE) will be determined.</p> <p><b>Quality of Life</b></p> <p>Quality of life will be assessed using the EORTC QLQ-C30 and STO-22 every 8 weeks together with tumor response assessment.</p>
<b>Translational Research</b>	<p>The following translational research is currently planned, but may be adapted taking into account new research data</p> <ul style="list-style-type: none"> <li>• Tumor-infiltrating lymphocytes (TiL) repertoire determination from tumor</li> <li>• Liquid biopsy next-generation sequencing (NGS) immunoprofiling (<i>TCRβ</i> &amp; <i>IgH</i>) before treatment initiation and before second cycle to determine response predictive immune signature (diversification pattern as read-out for ongoing immune activation, TiL clone expansion in peripheral blood)</li> <li>• In addition FFPE will be centrally tested for PD-L1, HER2 (IHC and ISH), MSI, EBV and HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA) and correlated with clinical efficacy.</li> <li>• CTC will be evaluated for changes in HER2 and PD-L1 status</li> <li>• ctDNA will be evaluated for HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA)</li> <li>• Central imaging review and determination of ORR and PFS according to modified RECIST.</li> </ul> <p>Thus, the tumor block for TiL analysis, HER2, PD-L1 and HER signaling assessment will be obtained at baseline. Blood will be collected prior to first treatment and beginning of cycle 2 and cycle 4 (Arm A) or cycle 5 (Arm B) and at progression (end of treatment). In addition, imaging will be retrospectively collected.</p>
<b>Statistical Considerations</b>	<p>The present trial is designed as a randomized phase II study, which aims to estimate the therapeutic efficacy of two experimental regimen. OS analysed according to the ITT principle is the primary efficacy endpoint. The efficacy assumptions are derived from historical data.</p> <p>The TOGA trial has defined the standard 1<sup>st</sup> line treatment with chemotherapy and trastuzumab with a 12-month-OS rate (OSR@12) of 55% (median OS of 13.8 months) (Bang, Van Cutsem et al. 2010). Nivolumab in chemotherapy refractory patients (median 3 prior treatment lines) results in an overall response rate of 11-14% and a median OS of about 5.3 months (Janjigian, Bendell et al. 2016, Kang, Satoh et al. 2017). The combination of nivolumab and ipilimumab in the same patient population results in an overall response rate of 26% and a median OS of about 6.9 months (Janjigian, Bendell et al. 2016).</p> <p>The INTEGA trial will evaluate two experimental regimen in 1<sup>st</sup> line HER2 positive EGA treatment, a chemo-free regimen with trastuzumab+nivolumab+ipilimumab and a intensified TOGA-like regimen with trastuzumab+nivolumab+FOLFOX. Each of the experimental arms would be considered promising, if the true 12-month-OS rate amounts to 70 %. This translates into a hazard ratio of 0.6 compared to the standard OSR@12 of 55% for chemotherapy and trastuzumab.</p>

	<p><b>Sample size estimation:</b></p> <p>Based on these assumptions, and an exponential shape of the survival curves, a one-sided logrank test with a sample size of 41 subjects achieves 80% power at a one-sided significance level of 0.05 to detect a hazard ratio of 0.6 when the proportion surviving with the current standard is 0.55 (OSR@12 months). Overall 82 patients will be included and randomized into the two experimental arms (41 in each experimental treatment group). The rate of drop-outs is estimated to be 15%. Hence, the total number of subjects to be recruited is N= 97. This calculation assumes an accrual time of 24 months, and a minimum follow-up of 15 months of all patients alive at the time point of analysis.</p> <p>Randomization will be performed according to the following stratification criteria:</p> <ul style="list-style-type: none"> <li>• Prior surgery of the primary tumour yes vs. no</li> <li>• HER2 status IHC 3+ vs. IHC 2+ and ISH amplified</li> </ul>
<b>Early Toxicity Analysis</b>	<p>Based on the novel combination regimen applied in this study the IDMC will monitor safety and efficacy data every 3 to 6 months throughout the trial. In addition a safety run-in phase will be conducted to detect potential safety risks early.</p> <p>Safety Run-In Phase for the first 15 patients After at least two months of treatment of the 5th, 10th and 15th patient per arm the IDMC will review the safety data respectively and decide about trial continuation.</p> <ul style="list-style-type: none"> <li>• Regular IDMC Meetings will be performed every 3 months until the last patient has passed the 2 months assessments and afterwards every 6 months to review safety data until the last administration of nivolumab.</li> </ul>

**AIO-STO-0417: Modified FOLFOX plus/minus Nivolumab and Ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction (The randomized phase II MOONLIGHT Trial)**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-STO-0417 - MOONLIGHT
Status:	in Vorbereitung
Rekrutierungszeitraum	2018 - 2020
Weitere Zentren:	interessierte Zentren wenden sich bitte an das <a href="#">IKF in Frankfurt</a>
Letzte Aktualisierung	April 2018

Study type	Randomized, open labelled, multicenter phase II trial
Authors of the proposal	Prof Dr. Sylvie Lorenzen, Munich Prof. Dr. Salah-Eddin Al-Batran, Frankfurt
Objectives / Endpoints (efficacy, safety)	<p>Primary endpoint: PFS based on the ITT population</p> <p>Secondary endpoints: Overall Response Rate (ORR) according to RECIST v1.1 Duration of response and disease stabilization Overall survival (OS) Safety (according to NCI-CTCAE V 4.03) and tolerability Quality of life (EORTC QLQ-C30). The QoL analyses will include QoL mean values, QoL response and time to symptom deterioration (TTSD)</p>

	Translational research: correlation of biomarkers potentially associated with clinical efficacy (OS, PFS and ORR) from nivolumab plus ipilimumab by molecular quantitation of target gene expression and immune cell composition
Background / Rationale	<p>Gastroesophageal (GE) cancers represent a major global healthcare problem. In 2002 approximately 1.4 million people worldwide developed GE cancers and 1.1 million died. When compared with best supportive care alone, chemotherapy yields a quite modest advantage of about 3 months until disease progression with Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (fluorouracil, capecitabine, and S1) being generally considered as the standard-of-care in 1L treatment. Cisplatin has been the most frequently administered platinum in gastroesophageal cancer treatment. Since the REAL-2 study demonstrated an oxaliplatin-based regimen to be non-inferior to cisplatin with a favorable safety profile (Cunningham et al 2008), oxaliplatin combinations with fluoropyrimidines have been studied in multiple Phase 2 and 3 trials, and showed similar efficacy trends across regions (Yamada et al 2015; Al-Batran et al 2008).</p> <p>A Phase 3 trial in esophageal/gastric/GEJ cancers comparing the FOLFOX regimen (5-fluorouracil plus leucovorin and oxaliplatin) vs FLP (5-fluorouracil plus leucovorin and cisplatin) showed no statistically significant differences between the 2 treatments, but favored the FOLFOX arm vs the FLP arm in terms of median PFS (the primary endpoint, 5.7 months vs. 3.9 months), response rate (35% versus 25%), and median survival (10.7 months vs 8.8 months) (Al-Batran et al 2008). As a result, oxaliplatin has become one of the major backbone platinum compounds in the 1L setting. Based on these observations, the oxaliplatin-based regimens FOLFOX is considered to be reasonable comparators in this Phase 2 study.</p> <p>The lack of a major benefit from the various newer-generation combination chemotherapy regimens has stimulated research to use targeted agents. Except trastuzumab, several monoclonal antibodies approved for other cancer indications including cetuximab and bevacizumab have failed to demonstrate efficacy as single agents and in combination with chemotherapeutics. Immunotherapeutic approaches have demonstrated clinical efficacy in several advanced cancer types. Anti PD-1 and PD-L1 inhibitors (eg, nivolumab, pembrolizumab, and avelumab) have been investigated in gastroesophageal cancer treatment and have demonstrated anti-tumor activity (Le et al 2016; Bang et al 2015; Chung et al 2015). Treatment with pembrolizumab achieved a 33% ORR by investigator assessment and 22% by central data review in gastric cancer subjects with PD-L1 expressing tumors (Bang et al 2015). The 6-month progression-free survival (PFS) rate was 26% and median PFS was 1.9 months.</p> <p>Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity (Curran et al 2010). The combined therapy of Nivolumab (BMS-936558), and ipilimumab (BMS-734016) has shown encouraging clinical activity with a confirmed ORR of 26% and a median OS of 6.9 months in patients with chemotherapy refractory gastric cancer disease (Janjigian et al 2016). Moreover, immunotherapy has been shown to improve the efficacy of chemotherapy (Kershaw et al 2013). In chemotherapy naïve non-small cell lung cancer, the phase II KEYNOTE 012 trial demonstrated a doubled response rate (55% vs 29%; p=0.0016) when pembrolizumab was added to a cisplatin-doublet chemotherapy with a manageable safety profile (Langer et al 2016). It is anticipated that the combination of standard chemotherapy with combined Nivolumab/ipilimumab immunotherapy will increase clinical activity, however, until now, no data exist for mGC .</p> <p>References:  Cunningham et al 2008; N Engl J Med 2008; 358:36-46.  Yamada et al; Annals of Oncology 2015;26:141-148.  Al-Batran et al; J Clin Oncol 2008;26:1435  Le et al; ASCO GI 2016, abstract 6  Bang et al; ASCO 2015, abstract 4001  Chung et al; ESMO 2015, Abstract No. 2364  Curran et al; PNAS 2010;107: 4275-80.</p>

	Janjigian et al; J Clin Oncol 34, 2016 (suppl; abstr 4010) Kershaw et al; OncoImmunology 2013 2:e25962. Langer et al; Lancet Oncol. 2016 Nov;17(11):1497-1508.
Population	Patients with advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction are eligible for this study.
Inclusion/exclusion criteria	<p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. All subjects must have inoperable, advanced or metastatic GC or GEJ adenocarcinoma.</li> <li>2. Subjects must have HER2-negative disease defined as either IHC 0 or I+ or IHC 2+, the latter in combination with ISH-, as assessed locally on a primary or metastatic tumour.</li> <li>3. Subject must be previously untreated with systemic treatment given as primary therapy for advanced or metastatic disease.</li> <li>4. Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization.</li> <li>5. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization.</li> <li>6. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D).</li> <li>7. ECOG performance status score of 0 or 1 (Appendix B).</li> <li>8. Life expectancy &gt; 12 weeks</li> <li>9. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03 ):       <ol style="list-style-type: none"> <li>a. WBC <math>\geq</math> 2000/uL</li> <li>b. Neutrophils <math>\geq</math> 1500/<math>\mu</math>L</li> <li>c. Platelets <math>\geq</math> 100x10<sup>3</sup>/<math>\mu</math>L</li> <li>d. Hemoglobin <math>\geq</math> 9.0 g/dL</li> <li>e. Serum creatinine <math>\leq</math> 1.5 x ULN</li> <li>f. AST <math>\leq</math> 3.0 x ULN (or <math>\leq</math> 5.0X ULN if liver metastases are present)</li> <li>g. ALT <math>\leq</math> 3.0 x ULN (or <math>\leq</math> 5.0X ULN if liver metastases are present)</li> <li>h. Total Bilirubin <math>\leq</math> 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of &lt; 3.0 x ULN)</li> </ol> </li> <li>10. Males and Females* <math>\geq</math> 18 years of age</li> <li>11. There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.</li> <li>12. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.</li> <li>13. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.</li> <li>14. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Women must not be breastfeeding.</li> <li>15. WOCBP must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. WOCBP should use an adequate method to avoid pregnancy for approximately 5 months (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug.</li> <li>16. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. Males who are sexually active with WOCBP must continue contraception for approximately 7 months (90 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. In addition,</li> </ol>

male subjects must be willing to refrain from sperm donation during this time.

**Exclusion Criteria:**

17. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
18. Subjects with untreated symptomatic CNS metastases. Subjects are eligible if CNS metastases are asymptomatic (this includes patients with unknown CNS metastatic status who have no clinical signs of CNS metastases) or those with asymptomatic or symptomatic CNS who are adequately treated and are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization. Patients with unknown CNS metastatic status and any clinical signs indicative of CNS metastases are eligible if CNS metastases are excluded using CT and/or MRI scans, or CNS metastases are confirmed but adequately treated as described above.
19. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the medical monitor be consulted prior to signing informed consent.
20. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
21. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
22. All toxicities attributed to prior anti-cancer therapy other than hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4.03) or baseline before administration of study drug.
23. > Grade 1 peripheral neuropathy according to CTCAE version 4.03
24. Known Dihydropyrimidine dehydrogenase (DPD) deficiency
25. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug.
26. Ascites which cannot be controlled with appropriate interventions.
27. Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry; congestive heart failure NYHA grade 3 and 4
28. Significant acute or chronic infections including, among others:
  - a. Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
  - b. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.
29. History of allergy or hypersensitivity to study drugs or any constituent of the products
30. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
- 31. Patients who are unable to consent because they do not understand**



	the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
Investigational and control drugs	Study drugs: Nivolumab and Ipilimumab Study treatment: FOLFOX + Nivolumab and Ipilimumab; FOLFOX
Investigational and Control Arm, Dose, regimen, treatment cycle	Randomisation 1 (experimental) :1 (control) Each Cycle: either: - Experimental Treatment: Arm A FOLFOX (Oxaliplatin 85 mg/m <sup>2</sup> , leucovorin 400 mg/m <sup>2</sup> and fluorouracil 400 mg/m <sup>2</sup> administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m <sup>2</sup> IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle, every 2 weeks) + Nivolumab 240mg "Flatdose" i.v. d1 every 2 weeks + Ipilimumab 1mg/kg i.v. d1 every 6 weeks Or - Standard Treatment Arm B FOLFOX (Oxaliplatin 85 mg/m <sup>2</sup> , leucovorin 400 mg/m <sup>2</sup> and fluorouracil 400 mg/m <sup>2</sup> administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m <sup>2</sup> IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle, every 2 weeks).  Duration of treatment Treatment with each of the components FOLFOX, nivolumab and/or ipilimumab will be administered until progression (according to RECIST v1.1), intolerable toxicity, patient's request, or end of study treatment phase (24 months). The study treatment will be limited to a maximum of 24 months.
Statistical considerations	PFS analysed according to the ITT principle is the primary efficacy endpoint. The expected median PFS in the standard arm is 5.5 months; the expected median PFS in the experimental arm is 8.5 months. We hypothesize that the experimental therapy is associated with clinically relevant improvement according to a HR of 0.68. In the frame of a phase II testing, the use of a one-sided significance level of 10% is justified. Based on this, 118 randomized subjects (59 in the control and 59 in the experimental treatment group) will be enrolled to provide 80% power for detecting an average HR of 0.68 using the log rank test at a one-sided type I error of 10% and assuming a 5% drop out rate. The sample size calculation is based on 2 years recruitment time and 1 year follow up time after last patient-in. So the minimum follow-up time is 3 years. 1:1 Randomization will be performed according to the following stratification criteria: <ul style="list-style-type: none"> <li>• ECOG PS (0 vs 1)</li> <li>• PD-L1 mRNA expression (lower vs. middle vs. upper tertile vs. not assessable)</li> </ul>
Key dates	FPFV: Q2 2018 Planned time for recruitment 2,0 years Follow-up after end of treatment (EOT): every 2 months for up to 1 year
Number of patients, and location	Total number of patients: 118 Location of sites: Germany

Lokal fortgeschrittenes oder metastasiertes Adenokarzinom des Magens oder gastroösophagealen Übergangs – palliative Therapie, 2nd-line

**AIO-STO-0415: Ramucirumab plus Irinotecan / Leucovorin / 5-FU versus Ramucirumab plus Paclitaxel in patients with advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction, who failed one prior line of palliative chemotherapy (RAMIRIS)**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-STO-0415 - RAMIRIS
Status:	in Rekrutierung
Rekrutierungszeitraum	2017 -
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Study type	Randomized, multicenter phase II trial
Principal Investigator	Prof. Dr. med. Sylvie Lorenzen Klinikum rechts der Isar der Technischen Universität München, Abteilung für Hämatologie und Onkologie, Ismaningerstr. 22, 81675 München Tel. 089/41409848; Fax 089/4140-3654822 sylvielorenzen@gmx.de
Objectives / Endpoints (efficacy, safety)	<p>Primary endpoint: OS rate after 6 months, based on an ITT population. The experimental therapy (FOLFIRI + Ramucirumab) would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true OS rate amounted to 65% or more, as this corresponds to the efficacy of the standard Ramucirumab-Paclitaxel regimen according to the RAINBOW (Wilke et al., 2014) study in the western population</p> <p>Secondary endpoints: To compare treatment arms with respect to</p> <ul style="list-style-type: none"> <li>• Progression-free survival</li> <li>• Objective response rate (CR + PR)</li> <li>• Tumor control rate (CR, PR, SD)</li> <li>• Duration of disease stabilization</li> <li>• Safety (according to NCI-CTCAE V 4.0) and tolerability</li> <li>• Assessments of quality of life, anxiety/depression and satisfaction during treatment and follow-up (EORTC QLQ C30).</li> </ul> <p>Exploratory endpoints (<b>optional</b>): Translational research analysis in serum samples, e.g. :</p> <ul style="list-style-type: none"> <li>• Chemokines and angiogenic factors in plasma (e.g. sCAIX, PGE2, Tryptase, PIGF, GM-CSF, G-CSF, S100A8, S100A9)</li> </ul>
Background / Rationale	<p>Ramucirumab is a proven option as monotherapy and in combination with paclitaxel as second line treatment in advanced gastric cancer (Fuchs et al 2014, Wilke et al. 2014) and has been approved in this indication. Irinotecan alone or combined with 5-FU/Folinic Acid (FOLFIRI) has shown significant improvement of overall survival compared to best supportive care (BSC) in the second line setting and is an accepted safe and efficient chemotherapeutic treatment for patients with refractory gastroesophageal cancer (Thuss-Patience et al., 2011, Kang et al., 2012, Assersohn et al., 2004). The FOLFIRI regimen could improve overall survival to 9.1 months, and patients achieved a response rate of 18% and a progression-free survival of 3.2 months with acceptable tolerability (Seo et al., 2008) in an Asian patient population. Therefore there is a need to investigate the effect of ramucirumab in combination to an irinotecan based regimen.</p> <p>More and more patients get treated with taxanes in the perioperative or 1<sup>st</sup> line metastatic setting. For those patients the benefit of a combination of</p>

	<p>ramucirumab and paclitaxel is unclear, and many physicians would choose an irinotecan based regimen as second line treatment. Therefore there is a great need to generate data of an irinotecan based regimen together with ramucirumab.</p> <p>Based on the data that paclitaxel is active in gastric cancer patients who are refractory to docetaxel containing chemotherapy (Ando et al. 2012), indicating that cross-resistance between docetaxel and paclitaxel in gastric cancer is incomplete, paclitaxel may also be used for patients who were refractory to docetaxel. Therefore this trial will also study the effects of paclitaxel/ramucirumab after a docetaxel containing therapy.</p> <p>In colorectal cancer FOLFIRI was tolerable together with ramucirumab (Tabernero et al., Lancet Oncol 2015).</p> <p>It is anticipated that FOLFIRI and ramucirumab can be safely administered also in patients with gastric cancer. This clinical trial will evaluate whether it is beneficial in terms of prolongation of survival to combine ramucirumab and FOLFIRI when compared to the standard treatment of ramucirumab plus paclitaxel. This trial aims to investigate the efficacy and safety of ramucirumab plus FOLFIRI compared to paclitaxel plus ramucirumab.</p>
Study design	Randomized, multicenter phase II study
Population	Patients with advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction are eligible for this study.
Inclusion/exclusion criteria	<p><b>Inclusion</b></p> <ol style="list-style-type: none"> <li>1. Signed written informed consent</li> <li>2. Male or female* <math>\geq 18</math> years of age; Patients in reproductive age must be willing to use adequate contraception during the study and for 3 months after the end of ramucirumab treatment (appropriate contraception is defined as surgical sterilization (e.g. bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)). Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start.</li> <li>3. Histologically proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction</li> <li>4. Metastatic or locally advanced disease, not amenable to potentially curative resection</li> <li>5. Documented objective radiological or clinical disease progression during or within 6 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline or docetaxel</li> <li>6. Measurable or non-measurable but evaluable disease</li> <li>7. ECOG performance status 0-1</li> <li>8. Life expectancy <math>&gt; 12</math> weeks</li> <li>9. Adequate hematological, hepatic and renal functions: <ul style="list-style-type: none"> <li>• Absolute neutrophil count (ANC) <math>\geq 1.5 \times 10^9/L</math></li> <li>• Platelets <math>\geq 100 \times 10^9/L</math></li> <li>• Total bilirubin <math>\leq 1.5</math> times the upper normal limit (UNL)</li> <li>• AST (SGOT) and ALT (SGPT) <math>\leq 2.5 \times UNL</math> in absence of liver metastases, or <math>\leq 5 \times UNL</math> in presence of liver metastases; AP <math>\leq 5 \times UNL</math></li> <li>• Creatinine <math>\leq 2 \times UNL</math></li> </ul> </li> <li>10. Ability to comply with scheduled assessments and with management of toxicities</li> </ol> <p><b>Exclusion</b></p> <p>Patients with any of the following will not be eligible for participation:</p> <ol style="list-style-type: none"> <li>1. Other tumor type than adenocarcinoma (e.g. leiomyosarcoma, lymphoma) or a second cancer except in patients with squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been effectively treated. Patients curatively treated and disease-free for at least 5 years will be discussed with the sponsor before inclusion</li> </ol>

2. Squamous gastric cancer
3. Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol
4. Previous therapy with paclitaxel or FOLFIRI
5. Current treatment with any anti-cancer therapy  $\leq 2$  weeks prior to study treatment start unless rapidly progressing disease is measured
6. Concurrent treatment with any other anti-cancer therapy
7. Previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study
8. Patient has undergone major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to first dose of protocol therapy. The patient has elective or planned major surgery to be performed during the course of the clinical trial
9. Grade 3-4 GI bleeding within 3 months prior to enrollment
10. History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to first dose of protocol therapy
11. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
12. Known brain or leptomeningeal metastases
13. Known allergic/ hypersensitivity reaction to any of the components of the treatment
14. Contraindications to the use of atropine
15. Other serious illness or medical conditions within the last 12 months prior to study drug administration
16. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol
17. The patient has uncontrolled or poorly-controlled hypertension ( $>160$  mmHg systolic or  $> 100$  mmHg diastolic for  $>4$  weeks) despite standard medical management
18. Active uncontrolled infection
19. Current history of chronic diarrhea
20. Active disseminated intravascular coagulation
21. Any other serious concomitant disease or medical condition that in the judgment of the investigator renders the subject at high risk of treatment complication or reduced the probability of assessing clinical effect
22. Known Dihydropyrimidine dehydrogenase (DPD) deficiency
23. Prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.
24. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy
25. The patient is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted
26. Concurrent treatment with other experimental drugs or participation in

	<p>another clinical trial with any investigational drug within 30 days prior to treatment start</p> <p>27. Known drug abuse/ alcohol abuse</p> <p>28. Lack of resolution of all toxic effects (excluding alopecia) of prior chemotherapy, prior radiotherapy or surgical procedure to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade <math>\leq 1</math>. Note: Neuropathy due to prior chemotherapy is allowed if not <math>&gt;</math> NCI Grade II according to CTCAE version 4.03</p> <p>29. Subject pregnant or breast feeding, or planning to become pregnant within 3 months after the end of treatment</p> <p>30. Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 3 months (male or female) after the end of treatment</p> <p>31. Patients known to have a HER 2 positive Cancer who have not been treated already with a HER 2 targeting agent.</p> <p>32. Patients with a psychiatric illness or patients imprisoned or working in the institution of the treating physician.</p>
Investigational and Control Arm, Dose, Regimen, treatment cycle	<p>Randomisation 2:1 Each Cycle: either:</p> <p>- Experimental Treatment: Arm A (FOLFIRI + Ramucirumab) Ramucirumab 8 mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle <u>plus</u> FOLFIRI (Irinotecan 180 mg/m<sup>2</sup>; i.v. bolus of 5-FU 400 mg/m<sup>2</sup>, i.v. infusion of leucovorin* 400 mg/m<sup>2</sup>, followed by a 46-hour continuous administration of 5-FU 2400 mg/m<sup>2</sup> on day 1 and 15 of a 28-day cycle)</p> <p>or</p> <p>- Standard Treatment: Arm B (Paclitaxel + Ramucirumab) Ramucirumab 8mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle <u>plus</u> Paclitaxel 0 mg/m<sup>2</sup> on day 1, 8, 15 Each cycle will be repeated after 28 days (from day 1) until the patient experiences progress</p> <p>(* Note: Leucovorin can be replaced by sodium folinate that is given according to local guideline.</p>
Statistical considerations	<p>The present trial is designed as a randomized phase II study which aims at estimating the therapeutic efficacy of the experimental regimen R-FOLFIRI in relation to the standard combination ramucirumab + paclitaxel (R-Pac). The statistical considerations are solely based on the experimental arm FOLFIRI + ramucirumab.</p> <p>The assumptions derived from the historical data on R-Pac are verified by a randomised reference group. Therefore, the standard arm paclitaxel + ramucirumab serves as an internal control to control for selection bias (calibration – arm).</p> <p>The OS rate of FOLFIRI + ramucirumab after 6 months is chosen as primary efficacy endpoint.</p> <p>The estimation of the efficacy rate of the experimental regimen is to be based on an explorative pilot study, since immediate embarking on a large scale comparative efficacy trial would not be acceptable from the point of view of resources. Moreover, this would induce ethical objections, as it does not seem to be justifiable to expose a large number of patients to an experimental approach without any exploratory indications of an improved risk-benefit ratio.</p> <p>Design and assumptions:</p> <ul style="list-style-type: none"> <li>• Explorative randomized phase II study with 2:1 randomization.</li> <li>• Primary endpoint: OS rate after 6 months, based on an ITT population.</li> <li>• The experimental therapy would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true OS rate amounted to 65% or more, as this corresponds to the efficacy of the standard R-Pac regimen according to the RAINBOW study.</li> </ul>

	<ul style="list-style-type: none"> <li>• On the other hand, the experimental therapy would be rated as insufficiently active, if the true OS rate is 50% or lower, as this suggests a distinct inferiority to R-Pac.</li> <li>• Probability to accept the experimental therapy as promising (<math>\geq 65\%</math> OS rate) with respect to efficacy, in spite of a true OS rate of <math>\leq 50\%</math>: 0.05 (type I error)</li> <li>• Probability to reject the experimental therapy as not sufficiently efficient (<math>\leq 50\%</math>), although the true OS rate is promising (<math>\geq 65\%</math>): 0.2 (type II error, corresponding to a power of 80%).</li> </ul>
Sample size calculation	According to these parameters, and using a standard single-stage phase II design by FLEMING (1981), $n = 67$ patients evaluable for efficacy have to be recruited in the R-FOLFIRI arm. About $n = 34$ patients are to be allocated to the reference R-Pac arm, according to the 2:1 randomization. The final conclusion of the phase II trial will depend on the definite OS rate (and its confidence interval), the respective findings in the R-Pac reference arm, as well as the information on type, frequency and severity of toxicities. Thus, a total number of about $67 + 34 = 101$ evaluable patients is required. Assuming a 10% drop out rate we are planning to include 111 pts
Key dates	FPFV: Q2 2017 Follow-up: every 2 months for up to 1 year
Number of patients, and location	Total number of patients: 111 (Arm A 67+ Arm B 34) Location of sites: Germany Participating sites: 13
Anzahl eingeschl. Pat.	50 (Stand 09.04.2018)
Weitere Zentren:	nein

### Plattenepithel Karzinom Ösophagus Zweitlinientherapie

**AIO-STO-0216/ass: A randomized, multicenter open label phase II trial of Paclitaxel + Ramucirumab versus Paclitaxel alone in patients with squamous-cell carcinoma of the esophagus, refractory or intolerant to combination therapy with Fluoropyrimidine and Platinum-based drugs – The RAMOS study**

#### AIO-assoziierte Studie

Studiennummer/-Code:	AIO-STO-0216/ass   RAMOS-Study
Status:	in Vorbereitung
Rekrutierungszeitraum	2018 - 2020 (geplant)
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Trial type	A randomized, multicenter open label phase II trial
Coordinating investigator	Prof. Dr. Sylvie Lorenzen Klinikum rechts der Isar der Technischen Universität München, Abteilung für Hämatologie und Onkologie, Ismaningerstr. 22, 81675 München
Medical condition	squamous-cell carcinoma of the esophagus
Objective(s)	OS rate after 6 months, based on an ITT population. The experimental therapy (Paclitaxel + Ramucirumab) would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true OS rate amounted to 66%, corresponding to a median OS of 10 months, as this is

	considered to be a clinically highly relevant benefit compared to published results with taxane mono-chemotherapy (median of about 7 months).
Intervention(s)	<p><b>Arm A (investigational arm)</b>  Paclitaxel 80 mg/m<sup>2</sup> on day 1, 8, 15  plus  Ramucirumab 8 mg/kg i.v. infusion on day 1 and 15  Start of next cycle on day 29 (qd 28).</p> <p><b>Arm B (control arm)</b>  Paclitaxel 80 mg/m<sup>2</sup> on day 1, 8, 15  Start of next cycle on day 29 (qd 28).</p>
Key inclusion and exclusion criteria	<p><u>Key inclusion criteria:</u></p> <ul style="list-style-type: none"> <li>- Histologically proven squamous cell carcinoma of the esophagus</li> <li>- Metastatic or locally advanced disease, not amenable to potentially curative resection</li> <li>- Refractory or intolerant to a combination therapy of platinum and a fluoropyrimidine for esophageal cancer. The definition of refractory should be defined as follows:</li> <li>- Patients whose PD or recurrence was confirmed by imaging during their initial chemotherapy (including chemoradiation) or within 8 weeks after the last dose of chemotherapy will be assessed as “refractory”.</li> <li>- Patients after radical resection in conjunction with chemotherapy, including neoadjuvant/adjuvant therapy and chemoradiation, whose recurrence was confirmed by imaging within 24 weeks after the last dose of chemotherapy, will be determined “refractory”.</li> <li>- Measurable or non-measurable but evaluable disease determined using guidelines in RECIST 1.1 as confirmed within 28 days before randomization</li> <li>- Adequate blood and biochemistry parameters</li> </ul> <p><u>Key exclusion criteria:</u></p> <ul style="list-style-type: none"> <li>- Other tumor type than squamous carcinoma (e.g. leiomyosarcoma, lymphoma) or a second cancer except in patients with squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been effectively treated. Patients curatively treated and disease-free for at least 5 years will be discussed with the sponsor before inclusion</li> <li>- Patients with significant malnutrition who receive intravenous hyperalimentation or require continuous infusion therapy with hospitalization.</li> <li>- Patients with apparent tumor invasion on organs located adjacent to the esophageal disease. Patients will be excluded if they are receiving stent therapy in esophagus or respiratory tract.</li> <li>- Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol</li> <li>- Previous therapy with paclitaxel or previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study</li> </ul>
Outcome(s)	<p><u>Primary endpoint:</u>  OS rate after 6 months</p> <p><u>Secondary endpoints:</u></p> <ul style="list-style-type: none"> <li>- Progression-free survival</li> <li>- Overall survival</li> <li>- Objective response rate (CR + PR)</li> <li>- Tumor control rate (CR, PR, SD)</li> <li>- Safety (according to NCI-CTCAE V 4) and tolerability</li> <li>- Quality of Life (EORTC QLQ C-30)</li> </ul>
Sample size	186 (93 per Arm)

Trial duration	First patient in to last patient out (months): 48
	Duration of the entire trial (months): 48
	Recruitment period (months): 36
Anzahl eingeschl. Pat.	0 (Studie in Vorbereitung)

**AIO-STO-0117: A multicenter open-label phase II trial to evaluate Nivolumab and Ipilimumab for 2nd line therapy in elderly patients with advanced esophageal squamous cell cancer [RAMONA]**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-STO-0117 - RAMONA
Status:	in Rekrutierung
Rekrutierungszeitraum	2018 - 2019
Weitere Zentren:	nein
Letzte Aktualisierung	April 2018

National Coordinating Investigator (LKP)	Prof. Dr. med. Matthias Ebert II. Medizinische Klinik Universitätsmedizin Mannheim, Heidelberg University Theodor-Kutzer-Ufer 1-3 68167 Mannheim Germany Phone: +49621 383 3284 Fax: +49621 383 3805 E-Mail: Matthias.Ebert@umm.de
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Study design	Open label, multicenter phase II trial
Duration of study	Enrollment: 12 months total study duration 36 months (incl. follow-up)
Indication	Second-line treatment for advanced esophageal squamous cell cancer (ESCC)
Target population	Elderly patients with ESCC progressing after prior systemic chemotherapy (radio-chemotherapy or systemic chemotherapy)
Total number of sites	34 / 23 initiated
Recruitment status	75 patients planned, 2 patients enrolled
Primary objective	The primary objective of this trial is to demonstrate a significant survival benefit of the combination therapy with nivolumab/ipilimumab treatment in advanced esophageal squamous cell cancer compared to historical data of standard chemotherapy regimens. Additionally, tolerability of nivolumab as single agent and in combination with ipilimumab will be investigated in terms of quality of life. Hence, a co-primary endpoint 'time to QoL deterioration' will be implemented.
Secondary objectives	Secondary objectives of this study are: a) to assess additional efficacy and safety parameters of an intensified



	<p>immunotherapy regimen.</p> <p>b) to assess and explore the predictive value of structured geriatric assessments for treatment-emergent toxicities and treatment discontinuation</p>
Inclusion criteria	<ul style="list-style-type: none"> <li>- Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>- Age <math>\geq</math> 65 years at time of study entry</li> <li>- Histologically confirmed advanced stage esophageal squamous cell carcinoma in 2<sup>nd</sup> line: <ul style="list-style-type: none"> <li>o stage 4 <u>OR</u></li> <li>o stage 3 non-responder to radio-chemotherapy <u>OR</u></li> <li>o stage 3 with early relapse &lt; 6 month after chemo-radiation</li> </ul> </li> <li>- Patients treated with Carboplatin/ Paclitaxel (+/- radiotherapy) or other chemotherapy in 1st line</li> <li>- Geriatric status: SlowGo or GoGo according to G8 and DAFI assessment (G8 &gt; 14 points or CGA/DAFI 0.2&lt;0.35)</li> <li>- At least 1 measurable lesion according to RECIST 1.1</li> <li>- Karnofski performance status <math>\geq</math> 50</li> <li>- Sufficient cardiac functional reserve defined as ejection fraction &gt; 50%</li> <li>- Adequate blood count, liver-enzymes, and renal function: <ul style="list-style-type: none"> <li>- neutrophil count &gt; <math>1.5 \times 10^6</math>/mL</li> <li>- WBC <math>\geq</math> 3000/<math>\mu</math>L</li> <li>- Platelet count <math>\geq</math> <math>100 \times 10^9</math>/L (&gt;100,000 per mm<sup>3</sup>)</li> <li>- hemoglobin <math>\geq</math> 9 g/dL</li> <li>- INR <math>\leq</math> 1.5 and PPT <math>\leq</math> 1.5 x lower limit during the last 7 days before therapy</li> <li>- AST (SGOT)/ALT (SGPT) &lt; 3 x institutional upper limit of normal (5 x lower limit in case of liver metastases)</li> <li>- bilirubin &lt; 1.5 x ULN</li> <li>- Serum Creatinine <math>\leq</math> 1.5 x institutional ULN or creatinine clearance (CrCl) <math>\geq</math> 30 mL/min (if using the Cockcroft-Gault formula below):  Female CrCl = <math>\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}</math>  Male CrCl = <math>\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}</math> </li> </ul> </li> <li>- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational products (nivolumab, ipilimumab). Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception).</li> <li>- Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.</li> </ul>
Exclusion criteria	<p><b>Methodological criteria:</b></p> <ul style="list-style-type: none"> <li>• Patients &lt;65 years of age</li> <li>• Frail patients (DAFI score <math>\geq</math> 0.35)</li> <li>• Esophageal adenocarcinomas, neuroendocrine tumors</li> <li>• Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-Programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)</li> <li>• Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lives of previously used trial medication, whichever is longer</li> <li>• Previous treatment in the present study (does not include screening failure).</li> </ul>

**Medical:**

- Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to:
  - Major surgery  $\leq$  28 days prior first dose of study treatment
  - Anticancer treatment during the last 30 days prior to start of nivolumab-monotherapy treatment, including systemic therapy, or major surgery [palliative radiotherapy has to be completed at least 2 weeks prior to start of study treatment]
  - history of interstitial lung disease
  - known acute or chronic pancreatitis
  - known active HBV, HCV or HIV infection
  - active tuberculosis
  - any other active infection (viral, fungal or bacterial) requiring systemic therapy
  - history of allogeneic tissue/solid organ transplant
  - diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of nivolumab-monotherapy treatment.
  - Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.
  - Live vaccine within 30 days prior to the first dose of nivolumab-monotherapy treatment or during study treatment.
  - Other clinically significant active malignancy requiring treatment OR less than 5 years disease free interval of another primary malignancy
  - Clinically significant or symptomatic cardiovascular/cerebrovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment
  - History or clinical evidence of CNS metastases  
Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:
    1. are asymptomatic and
    2. have no requirement for steroids 6 weeks prior to start of nivolumab-monotherapy treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases

**Drug related criteria:**

- Medication that is known to interfere with any of the agents applied in the trial.
- Has known hypersensitivity to nivolumab or ipilimumab or any of the constituents of the products.
- Any other efficacious cancer treatment except protocol specified treatment at study start.
- Patient has received any other investigational product within 28 days of study entry.

**Safety criteria:**

- Patient has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. [Subjects with  $\leq$  Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.]
- Female subjects who are pregnant, breast-feeding or male/female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner]. Women of childbearing potential must have a negative pregnancy test (serum  $\beta$ -HCG) at screening.

	<p><b>Regulatory and ethical criteria:</b></p> <ul style="list-style-type: none"> <li>• Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.</li> <li>• Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</li> <li>• Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</li> </ul>
Investigational agents	<ul style="list-style-type: none"> <li>• nivolumab</li> <li>• ipilimumab</li> </ul>
Treatment schedule	<p>Subjects enrolled in this trial will initiate 2nd line palliative systemic treatment with nivolumab monotherapy (240 mg Q2W) for 3 consecutive cycles (safety run-in). After three cycles of nivolumab monotherapy study subjects will be assessed for the occurrence of specific treatment-emergent adverse events (TEAE).</p> <p>Study subjects without significant TEAEs are eligible to escalate treatment to a nivolumab/ipilimumab combination therapy:  <b>Arm A:</b> Nivolumab 240 mg fixed dose IV Q2W; Ipilimumab 1mg/kg IV Q6W (starting in week 7 after safety assessment)</p> <p>Subjects with significant TEAEs who still qualify for nivolumab treatment continue nivolumab mono-therapy:  <b>Arm B: Nivolumab 240 mg IV fixed dose Q2W</b></p> <p>In both arms treatment continues until progressive disease or intolerable toxicity or withdrawal of consent or death.</p> <p>Tumor assessments:  c) 1st restaging assessment after 12 weeks of therapy  d) thereafter Q8W (post-progression nivolumab after 1st assessment included)</p>
Primary endpoint	Overall survival
Secondary endpoints	<ul style="list-style-type: none"> <li>• Time to QoL deterioration defined as a loss of <math>\geq 10</math> points in the EORTC QLQ-C30 compared to base-line</li> <li>• PFS</li> <li>• ORR according to RECIST 1.1 and immune related response criteria (modified RECIST)</li> <li>• Duration of Response (DOR)</li> <li>• Duration of treatment</li> <li>• cumulative dose intensity</li> <li>• QoL (EORTC QLQC30 and ELD14)</li> <li>• AEs/SAEs</li> </ul> <p>Geriatric assessments:</p> <ul style="list-style-type: none"> <li>• Evaluation of the predictive value of the GA containing tests (DAFI, G8-Questionnaire etc.) for the occurrence of <math>\geq</math> grade 3 toxicities.</li> <li>• Predictive value of the assessed geriatric tests for treatment discontinuation</li> </ul>
Exploratory objectives and endpoints	<ul style="list-style-type: none"> <li>• predictive biomarkers in tumor tissue (pre-treatment and re-biopsies) and blood</li> </ul>
Rationale Hypothesis	<p>ESCC is frequently diagnosed in advanced tumor stages, and in elderly patients with additional comorbidities. In addition, the role of chemotherapy in advanced ESCC is still poorly defined. While most patients undergo chemotherapy and/or chemo-radiation in first line, mostly according to the CROSS protocol using paclitaxel and carboplatin, the role of second line chemotherapy is even less well understood [1]. PD-L1 has been identified as a significant predictor for poor treatment response and shorter survival in ESCC [2]. Recent data indicate that Nivolumab is effective in second line treatment of advanced squamous-cell non-small-cell lung cancer (NSCLC)</p>

	<p>[3]. Preliminary results from a Japanese study indicate efficacy of Nivolumab in esophageal cancer [4]. From 64 heavily pre-treated patients 17.2% elicited an objective tumor response and 25% demonstrated stable disease. The median overall survival was 12.1 months in this trial population (unselected for PD-L1 expression status). Furthermore the Checkmate 012 trial demonstrated that overall response rates can be doubled when PD-L1 inhibitor Nivolumab (3mg/kg IV Q2W) is combined with CTLA-4-inhibitor Ipilimumab (1mg/kg IV Q6W) in advanced NSCLC patients. In this trial treatment related adverse events leading to discontinuation were only slightly enhanced when compared to Nivolumab monotherapy (10% vs. 13%) [9].</p> <p>The increasing need for improved treatment strategies for elderly ESCC patients acknowledging the challenges of functional limitations and comorbidities in this increasing population, the poor knowledge of the role of chemotherapy and immunotherapy in these individuals due to lack of enrolment of these patients in clinical trials, the medical need of improved second line treatment strategies in ESCC and the current success of checkpoint inhibitors in treatment of various squamous cell cancers form the rationale and basis for the RAMONA trial in which the novel agents Nivolumab and Ipilimumab will be assessed in the second line therapy of advanced ESCC in the elderly population.</p> <p><b>Research hypothesis:</b></p> <ul style="list-style-type: none"> <li>• Nivolumab in combination with Ipilimumab improves overall survival compared to standard chemotherapy (historical control) in elderly patients with esophageal squamous cell cancer.</li> <li>• Nivolumab alone and in combination with Ipilimumab improves time to QoL deterioration compared to standard chemotherapy (historical control) in elderly ESCC patients.</li> </ul>												
Safety data	<ul style="list-style-type: none"> <li>• AEs, SAEs and treatment emergent adverse events according to CTC 4.03</li> <li>• Frequency of clinically significant abnormal laboratory parameters</li> </ul>												
<p>Sample size estimation and</p> <p>Statistical analysis considerations</p>	<p>It is hypothesized that Nivolumab and Ipilimumab will increase overall survival. It is assumed that an immunotherapy approach consisting of a nivolumab monotherapy in conjunction with a safety guided treatment escalation to a NIVO/IPI combination regimen increases the 1-year overall survival rate by a margin of 13% compared to historical control for standard chemotherapy (i.e. Nivolumab-monotherapy followed by a conditional Nivolumab + Ipilimumab therapy 1-yr-OS = 30% vs CTx-control 1-yr-OS = 17%).</p> <p>Sample size estimation: A one-sided, one-sample log rank test calculated from a sample of 69 subjects achieves 90.3% power at a alpha=0.05 one-sided significance level to detect a proportion surviving of 0.3 in the experimental group when the proportion surviving in the historic control group is 0.17. These proportions surviving are for a period of 12 month (1-year-OS rate). Subjects are accrued for a period of 12 month. Follow-up continues for a period of 24 month after the last subject is added. The probability that a subject experiences an event during the study is 0.9477. The expected number of events during the study is 65.</p> <p>To compensate for uninformative drop-outs a total of <b>N=75</b> subjects need to be recruited.</p>												
Study plan / time lines	<table border="0"> <tr> <td>First Patient In (FPI):</td> <td>Q1/2018</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 12 month</td> </tr> <tr> <td>Last Patient Last treatment (LPLT):</td> <td>after approx. 20 month</td> </tr> <tr> <td>End of follow-up period after LPI:</td> <td>after approx. 36 month</td> </tr> <tr> <td>Study report:</td> <td>after approx. 45 month</td> </tr> <tr> <td>Publication:</td> <td>after approx. 45 month</td> </tr> </table>	First Patient In (FPI):	Q1/2018	Last Patient In (LPI):	after approx. 12 month	Last Patient Last treatment (LPLT):	after approx. 20 month	End of follow-up period after LPI:	after approx. 36 month	Study report:	after approx. 45 month	Publication:	after approx. 45 month
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End of follow-up period after LPI:	after approx. 36 month												
Study report:	after approx. 45 month												
Publication:	after approx. 45 month												

Retrospektive Studie**AIO-STO-0116: Langzeitansprechen unter Trastuzumab bei Patienten mit fortgeschrittenen Her2/neu+ gastro-ösophagealen Karzinomen**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-STO-0116
Status:	in Rekrutierung
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2017

Studienleiter	Prof. Dr.med. Ralf Hofheinz Interdisziplinäres Tumorzentrum, TTZ, Haus 9 Universitätsmedizin Mannheim Theodor-Kutzer Ufer 1-3 68167 Mannheim
Geplante Studie	Charakterisierung prädiktiver Faktoren für das Langzeitüberleben unter Trastuzumab-Erhaltungstherapie beim fortgeschrittenen Her2/neu+ gastro-ösophagealen Karzinomen.
Hintergrund	<p>Her2/neu (human epidermal growth factor receptor 2) gehört zur Familie der epidermalen Wachstumsfaktorrezeptoren (EGF-Rezeptor). Der Her2/neu-Antikörper Trastuzumab spielt eine wichtige Rolle in der Behandlung des Mammakarzinoms.</p> <p>Die Wirksamkeit von Trastuzumab in der Behandlung des Her2/neu überexprimierenden Magenkarzinoms wurde im Rahmen der ToGA, einer internationalen, Phase III Studie, untersucht. Dort wurden Patienten eingeschlossen, deren Tumoren eine Überexpression des Her2/neu Proteins in der Immunhistochemie oder in der FISH Diagnostik gezeigt hatten. Insgesamt waren 594 Patienten entweder mit Chemotherapie allein oder in Kombination mit Trastuzumab (1:1 Randomisierung) behandelt worden. Das mediane Gesamtüberleben war 13.8 für Patienten mit Trastuzumab/Chemotherapie-Behandlung versus 11.1 für Patienten, die nur Chemotherapie erhielten.</p> <p>Nach 6 Zyklen kombinierter Chemo- und Antikörpertherapie werden Patienten mit Her2/neu überexprimierendem Magenkarzinom aktuell mit einer Erhaltungstherapie mit Trastuzumab allein (alle drei Wochen) behandelt.</p> <p>Die klinische Erfahrung hat gezeigt, dass einige Patienten während der Erhaltungstherapie innerhalb von Wochen bis wenigen Monaten ein erneutes Tumorwachstum erleiden. Bei anderen Patienten ist der Tumor während der Erhaltungstherapie über lange Zeit – teilweise über Jahre – gut kontrolliert und zeigt kein erneutes Wachstum.</p> <p>Derzeit gibt es keine prädiktiven Marker, die ein Langzeitansprechen bzw. ein nicht-Ansprechen auf eine Trastuzumab Therapie vorhersagen. Unsere retrospektive Studie wird zwei Gruppen von Patienten zu analysieren. Einmal die Gruppe der Patienten, die innerhalb der kombinierten Therapie mit Chemotherapie und Trastuzumab innerhalb von 18 Wochen nach Therapiebeginn bereits progredient waren.</p> <p>Zum anderen die Gruppe der sogenannten „Langzeitüberleber“, definiert als die Patienten, die im Rahmen der Trastuzumab-Erhaltungstherapie länger als ein Jahr keine Tumorprogression aufweisen.</p>
Studiendesign	Retrospektive Analyse von Patienten, die sich mehr als 1 Jahr unter einer Trastuzumab-Erhaltungstherapie befinden, sowie einer Kontrollgruppe von „rapid progressors“ (definiert als „progressive disease“ ≤ 18 Wochen seit Beginn einer Cisplatin/5-FU und Trastuzumab-Therapie)
Patientenzahl	<b>Geplante Anzahl der eingeschlossenen Patienten:</b>

	<p>Jeweils 30 Patienten pro Gruppe.</p> <p><b>Folgende Patienten sollen eingeschlossen werden:</b></p> <p>Patienten <math>\geq 18</math> Jahre mit fortgeschrittenen Her2/neu positivem (immunhistochemisch und/oder mittels in-situ Hybridisierung) gastro-ösophagealen Karzinomen, die eine Chemotherapie in Kombination mit Trastuzumab, bzw. anschließende Erhaltungstherapie erhalten haben und entweder innerhalb von 18 Wochen nach Beginn der kombinierten Chemotherapie/Antikörpertherapie progredient waren, sowie die Gruppe der "Langzeitüberleber", die länger als ein Jahr nach Beginn der Erhaltungstherapie mit Trastuzumab noch in Remission sind.</p> <p>Patienten werden in zwei Gruppen aufgeteilt:</p> <ol style="list-style-type: none"> <li>"rapid progressors": Progress innerhalb von 18 Wochen nach Beginn der initialen Chemotherapie in Kombination mit Trastuzumab</li> <li>Patienten, die länger als ein Jahr nach Beginn einer Erhaltungstherapie mit Trastuzumab in "Remission" sind.</li> </ol>
Weitere teilnehmende Zentren erwünscht?	ja
Parameter	<ol style="list-style-type: none"> <li>1. Patienten- und Tumorcharakteristika</li> <li>2. Ansprechen auf die Erstlinien- und Erhaltungstherapie</li> <li>3. Progressionsfreies und Gesamtüberleben</li> <li>4. Erfassung aller potentiellen Nebenwirkungen der Trastuzumab-Therapie, z.B. Kardiotoxizität</li> <li>5. Erweiterung der klassischen Her-2/neu Bestimmung um weitere Analysen, inklusive weiterer molekularer Marker.</li> </ol>
Haupt-Ausschlusskriterien / Key exclusion criteria	<ul style="list-style-type: none"> <li>• Alter &lt; 18 Jahre</li> <li>• Schwangere oder stillende Mütter</li> <li>• Patienten mit bekannten schwerwiegenden psychiatrischen Erkrankungen</li> </ul>
Geplante Analysen	<ol style="list-style-type: none"> <li>a) Retrospektive Erhebung klinischer Parameter der Patienten (Alter, Komorbiditäten, initiale Histologie des Tumor, Verträglichkeit der Therapie, Ansprechen auf die Therapie, Nebenwirkungen der Trastuzumabtherapie (insbesondere Kardiotoxizität).</li> <li>b) Molekularpathologische Analysen an bereits vorhandenen Tumorbiopsien: Her-1-Her-4 Signaling mittels quantitativer PCR Technologie, Gesamt-Transkriptom Analysen, Protein und Phosphoprotein-Arrays sowie Immunhistochemie. Globale genetische Charakterisierung des Tumors mittels "next generation sequencing", sowie Erfassung des Spektrums der Kopienzahlalterationen (Oncoscan). Hochauflösende Mikroskopie zur HER2 Rezeptorinternalisierung.</li> </ol>
Gewebeanalyse	<p>Bereits vorhandene Tumorbiopsien (Primarius und/oder Metastasen, die den Patienten zu Untersuchungszwecken entnommen wurden und sich im Pathologischen Institut des jeweiligen Zentrums befinden). Wir bitten um Übersendung mindestens eines tumortragenden FFPE-Blocks sowohl von der Biopsie als vom Resektat, als auch um Übersendung eines FFPE-Blocks mit Normalgewebe (am besten Resektionsrand).</p> <p>Nach Abschluss der Studie schicken wir das nicht verwendete Restgewebe selbstverständlich wieder an die dezentrale Pathologie zurück.</p> <p>Die von den Patienten zur Verfügung gestellten Gewebeproben und Daten werden ausschließlich für die medizinische Forschung im Rahmen der hier beschriebenen Studie verwendet. Es ist nicht geplant, neue Gewebebiopsien zu entnehmen.</p> <p><b>Durchführung der Gewebeanalysen:</b></p>

	<p>Pathologisches Institut des Universitätsklinikums Mannheims, Theodor-Kutzer-Ufer 1-3; D-68167 Mannheim; Ansprechpartner: Prof. Dr. Timo Gaiser, Leitender Oberarzt und Leiter der Molekularpathologie.</p> <p>Risiko für den Patienten: Es ist kein zusätzliches Risiko für den Patienten gegeben. Der Patient wird entweder bereits mit einer regelmäßigen Trastuzumab-Erhaltungstherapie behandelt, oder die Trastuzumab-Therapie wurde aufgrund eines frühzeitigen Progresses abgebrochen.</p>
Einverständniserklärung	<p>Patienten, die sich aktuell in einer Erhaltungstherapie mit Trastuzumab befinden, werden mithilfe des beigefügten Aufklärungsbogen umfassend aufgeklärt. Ihre Unterschrift ist zur Studienteilnahme erforderlich.</p> <p>Patienten aus der Kontrollgruppe, die unter eine Chemotherapie in Kombination mit Trastuzumab bereits nach 18 Wochen oder weniger progredient waren, können in der Regel nicht mehr nachträglich aufgeklärt werden, da sie bereits verstorben sind. Wir würden für diese Patienten, da es sich um eine retrospektive Analyse handelt, kein Einverständnis einholen.</p>

## Arbeitsgruppe Pankreaskarzinom

### Pankreaskarzinom – adjuvante Therapie

#### **AIO-PAK-0213/ass: Adjuvant Gemcitabine versus NEOadjuvant Gemcitabine/Oxaliplatin plus adjuvant Gemcitabine bei resektablem Pankreaskarzinom (NEOPAC)**

<b>AIO-assozierte Studie</b>	
Studiennummer/-Code:	AIO-PAK-0213/ass - NEOPAC
Status:	nicht bekannt
Rekrutierungszeitraum:	2013 - 2018
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2016

Verantwortliche Studienleiter nach AMG	PD Dr. med. S. Heinrich Prof. Dr. med. M. Möhler
Kontaktadresse/ Kontaktpersonen	Universitätsmedizin Mainz Langenbeckstrasse1 55130 Mainz Tel. 06131-17 2738 E-Mail: stefan.heinrich@unimedizin-mainz.de
Studienziel	Verbesserung des rezidiv-freien und Gesamtüberlebens von Patienten mit resektablem Pankreaskarzinom
Studienendpunkte	<b>Primärer Studienendpunkt:</b> progressions-freies Überleben  <b>Sekundäre Endpunkte:</b> histologisches Ansprechen, Gesamtüberleben, chirurgische Komplikationsrate, Machbarkeit der adjuvanten Therapie
Patientenzahl	310 Patienten; bereits eingeschlossen: 36 (Apr 2016)
Einschlusskriterien	<ul style="list-style-type: none"> <li>• resektables Adenokarzinom des Pankreaskopfes</li> <li>• T1-3, Nx, M0 (UICC Version 6, 2002)</li> <li>• Pfortaderinfiltration &lt;180°</li> <li>• zytologischer oder histologischer Karzinomnachweis</li> <li>• Alter &gt;18 Jahre</li> <li>• schriftliches Einverständnis</li> </ul>
Ausschlusskriterien	<ul style="list-style-type: none"> <li>• Kontraindikation gegen Pankreaskopfresektion</li> <li>• Pfortaderinfiltration &gt;180°</li> <li>• Tumorkontakt zur A. mesenterica superior</li> <li>• Infiltration der A. mesenterica superior oder des Truncus coeliacus</li> <li>• chronische Neuropathie &gt; °2</li> <li>• WHO Performance-Status &gt; °2</li> <li>• Patientinnen im gebärfähigen Alter, die keine adequate Kontrazeption durchführen (orale or subkutane Kontrazeptiva, Intrauterinpeessar, Kondom)</li> <li>• schwangere oder stillende Frauen</li> <li>• geistige oder körperliche Behinderungen, die mit dem Einverständnis interferieren</li> <li>• weitere maligne Erkrankungen innerhalb der letzten 5 Jahre ausser non-Melanom Hautkrebs oder nicht-invasives Zervixkarzinom</li> <li>• perkutane Biopsie des Primärtumors</li> </ul>



Therapieschemata	<p><b>Arm A:</b> Pankreaskopfresektion + adjuvant Gemcitabine 1000mg/m<sup>2</sup> (6x d 1,8,15)</p> <p><b>Arm B:</b> Gemcitabine 1000mg/m<sup>2</sup> + Oxaliplatin 100mg/m<sup>2</sup> (2x d 1,15) + Pankreaskopfresektion + adjuvant Gemcitabine 1000mg/m<sup>2</sup> (6x d 1,8,15)</p>
Follow-up	CT-Thorax/Abdomen 9, 12, 15, 21, 27 ... (jede 6 Monate) nach Studieneinschluss bis zum Rezidiv
Rationale	Ein Grossteil an Patienten kann nach einer Pankreaskopfresektion keine adjuvante Chemotherapie erhalten. Eine neoadjuvante Chemotherapie können hingegen alle Patienten erhalten, und sie verbessert den Ernährungszustand der Patienten. Daher soll der zusätzliche Effekt einer neoadjuvanten Chemotherapie zur Standardtherapie untersucht werden.
Statistik	Unter der Annahme eines progressions-freien Überlebens 1 Jahr nach Randomisierung von 40% in Arm A und von 55% in Arm B müssen bei 1:1 Randomisierung 310 Patienten (155 pro Arm) eingeschlossen werden, um einen signifikanten Unterschied bei einem $\alpha$ -Fehler von 0.05 und einer Power von 80% zu detektieren.

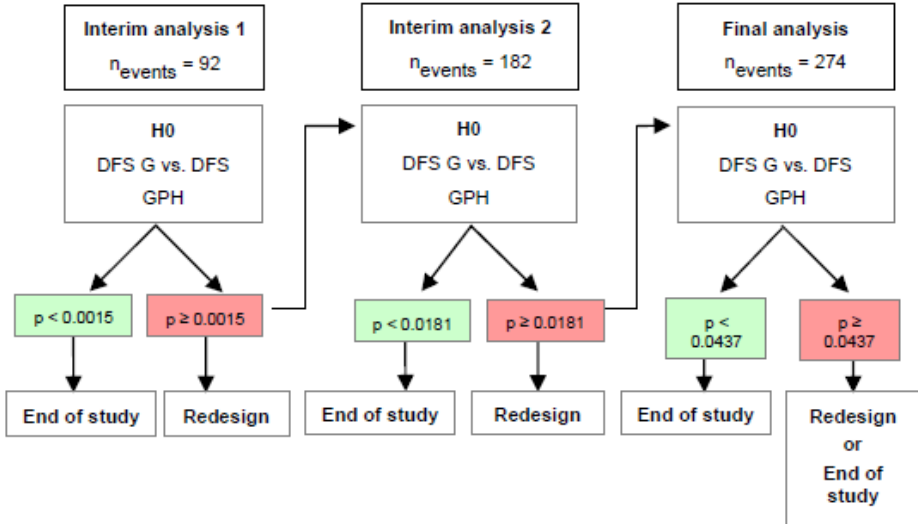
**AIO-PAK-0111/ass: A randomized two-armed open study on the adjuvant therapy in patients with R0/R1 resected pancreatic carcinoma with Gemcitabine plus Capecitabine (Arm GC) vs. Gemcitabine plus Cisplatin with regional hyperthermia (Arm GPH)**

AIO-assoziierte Studie	
Studiennummer/-Code:	AIO-PAK-0111/ass - HEAT
Status:	Rekrutierung ist aktiv
Rekrutierungszeitraum:	2013 - 2019
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	Oktober 2017

Study Type	Multicenter, national, randomized (stratification: R0/1; N+/-; surgical study center/surgical non-study center)
Sponsor	Klinikum Grosshadern Medical Center, University of Munich represented by the medical director, D-81377 Munich
Coordinating Investigator	Prof. Dr. Rolf Issels Dept. Internal Medicine III, Klinikum Grosshadern Medical Center University of Munich, D-81377 Munich
Trial Office	Prof. Dr. Rolf Issels / Coordinating center: Nelli Dieterle Phone: +49-89-4400-77776 / -74768 E-mail: heat@med.uni-muenchen.de
Condition	R0/R1 resected ductal pancreatic adenocarcinoma
Rationale	Improvement of the disease free survival of patients with R0/R1-resectable pancreatic cancer through an intensified adjuvant treatment including the additional application of cisplatin and regional deep hyperthermia
Treatment Scheme	Multicenter, national, randomized (stratification: R0/1; N+/-; surgical study center/surgical non-study center)

	<pre> graph TD     A[Resektion R0/R1 (N+/-, M0)] --&gt; B[Staging]     B --&gt; C[Randomisierung STUDIENSTART]     C --&gt; D[Start: 4 - 12 Wochen post-Op.]     D --&gt; E[Arm GC: Gemcitabin/Capecitabin, 24 Wochen]     D --&gt; F[Arm GPH: Gemcitabin/Cisplatin + RHT, 24 Wochen]     E --&gt; G[Follow up Primärer Endpunkt: DFS]     F --&gt; G   </pre>
Objektives	<p><i>Improvement of the outcome of resectable pancreatic carcinoma through an intensified adjuvant treatment with gemcitabine, cisplatin and regional deep hyperthermia as compared to standard chemotherapy.</i></p>
Intervention	<p>Course: A course is defined as a period of 28 days.</p> <p><b>Intervention 1 (GC): Gemcitabine + Capecitabine</b>      Gemcitabine: 1000 mg/m<sup>2</sup> as iv-infusion on days 1, 8 and 15 of each course (Total dose: 18 g/m<sup>2</sup>)      Capecitabine: daily dose of 1660 mg/m<sup>2</sup>; administered orally for 21 days followed by 7 days' rest (one cycle) for six cycles</p> <p>Patients who are randomized to treatment arm GC (standard treatment gemcitabine) are allowed to receive this standard oncologic therapy at an oncologist close to the home town and are not obliged to travel to a study center once a week (Ethics vote: June 27<sup>th</sup>, 2012)</p> <p><b>Intervention 2 (GPH): Gemcitabine + Cisplatin + regional hyperthermia</b>      Gemcitabine: 1000 mg/m<sup>2</sup> as iv-infusion on days 1 and 15 of each course (Total dose: 12 g/m<sup>2</sup>)      Cisplatin: 25 mg/m<sup>2</sup> as iv-infusion on days 2, 3* and 16, 17* of each course (Total dose: 600 mg/m<sup>2</sup>)      Regional hyperthermia: 60 minutes on days 2, 3* and 16, 17* of each course</p> <p>* as an exception: for medical or logistic reasons RHT and cisplatin can be applied on day 4 instead of 3 and day 18 instead of 17.</p> <p>Duration of treatment: It is planned to administer 6 courses. Treatment will be stopped in case of a recurrence of pancreatic carcinoma (local recurrence or distant metastases), unacceptable toxicity, patient's wish or other conditions under which continuation of treatment would not be in the best interest of the patient according to the investigator's opinion.</p>
Number of Patients:	336 patients (168 per arm) - actually 75 patients recruited (Okt. 2017)
Recruitment	Recruitment start: March 2012 Recruitment phase: 36 months
Further study centers requested?	Yes
Inclusion criteria	1. Any ductal adenocarcinoma of the pancreas confirmed by histology

	<ol style="list-style-type: none"> <li>2. Previous R0 or R1 resection of pancreatic tumor with a standardized procedure</li> <li>3. No other previous or concomitant treatment of pancreatic carcinoma like radiation, neoadjuvant therapy or immunotherapy</li> <li>4. No tumor recurrence after surgery</li> <li>5. Performance status ECOG 0-2</li> <li>6. Adequate bone marrow function defined as: <ul style="list-style-type: none"> <li>• WBC count <math>\geq 3.5 \times 10^9/L</math></li> <li>• platelets <math>\geq 150 \times 10^9/L</math></li> <li>• hemoglobin <math>\geq 9</math> g/dl</li> </ul> documented within 1 week prior to randomization </li> <li>7. Adequate renal function defined as: <ul style="list-style-type: none"> <li>• serum creatinine <math>\leq 1.2</math> mg/dl</li> <li>• calculated GFR <math>\geq 60</math> mL/min</li> </ul> documented within 1 week prior to randomization </li> <li>8. Adequate coagulatory function defined as: <ul style="list-style-type: none"> <li>• Quick-value <math>\geq 70\%</math></li> <li>• aPTT <math>\leq 1.5 \times</math> ULN</li> </ul> documented within 1 week prior to randomization </li> <li>9. Transaminases (AST, ALT) <math>\leq 3 \times</math> ULN and bilirubin <math>\leq 2 \times</math> ULN documented within 1 week prior to randomization</li> <li>10. At least 18 years of age</li> <li>11. Women with childbearing potential and fertile men must use adequate contraceptive measures during and for at least 3 months (female) and 6 months (male) after completion of study therapy (Adequate methods for women are oral contraceptives with estrogen and progesterone, vaginal rings, contraceptive patches, estrogen-free ovulation inhibitors, intrauterine devices with progesterone, 3-month injections with depot progesterone, implants setting free progesterone, abstinence or sterilization (vasectomy) of the male partner. Men must use condoms.)</li> <li>12. Women with childbearing potential must have a negative pregnancy test within 1 week prior to randomization (postmenopausal women with amenorrhea for more than 1 year are regarded as having no childbearing potential)</li> <li>13. Written informed consent</li> </ol>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Cystic carcinoma of the pancreas</li> <li>2. Periapillary, papillary cancer</li> <li>3. Metastatic disease</li> <li>4. Presence of an active infection grade 3 or higher</li> <li>5. Other severe disease which could impair the patient's ability to participate in the study according to the investigator's opinion</li> <li>6. Pregnant or breastfeeding women</li> <li>7. Known allergies or contraindications with regard to substances or procedures of study therapy</li> <li>8. Severe, non-healing wounds, ulcers or bone fractures</li> <li>9. Participation in another clinical trial during this study or within 4 weeks prior to randomization Exception: participation in a surgical trial prior to this study, for instance RECO-PANC trial, comparing two different surgical procedures of pancreas resection (Ethics vote: January 21<sup>st</sup>, 2013)</li> <li>0. Past or current abuse of illegal or legal drugs or alcohol</li> <li>1. Other primary malignant diseases in the medical history during the last 5 years (exceptions: carcinoma in situ of the cervix or adequately treated basal cell carcinoma of the skin).</li> <li>2. Permanent cardiac pacemaker</li> <li>3. Gross adiposity defined as BMI <math>&gt; 40</math> kg/m<sup>2</sup></li> <li>4. Treatment with regional hyperthermia not possible for technical reasons (e.g. metal implant)</li> <li>15. <i>Clinically significant cardiovascular or vascular disease or disorder <math>\leq 6</math> months before study enrolment (e.g. myocardial infarction, unstable angina pectoris, chronic heart failure NYHA <math>\geq</math> grade 2, uncontrolled arrhythmia, cerebral infarction)</i></li> </ol>

	6. „Known documented dihydropyrimidine dehydrogenase (DPD) deficiency“
Criteria for evaluation	<p>Primary efficacy criterion: Disease free survival (DFS)          Secondary efficacy criterion: Overall Survival (OS)          Safety: Adverse events (including abnormal laboratory values) scored according to CTCAE (version 4.0)          Quality of Life: EORTC QLQ C30          Assessment for efficacy is scheduled every 12 weeks; quality of life is assessed every two weeks adverse events are recorded on an ongoing basis. Full safety laboratory tests are required prior to the start of each course and after the end of complete study treatment. Other required laboratory tests will be performed as indicated in the study flow chart page 16.</p>
Sample size	<p>For sample size calculation we use a group-sequential design with two interim analyses and the following assumptions:          Median DFS with treatment group 1 (G): 14 months (<math>\lambda_G = 0.05</math>)          Median DFS with treatment group 2 (GPH): 19 months (<math>\lambda_{GPH} = 0.036</math>)</p> <p>For specified alpha = 0.05, hazards <math>\lambda_G = 0.05</math>, <math>\lambda_{GPH} = 0.036</math> (hazard ratio = 0.737) and power of 80.0% the design would require a maximum of 336 patients to be recruited. Hence, a total number of 168 patients per arm is recruited. Interim analyses are planned after occurring of 92, 182 and 274 events on an appropriate significance levels using the stratified Cox proportional hazards model. Assuming a recruitment rate of 122 patients per year and a follow-up of two years the duration of the trial will be <i>estimated to be about five years</i>.</p>
Statistical analysis	<p>Primary efficacy criterion:          We test the following null-hypothesis (H<sub>0</sub>):          DFS under treatment group 1 (G) == to DFS under treatment group 2 (GPH)          In order to test this null hypothesis a stratified Cox proportional hazards model is used to trial the differential effect between the treatment group 2 (GPH) and treatment group 1 (G) with respect to DFS. The proportional hazards model will be stratified by the factors R0/1, N+/- and surgical study center / surgical non-study center. Each trial center will be represented by a gamma-distributed frailty effect. The p-value for the treatment effect will be calculated by a likelihood ratio test between this model and a model which is reduced by the treatment covariate. The analysis is performed on all randomized patients (ITT).</p> <p>We use a group-sequential design according to O'Brien and Fleming with a maximum of three stages. Therefore, two interim analyses and one final analysis are planned as displayed below.</p>  <pre> graph TD     subgraph IA1 [Interim analysis 1]         H0_1[H0 DFS G vs. DFS GPH]         p1_1[p &lt; 0.0015]         p1_2[p ≥ 0.0015]         End1[End of study]         Red1[Redesign]         H0_1 --&gt; p1_1         H0_1 --&gt; p1_2         p1_1 --&gt; End1         p1_2 --&gt; Red1     end      subgraph IA2 [Interim analysis 2]         H0_2[H0 DFS G vs. DFS GPH]         p2_1[p &lt; 0.0181]         p2_2[p ≥ 0.0181]         End2[End of study]         Red2[Redesign]         H0_2 --&gt; p2_1         H0_2 --&gt; p2_2         p2_1 --&gt; End2         p2_2 --&gt; Red2     end      subgraph FA [Final analysis]         H0_3[H0 DFS G vs. DFS GPH]         p3_1[p &lt; 0.0437]         p3_2[p ≥ 0.0437]         End3[End of study]         Red3[Redesign or End of study]         H0_3 --&gt; p3_1         H0_3 --&gt; p3_2         p3_1 --&gt; End3         p3_2 --&gt; Red3     end      Red1 --&gt; H0_2     Red2 --&gt; H0_3   </pre> <p>Secondary efficacy criterion:          For overall survival (OS) we follow the same procedures as described for the primary endpoint DFS. Quality of life together with OS will be analysed in a</p>

	<p>joint model.</p> <p><u>Prespecified subgroup analyses:</u>                  Analysis (DFS and OS) of patients who received <u>at least</u> 4 cycles of standard gemcitabine (12 x G) plus capecitabine (4 x 21 days on treatment) vs at least 4 cycles of standard gemcitabine (8 x G) + Cisplatin (16 x P) plus RHT (16 x H); patients with early progression or death will be included. The comparison is based upon a thermal dose concept according to the number of RHT treatments. Prespecified analysis using hsp27 (heat shock protein 27, MW 27kDa) and hsp70 (heat shock protein 70, MW 70 kDa) as predictive factor will be performed.</p> <p><u>Sensitivity analyses:</u>                  Sensitivity analyses are performed to test the stability of the efficacy finding (adjustment for relevant prognostic factors, per-protocol analysis, and further exploratory analyses, if applicable). Details of the analyses will be provided in a statistical analysis plan (SAP) which is determined prior to each analysis.</p> <p><u>Safety:</u>                  The incidences of adverse events in the treatment arms will be presented by type and severity.                  At each interim analysis there is a chance for redesigning the group sequential trial as a consequence of deviations from the trial plan: decreased recruitment, loss or gain of centers, etc. The reanalysis will be based on the proposal of Müller &amp; Schäfer (SIM, 2004).</p>
<p>Trial duration</p>	<p>First patient in to last patient in: 3 years                  Duration of the entire trial: 5 years                  Flow for stage I of trial</p> <p>Timeline diagram showing trial duration and key events:</p> <ul style="list-style-type: none"> <li>0 months: Start of study</li> <li>12 months: Recruitment phase</li> <li>24 months: Recruitment phase</li> <li>25 months: First interim analysis</li> <li>36 months: End of recruitment phase</li> <li>39 months: Second interim analysis</li> <li>48 months: Follow-up phase</li> <li>60 months: Final analysis / End of study or possible redesign</li> </ul>

Neoadjuvante Therapie des resektablen Pankreaskarzinoms**AIO-PAK-0313: Neoadjuvant plus adjuvant or only adjuvant nab-Paclitaxel plus Gemcitabine for resectable pancreatic cancer: - A prospective, randomized, controlled, phase II study of the AIO Pancreatic Cancer Group (NEONAX)****AIO-Studie**

Studiennummer/-Code:	AIO-PAK-0313 - NEONAX
Status:	in Rekrutierung
Rekrutierungszeitraum:	2015 - 2019
Weitere Zentren:	weiteren Zentren in Vorbereitungen
Letzte Aktualisierung	April 2018

Study Type	An interventional, prospective, randomized, controlled, open label, two sided, survival phase II study against a fixed survival probability
Principal investigator	Prof. Dr. med. Thomas Seufferlein Dept. of Internal Medicine I, University of Ulm Albert-Einstein-Allee 23, 89081 Ulm, Germany Phone: +49 731 50044501 E-mail: thomas.seufferlein@uniklinik-ulm.de
Sponsor:	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany Tel: +49 30-8145 344 32, Fax: +49 30-3229329-26 E-Mail: info@aio-studien-ggmbh.de
Objectives	<p><u>Primary objective:</u></p> <ul style="list-style-type: none"> <li>• Disease free survival (DFS) rate as assessed by imaging 18 months after randomization (Improvement of DFS rate at 18 months in at least one arm to <math>\geq 55\%</math>)</li> </ul> <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> <li>• Effect of neoadjuvant nab-Paclitaxel/Gemcitabine on tumor response according to RECIST, histological tumor regression and R0 resection rate as defined in the German S3 guidelines</li> <li>• Effect of perioperative or adjuvant nab-Paclitaxel/Gemcitabine on DFS and OS 3 year after randomization</li> <li>• Safety of perioperative and adjuvant nab-Paclitaxel/Gemcitabine</li> <li>• Potential association between tumor regression and R0 resection rate, DFS, OS and biomarkers in the perioperative arm</li> <li>• Pre- and postoperative morbidity and mortality</li> <li>• Dropout rate due to toxicity</li> <li>• Disease progression during neoadjuvant therapy</li> <li>• R0 and R1 resection rate as assessed according to the German S3 guidelines</li> <li>• Correlation of tumor regression and R0 resection rate with response according to Recist 1.1 in the perioperative study arm</li> <li>• Overall survival (OS)</li> <li>• First site of tumor recurrence</li> <li>• Health related quality of life (EORTC QLQ-PAN26, QLQ-C30 and HADS-D questionnaires)</li> <li>• Correlation of DFS, OS and tumor regression with pharmacogenomic markers, tumor biomarkers and molecular analyses (cfDNA, transcriptome, miRNA-arrays)</li> </ul>
Number of patients	<b>Randomized: 72 patients</b> To be assessed for eligibility: n = 190 To be allocated to trial: n = 166

	To be analyzed: n = 116 (58 patients per treatment group)
Recruitment	<p>Duration of Intervention per patient:</p> <p>Perioperative arm: 37 weeks</p> <p>Adjuvant arm: 34 weeks</p> <p>Start of trial/First patient in (FPI)/Randomization: Q III/2015</p> <p>Last patient in (LPI) Q IV/2019</p> <p>Planned End of Treatment last patient Q III/2020</p> <p>Planned last visit for primary objective last patient Q II/2021</p> <p>LPLV (last patient last visit) date Q III/2023</p> <p>Recruitment period (months): 54 months</p> <p>Follow-up-period: 3 years</p>
Number of study centers	25 study centers in Germany (university hospitals or high-volume centers for PDAC surgery) Number of initiated sites: 29
More centers?	No
Key inclusion criteria	<ul style="list-style-type: none"> <li>• Histologically or cytological proven confirmed, clearly resectable ductal adenocarcinoma of the pancreas (PDAC) <math>\leq</math> cT3 with no prior tumor specific treatment.</li> <li>• No evidence of metastases to distant organs (e.g. liver, peritoneum, lung).</li> <li>• Resectable tumor. Determination of resectability based on spiral CT scans with both oral and i.v. contrast enhancement or on MRI using a recent consensus definition (Resectability: Clear fat planes around the celiac artery, hepatic artery and superior mesenteric artery).</li> <li>• ECOG performance status 0 or 1</li> <li>• Creatinine clearance <math>\geq</math> 30 ml/min</li> <li>• Serum total bilirubin level <math>\leq</math> 2.5 x ULN (not necessary for enrollment or randomization, but before start of neoadjuvant chemotherapy)</li> <li>• ALT and AST <math>\leq</math> 2.5 x ULN (not necessary for enrollment or randomization, but before start of neoadjuvant chemotherapy)</li> <li>• In case of biliary obstruction, biliary decompression is required. Postinterventional bilirubin levels must be <math>\leq</math> 2.5 x ULN if the patient was randomized to receive neoadjuvant chemotherapy (arm A)</li> <li>• White blood cell count <math>\geq</math> 3.5 x 10<sup>6</sup>/ml, neutrophil granulocytes count <math>\geq</math> 1,5 x 10<sup>6</sup>/ml, platelet count <math>\geq</math> 100 x 10<sup>6</sup>/ml</li> <li>• Signed informed consent incl. participation in translational research</li> <li>• Age <math>\geq</math> 18 years</li> </ul>
Key exclusion criteria	<ul style="list-style-type: none"> <li>• Borderline resectable PDAC by radiologic criteria</li> <li>• Papillary cancer</li> <li>• Neuroendocrine Cancer</li> <li>• Tumor specific pre-treatment</li> <li>• Local recurrence</li> <li>• Peritoneal or other distant metastases</li> <li>• Radiographic evidence of severe portal hypertension/cavernous transformation</li> <li>• Infiltration of extrapancreatic organs (except duodenum)</li> <li>• Ascites</li> <li>• Gastric outlet obstruction</li> <li>• Global respiratory insufficiency requiring oxygen supplementation</li> <li>• Chronic infectious diseases, immune deficiency syndromes</li> <li>• Premalignant hematologic disorders, e.g. myelodysplastic syndrome</li> <li>• Disability to understand and sign written informed consent document</li> <li>• Past or current history of malignancies except for the indication under this study and curatively treated: <ul style="list-style-type: none"> <li>- Basal and squamous cell carcinoma of the skin</li> <li>- In-situ carcinoma of the cervix</li> <li>- Other malignant disease without recurrence after at least 5 years of</li> </ul> </li> </ul>

	<p>follow-up</p> <ul style="list-style-type: none"> <li>• Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment</li> <li>• Clinically relevant or history of interstitial lung disease, e.g. non-infectious pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan or chest x-ray.</li> <li>• History of or evidence upon physical examination of CNS disease unless adequately treated (e.g. primary brain tumour, seizure not controlled with standard medical therapy or history of stroke).</li> <li>• Pre-existing neuropathy &gt; grade 1 (NCI CTCAE)</li> <li>• Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy</li> <li>• Severe non-healing wounds, ulcers or bone fractures</li> <li>• Evidence of bleeding diathesis or coagulopathy</li> <li>• Patients not receiving therapeutic anticoagulation must have an INR &lt; 1.5 ULN and PTT &lt; 1.5 ULN within 28 days prior to randomization. The use of full dose anticoagulants is allowed as long as the INR or PTT is within therapeutic limits (according to the medical standard in the institution)</li> <li>• Major surgical procedures, except open biopsy, nor significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgical procedure during the course of the study except for surgery of pancreatic cancer with curative intent and central intravenous line placement for chemotherapy administration.</li> <li>• Pregnancy or breastfeeding women.</li> <li>• Subjects with known allergies to the study drugs or to any of its excipients.</li> <li>• Current or recent (within the 28 days prior randomization) treatment with another investigational drug or participation in another investigational study.</li> <li>• Any psychological, familial, sociological or geographical condition potentially compromising compliance with the study protocol and the follow-up schedule; those conditions should be discussed with the patient prior to registration in the trial</li> </ul>
Scheme of therapy	<p><b>Arm A (neoadjuvant arm):</b> 2 cycles of nab-Paclitaxel/Gemcitabine (nab-Paclitaxel 125 mg/m<sup>2</sup>, Gemcitabine 1000 mg/m<sup>2</sup> on day 1, 8 and 15 of a 28 day-cycle) followed by 3 weeks of rest and subsequent tumor surgery. Re-Start of chemotherapy within 12 weeks after surgery with in total 4 cycles of nab-Paclitaxel/Gemcitabine (nab-Paclitaxel 125 mg/m<sup>2</sup>, Gemcitabine 1000 mg/m<sup>2</sup> on day 1, 8 and 15 of a 28 day-cycle) in the adjuvant setting.</p> <p><b>Arm B (adjuvant arm):</b> Tumor surgery followed by adjuvant chemotherapy with 6 cycles of nab-Paclitaxel/Gemcitabine (nab-Paclitaxel 125 mg/m<sup>2</sup>, Gemcitabine 1000 mg/m<sup>2</sup> on day 1, 8 and 15 of a 28 day-cycle, starting within 12 weeks after surgery).</p> <p><b>Duration of intervention per patient:</b> <b>Arm A:</b> Neoadjuvant chemotherapy (8 weeks) preceding surgery (3 weeks after completion of chemotherapy) followed by adjuvant chemotherapy (16 weeks, starting within 12 weeks after surgery). <b>Arm B:</b> Surgery followed by adjuvant chemotherapy (24 weeks, starting within 12 weeks after surgery), Follow-up per patient: Until end of study or death.</p>
Sample size and statistical analysis	<p>According to published literature the DFS rate after adjuvant Gemcitabine at 18 months is about 38 %. An expected increase in the DFS rate at 18 months to 55 % can be found with a power of 90 % and a significance level of 5 % with a one-sample logrank-test (two sided) if 58 patients per treatment group (116 in total) are included in the study. This calculation assumes exponential survival, an accrual time of 36 months and a total observation time of 57 months. A 30 % dropout rate is expected in both groups. Thus, the total</p>



	<p>sample size is 166 patients (2 x 83). Sample size was computed by “SWOG One arm survival sample size and power” (<a href="http://www.swogstat.org/stat/public/one_survival.htm">http://www.swogstat.org/stat/public/one_survival.htm</a>).</p> <p>The primary objective, DFS rate @ 18 months as assessed by imaging, will be evaluated by a one-sample log-rank test in each group. The significance level will be set to 5 % in each group on an intention-to-treat basis. Because of the independency of both study arms there is no need for adjustment for multiple testing. As an explorative effect estimate we will report the hazard ratio (with its corresponding 95 % confidence interval) from a parallel Cox regression model using various explaining variables including treatment group. The analysis will be performed on an intention-to-treat basis.</p> <p>The randomization between the two independent experimental arms is eminent to get two comparable patient groups and to investigate, which group and hereby which therapeutic concept (perioperative vs. adjuvant), compared to the fixed disease free survival probability of 38 % at 18 months, achieves the better outcome in this explorative setting. No proof of superiority between the two treatment groups can be achieved with this study design because of low power, but this is not intended in this study.</p> <p>Analyses for secondary objectives are considered purely descriptive and are given as risk or mean differences for binary and continuous responses, or as hazard ratio for survival outcomes, all of them accompanied with the respective 95% confidence intervals. There will be no interim analyses on efficacy or subgroup analyses. Regarding safety, frequencies of SAEs and SUSARs will be reviewed regularly by the Data and Safety Monitoring Board. The final analysis on safety will include a comparison of risk differences between groups.</p>
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### Neoadjuvante Therapie des lokal fortgeschrittenen Pankreaskarzinoms

#### **AIO-PAK-0113: Intensivierte neoadjuvante Chemotherapie des lokal fortgeschrittenen Pankreaskarzinoms – eine prospektive, randomisierte Phase-II Studie (NEOLAP)**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-PAK-0113 - NEOLAP
Status:	in Rekrutierung
Rekrutierungszeitraum:	2014 - 2018
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

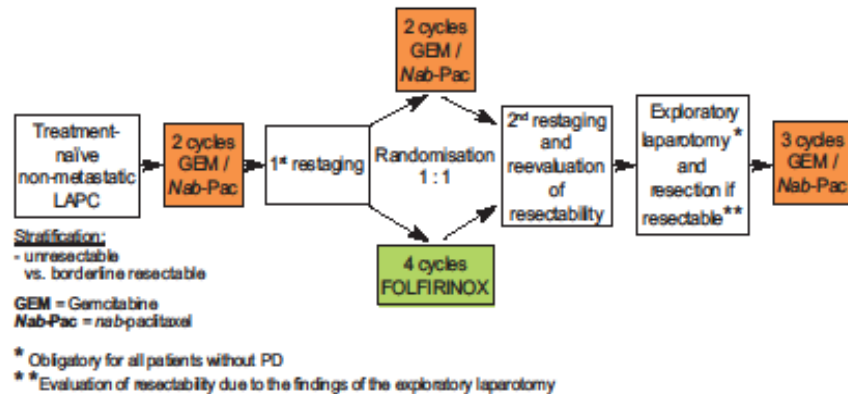
Study design	Prospective open randomized multicenter phase II trial with two arms for neoadjuvant treatment
Coordinating Investigator	Prof. Dr. V. Kunzmann Universitätsklinikum Würzburg / Comprehensive Cancer Center Mainfranken Medizinische Klinik und Poliklinik II, Schwerpunkt Med. Onkologie Oberdürrbacherstr. 6-8, D-97080 Würzburg E-Mail: kunzmann_v@medizin.uni-wuerzburg.de
Sponsor:	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany Tel: +49 30-8145 344 33, Fax: +49 30-3229329-26 E-Mail: info@aio-studien-ggmbh.de
Primary objective	<ul style="list-style-type: none"> <li>To compare the effect of intensified neoadjuvant chemotherapy on conversion rate to resectability in LAPC.</li> </ul>

Secondary objectives	<ul style="list-style-type: none"> <li>• To evaluate safety and tolerability of intensified neoadjuvant chemotherapy</li> <li>• To assess objective tumor response rate (ORR) to intensified neoadjuvant chemotherapy</li> <li>• To assess disease control rate (DCR) after intensified neoadjuvant chemotherapy</li> <li>• To assess CA 19-9 change during/after neoadjuvant chemotherapy</li> <li>• To assess rate of R0 and R1 resections</li> <li>• To assess rate of grade 3 + 4 pathological responses according to grading scheme of treatment responses by Evans in resected patients</li> <li>• To assess relapse-free survival (RFS) and progression-free survival (PFS)</li> <li>• To assess 1 year- and 2 year-survival rate, and overall survival</li> <li>• To assess perioperative morbidity and mortality (within 60 days)</li> <li>• To compare conversion to resectability as evaluated by means of imaging procedures with actual conversion to resectability during exploratory laparotomy</li> </ul>
Objectives of optional translational research	Exploratory analyses for potential biomarkers of possible prognostic or predictive value for efficacy of neoadjuvant chemotherapy in LAPC; including analyses of circulating tumor cells, molecular pathways of pancreatic adenocarcinoma including SPARC expression
Trial centers	Up to 35 trial centers in Germany
Start of recruitment	Q4 2014
Number of patients	161 patients enrolled, 119 patients randomized (04/2018)
End of recruitment	Q2 2018
More centres?	no
Sample Size	158 patients ensure a power of 80% to detect a significant deviation from the null hypothesis of equal proportions of resectability for both treatment strategies. Furthermore, assuming 2.5% dropouts during the first two cycles before randomization and again 2.5% dropouts from randomization to terminal staging, $2 \times 84 = 168$ patients will be enrolled. Currently 161 patients are recruited (04/2018)
Inclusion criteria	<ul style="list-style-type: none"> <li>• Adult patients <math>\geq 18</math> years and <math>\leq 75</math> years of age</li> <li>• Histologic or cytologic proven ductal adenocarcinoma of the pancreas (histologic confirmation of diagnosis is preferred)</li> <li>• No distant metastases</li> <li>• De novo, treatment-naïve unresectable or borderline resectable LAPC; evaluation of unresectable and borderline resectable status based on recommendations in NCCN- Clinical Practice Guidelines in Oncology “pancreatic adenocarcinoma” version 1.2015. Applicable criterion/criteria have to be indicated.</li> <li>• Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1</li> <li>• Total bilirubin <math>\leq 2</math> mg/dL. Patients with a biliary stent may be included provided that bilirubin level after stent insertion decreased to <math>\leq 2</math> mg/dL and there is no cholangitis.</li> <li>• Adequate renal, hepatic and bone marrow function, defined as <ul style="list-style-type: none"> <li>▪ Serum creatinine <math>\leq 1.25</math> x ULN</li> <li>▪ Calculated creatinine clearance <math>\geq 60</math> mL/min according to CKD-EPI formula</li> <li>▪ AST/GOT and/or ALT/GPT <math>\leq 3.0</math> x ULN</li> <li>▪ PTT <math>\leq 1.5</math> x ULN and Quick value <math>\geq 70\%</math></li> <li>▪ Absolute neutrophil count (ANC) <math>\geq 1.5</math> x <math>10^9/L</math></li> <li>▪ Haemoglobin <math>\geq 8g/dL</math></li> <li>▪ Platelets <math>\geq 100 \times 10^9/L</math></li> </ul> </li> <li>• Females of childbearing potential (FCBP) must have a negative</li> </ul>

	<p>pregnancy test within 7 days of the first application of study treatment and must agree to use effective contraceptive birth control measures (Pearl Index &lt; 1) during the course of the trial and for at least 1 month after last application of study treatment.</p> <p>A female subject is considered to be of childbearing potential unless she is age <math>\geq 50</math> years and naturally amenorrhoeic for <math>\geq 2</math> year, or unless she is surgically sterile.</p> <ul style="list-style-type: none"> <li>• Males must agree not to father a child during the course of the trial and for at least 6 months after last administration of study drugs.</li> <li>• Signed and dated informed consent before the start of any specific protocol procedures</li> <li>• • Patient's legal capacity to consent to study participation</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>• Evidence of distant metastases. In case of radiological suspicion of peritoneal carcinomatosis or ascites histological or cytological verification is required e.g. by means of exploratory laparoscopy</li> <li>• Local relapse of the pancreatic adenocarcinoma prior treated with surgical resection</li> <li>• Any previous treatment of the pancreatic carcinoma (radiotherapy, chemoradiotherapy, chemotherapy, targeted tumor therapy, local ablative therapy)</li> <li>• Contraindication for pancreas resection (pancreatic head resection, distal pancreatectomy with splenectomy, or complete pancreatectomy)</li> <li>• Larger surgical interventions within 4 weeks before study enrolment and/or diagnostic laparotomy with or without gastroenterostomy and with or without biliodigestive anastomosis within 2 weeks before first application of study treatment. Wound healing must be also completed before first application of study treatment.</li> <li>• Known chronic diarrhoea</li> <li>• Peripheral polyneuropathy &gt; grade 1</li> <li>• Known dihydropyrimidine dehydrogenase (DPD) deficiency</li> <li>• Medical history of interstitial lung disease (ILD) or pulmonary fibrosis</li> <li>• Hypersensitivity against any of the study drugs (nab-paclitaxel, gemcitabine, oxaliplatin, irinotecan, 5-fluorouracil, folinic acid), or the ingredients of these drugs</li> <li>• Active or uncontrolled bacterial, viral, or fungal infection that requires systemic treatment</li> <li>• Known HIV- infection or active HBV- or HCV –infection</li> <li>• Convulsion disorder that requires anticonvulsive treatment</li> <li>• Clinically significant cardiovascular or vascular disease or disorder <math>\leq 6</math> months before study enrolment (e.g. myocardial infarction, unstable angina pectoris, chronic heart failure NYHA <math>\geq</math> grade 2, uncontrolled arrhythmia, cerebral infarction)</li> <li>• Any other severe concomitant disease or disorder, which could influence patient's ability to participate in the study and his/her safety during the study or interfere with interpretation of study results e.g. severe hepatic, renal, pulmonary, metabolic, or psychiatric disorders</li> <li>• Requirement for concomitant antiviral treatment with sorivudine or brivudine</li> <li>• Requirement of immunosuppressive treatment</li> <li>• Continuing anticoagulant therapy with coumarin derivatives (treatment with low-molecular weight heparin allowed)</li> <li>• Continuing abuse of alcohol, drugs, or medical drugs</li> <li>• Pregnant or breast feeding females</li> <li>• Participation in any other clinical trial or treatment with any experimental drug within 28 days before enrolment to the study or during study participation until the end of treatment visit.</li> <li>• Previous or concurrent malignant tumor disease other than underlying tumor disease with the exception of cervical cancer in situ, adequately treated basal cell carcinoma or squamous cell carcinoma of the skin,</li> </ul>

superficial bladder tumors (Ta,Tis, and T1) or any curatively treated tumors > 5 years prior to enrolment

### Scheme of therapy



### Neoadjuvant chemotherapy

All patient receive:

2 cycles gemcitabine/nab-paclitaxel ([Gem/nab-Pac]; duration of each cycle 28 days)

Nab-paclitaxel 125 mg/m<sup>2</sup>, IV infusion over 30 minutes followed by gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute IV infusion on D1, D8, D15 of each 28-day cycle

After two cycles Gem/nab-Pac 1st restaging is performed based on imaging criteria. Randomisation in Arm A and Arm B will take place for all patients with at least stable disease (SD).

Arm A:

2 further cycles Gem/nab-Pac (duration of each cycle 28 days)

Nab-paclitaxel 125 mg/m<sup>2</sup>, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute IV infusion on D1, D8, D15 of each 28-day cycle

Arm B:

4 cycles FOLFIRINOX (duration of each cycle 14 days)

Oxaliplatin 85 mg/m<sup>2</sup>, given as a 2-hour intravenous infusion D1

Folinic acid 400 mg/m<sup>2</sup>, given as a 2-hour intravenous infusion D1

Irinotecan 180 mg/m<sup>2</sup>, given as a 90-minutes intravenous infusion D1

(application through a Y-connector parallel to infusion of folinic acid or 30 minutes after start of folinic acid possible)

Fluorouracil 400 mg/m<sup>2</sup>, administered by intravenous bolus, followed by a continuous intravenous infusion of fluorouracil 2400 mg/m<sup>2</sup> over a 46-hour period D1.

To be repeated on D1 of each cycle.

Patient with progression or unacceptable toxicity at any time during neoadjuvant chemotherapy (including those with progression at 1st and 2nd restaging) have to discontinue neoadjuvant chemotherapy.

After neoadjuvant chemotherapy 2nd restaging is performed based on imaging criteria.

Patients with at least SD will undergo obligatory exploratory laparotomy for surgical evaluation of resectability irrespective of imaging criteria to assess resectability.

All patients in whom successful pancreatic resection in curative intent (R0, R1) is performed will receive the following adjuvant chemotherapy:

### Adjuvant chemotherapy

3 cycles Gem/nab-Pac (duration of each cycle 28 days)

Nab-paclitaxel 125 mg/m<sup>2</sup>, IV infusion over 30 minutes followed by gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute IV infusion on D1, D8, D15 of each 28-day cycle

Adjuvant chemotherapy has to be started 4-8 weeks after pancreatic resection.

	<p>Further treatment of patients with progressive disease (PD) after 1st or 2nd restaging as well as patients with unresectable status based on exploratory laparotomy is under the discretion of the local investigators (e.g. second-line chemotherapy in case of distant relapse or local radiochemotherapy in case of local progression or definitive irresectability).</p>
Rationale	<p>Pancreatic adenocarcinoma ranks at the fourth position as cause of all cancer-related mortalities. Patients with a locally advanced, non-metastatic pancreatic cancer (LAPC) represent up to 30% of all patients with pancreatic cancer at the time of diagnosis with a very poor outcome. Reported overall median survival ranges from 9 to 13 months. At present, the only chance for cure and prolonged survival seems to be surgical resection with macroscopic tumor clearance.</p> <p>Since more than a decade, gemcitabine has been established as chemotherapeutic standard in the treatment of advanced and metastatic pancreatic cancer. A number of more intensive gemcitabine-based combination chemotherapies utilizing 5-fluorouracil or its oral analogues, platin compounds as well as other targeted agents have been investigated in clinical trials, but mostly failed to show a clinically relevant survival benefit compared to gemcitabine monotherapy.</p> <p>Only recently, two new regimens have demonstrated significant improvement in first-line treatment of metastatic pancreatic cancer.</p> <p>First, Conroy et al reported that the combination of 5-fluorouracil/folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) improved median overall survival (11.1 months vs. 6.8 months for gemcitabine alone; HR: 0.57), 1-year survival (48.4 % vs. 20.6%) and objective response rate (31.6 % vs. 9.4 %).</p> <p>Secondly, Von Hoff et al. showed first in a phase I/II trial in metastatic pancreatic cancer that the addition of nab-paclitaxel, an albumin-bound particle form of paclitaxel, to gemcitabine resulted in a very promising objective response rate of 48% in the 125 mg/m<sup>2</sup> nab-paclitaxel cohort. In the consecutive randomized phase III trial (MPACT) in metastatic pancreatic cancer objective response rate (ORR; 23% vs. 7%), progression-free survival (PFS; 5.5 months vs. 3.7 months), and overall survival (OS; 8.7 months vs. 6.6 months; p&lt;0.001) were significantly improved in the nab-paclitaxel/gemcitabine arm.</p> <p>Rationale of the present study is to investigate the efficacy and safety of these two new intensified chemotherapy regimens (gemcitabine/nab-paclitaxel, FOLFIRINOX) as neoadjuvant chemotherapy protocol in LAPC and consecutive conversion of the tumor to resectability. Resectability (with the aim of R0-resection) and unresectability, respectively are evaluated by surgical exploration instead of exclusive evaluation with imaging criteria. Both regimens were chosen as neoadjuvant chemotherapy protocols, firstly, because both regimens reported the highest objective response rates in advanced pancreatic cancer so far, and secondly, because sequential usage of both regimens might further increase response rate and overcome chemotherapy resistance of LAPC which might then increase the rate of conversion to resectability and pCR rate. In addition, reducing the dense tumor stroma by nab-paclitaxel, which is a histological hallmark of LAPC, may theoretically allow simultaneous (gemcitabine) and subsequent (FOLFIRINOX) chemotherapy to reach the tumor tissue more efficiently and thus increase the downsizing effect of the primarily unresectable tumor. This concept has already been applied in a pilot study with 8 patients with promising results.</p>
Statistics	<p>Primary goal of the study is to compare the conversion rate to resectability in both treatment groups. Based on all patients randomized, the rates will be evaluated by a two-sided unpooled z-test at significance level 0.05.</p> <p>Interim analysis (for futility):</p> <p>After assessment whether conversion to resectability has been achieved or not for the first 25 patients in each treatment arm, the futility of the new treatment strategy Gem/nab-Pac followed by FOLFIRINOX will be assessed. If the number of patients with resectability achieved in the "Gem/nab-Pac followed by FOLFIRINOX" Arm is by more than 0.15 (15 %) lower than the</p>

	respective number in the "Gem/nab-Pac alone" Arm, the trial will be stopped for futility. For 25 patients in both arms this corresponds to the following stopping criterion: the number of patients with resectability achieved in the "Gem/nab-Pac followed by FOLFIRINOX" Arm is at least by 4 lower to the respective number in the "Gem/nab-Pac alone" Arm.
Stratification	The following stratification will be performed: Patients initially assessed as unresectable versus patients initially assessed as borderline-resectable based on recommendations in NCCN-guidelines for pancreatic adenocarcinoma version 1.2015.

### Metastasiertes Pankreaskarzinom - Erstlinientherapie

**AIO-PAK-0317/ass: A multicenter randomized phase II/III study to determine the optimal first line chemotherapy regimen in medically fit patients diagnosed with metastatic pancreatic cancer (FOOTPATH)**

<b>AIO-assoziierte Studie</b>	
Studiennummer/-Code:	AIO-PAK-0317/ass - FOOTPATH
Status:	In Vorbereitung
Rekrutierungszeitraum:	Q3/2018 – Q3/2023
Weitere Zentren:	Erwünscht (40 Zentren geplant)
Letzte Aktualisierung	09.04.2018

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OBJECTIVE(S)	To determine the optimal first line regimen in metastatic pancreatic cancer.

INTERVENTION(S)	<p><b><u>Arm A: Gemcitabine &amp; nab-paclitaxel (Standard)</u></b></p> <ul style="list-style-type: none"> <li>• Nab-paclitaxel 125 mg/m<sup>2</sup>, i.v. infusion over about 30 minutes followed by</li> <li>• Gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute i.v. infusion on D1, D8, D15 of a 28-day cycle.</li> </ul> <p>Treatment is given until disease progression or the occurrence of unacceptable toxicity.</p> <p><b><u>Arm B: NAPOLI regimen (Investigational 1)</u></b></p> <p>On Day 1 of a 14-day cycle:</p> <ul style="list-style-type: none"> <li>• Liposomal irinotecan 80 mg/m<sup>2</sup> i.v. over about 90 minutes followed by</li> <li>• Folinic acid 400 mg/m<sup>2</sup> i.v. over about 30 minutes followed by</li> <li>• 5-FU 2400 mg/m<sup>2</sup> i.v. over about 46 h (pump)</li> </ul> <p>Treatment is given until disease progression or the occurrence of unacceptable toxicity.</p> <p><b><u>Arm C: Alternating NAPOLI/mFOLFOX6 (aNAPOLINOX) (Investigational 2):</u></b></p> <p>The NAPOLI regimen and the mFOLFOX6 regimen are applied in an alternating fashion, starting with the NAPOLI regimen.</p> <p><b><u>NAPOLI:</u></b></p> <p>On Day 1 of a 14-day cycle:</p> <ul style="list-style-type: none"> <li>• Liposomal irinotecan 80 mg/m<sup>2</sup> i.v. over about 90 minutes followed by</li> <li>• Folinic acid 400 mg/m<sup>2</sup> i.v. over about 30 minutes followed by</li> <li>• 5-FU 2400 mg/m<sup>2</sup> i.v. over about 46 h (pump)</li> </ul> <p><b><u>mFOLFOX6:</u></b></p> <p>On Day 1 of a 14-day cycle:</p> <ul style="list-style-type: none"> <li>• Oxaliplatin 85 mg/m<sup>2</sup> i.v.</li> <li>• Folinic acid 400 mg/m<sup>2</sup> i.v.</li> </ul> <p>followed by</p> <ul style="list-style-type: none"> <li>• 5-FU 2400 mg/m<sup>2</sup> i.v. over about 46 h (pump)</li> </ul> <p>Treatment is given until disease progression or the occurrence of unacceptable toxicity.</p> <p><b><u>Recommended second-line regimens:</u></b></p> <p>Second-line treatment is not part of the study protocol. After treatment on the study, all further decisions are up to the treating physician. However, the following recommendations may be followed:</p> <p><b>Arm A:</b> After failure of gemcitabine/nab-paclitaxel the recommended second-line treatment would be the NAPOLI regimen.</p> <p><b>Arms B and C:</b> After failure of the NAPOLI-regimen, a gemcitabine-based regimen, preferentially gemcitabine/nab-paclitaxel, would be recommended.</p>
KEY EXCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Locally advanced PDAC without metastasis</li> <li>• Known DPD-deficiency (special screening test not required)</li> <li>• Symptomatic clinically significant ascites (expected indication for repeated paracentesis)</li> <li>• Known metastatic disease to the brain. Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients.</li> <li>• Previous palliative chemotherapy or other palliative systemic tumor therapy for metastatic disease of PDAC</li> <li>• Previous gemcitabine/5-FU treatment <b>with exception of</b> gemcitabine/5-FU treatment applied in the adjuvant setting (after potential curative R0 or R1 resection) <b>and</b> if the adjuvant chemotherapy was terminated at least 6 months before study entry</li> <li>• Previous radiotherapy of PDAC</li> </ul>

	<ul style="list-style-type: none"> <li>• Any major surgery within the last 4 weeks before study entry</li> <li>• Clinical significant decrease in performance status within 2 weeks of intended first application of study medication (by medical history)</li> <li>• Severe tumor-related cachexia and/or known weight loss &gt; 15% within one month before study enrollment</li> <li>• Pre-existing polyneuropathy <math>\geq</math> grade 2 according to CTCAE version 4.03</li> <li>• Gastrointestinal disorders that might interfere with the absorption of the study drug and gastrointestinal disorders with diarrhoea as a major symptom (e.g. Crohn's disease, malabsorption), and chronic diarrhoea of any aetiology CTCAE version 4.03 grade <math>\geq</math> 2</li> <li>• Any other severe concomitant disease or disorder, which could influence patient's ability to participate in the study and his/her safety during the study or interfere with interpretation of study results e.g. active infection, uncontrolled hypertension, clinically significant cardiovascular disease e.g. cerebral vascular accident (<math>\leq</math> 6 months before study start), myocardial infarction (<math>\leq</math> 6 months before study start), unstable angina, heart failure <math>\geq</math> NYHA functional classification system grade 2, severe cardiac arrhythmia requiring medication, metabolic dysfunction, severe renal disorder.</li> <li>• Any other malignancies than PDAC within the last 5 years before study start, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer</li> <li>• Hypersensitivity to the study drugs or to any of the excipients or to compounds with similar chemical or biologic composition</li> <li>• Use of strong CYP3A4 inhibitors (CYP3A4 inhibitors have to be discontinued at least one week prior to start of study treatment). Use or strong UGT1A1 inhibitors or strong CYP3A4 inducers unless there are no therapeutic alternatives.</li> <li>• Patient known to be homozygous for UGT111*28 or strongly suspected to be homozygous for the UGT111*28 allele</li> <li>• Requirement for concomitant antiviral treatment with sorivudine or brivudine</li> <li>• Continuing abuse of alcohol, drugs, or medical drugs</li> <li>• Pregnant or breast-feeding females or FCBPs unable to either perform highly effective contraceptive measures or practice complete abstinence from heterosexual intercourse</li> <li>• Current or recent (within 4 weeks prior to first application of study treatment) treatment with an investigational drug or participation in an investigational clinical trial</li> </ul>
KEY INCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Adult patients <math>\geq</math> 18 years of age and <math>\leq</math> 75 years</li> <li>• Histologically (not cytologically) confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma (PDAC) (Stage IV according to UICC TNM edition 8 of 2016) (each T, each N, M1)</li> <li>• No option for surgical resection or radiation in curative intent</li> <li>• At least one unidimensionally measurable tumor lesion (according to RECIST 1.1)</li> <li>• ECOG performance status 0 - 1</li> <li>• Life expectancy at least 3 months</li> <li>• Adequate hepatic, renal and bone marrow function, defined as: <ul style="list-style-type: none"> <li>▪ Absolute neutrophil count (ANC) <math>\geq</math> <math>1.5 \times 10^9/L</math></li> <li>▪ Haemoglobin <math>\geq</math> 9 g/dL</li> <li>▪ Thrombocytes <math>\geq</math> <math>100 \times 10^9/L</math></li> <li>▪ Total bilirubin <math>\leq</math> 1.5 x ULN. Patients with a biliary stent may be included provided that bilirubin level after stent insertion decreased to <math>\leq</math> 1.5 x ULN and there is no cholangitis.</li> <li>▪ AST/GOT and/or ALT/GPT <math>\leq</math> 2.5 x ULN or in case of liver metastasis <math>\leq</math> 5 x ULN)</li> <li>▪ Serum creatinine within normal limits or creatinine clearance <math>\geq</math> 60 mL/min/1.73 m<sup>2</sup> as calculated by CKD-EPI formula for patients</li> </ul> </li> </ul>



	<p>with serum creatinine levels above or below the institutional normal value.</p> <ul style="list-style-type: none"> <li>▪ Acceptable coagulation studies defined as prothrombin time (or INR) and PTT <math>\leq 1.5 \times</math> ULN</li> <li>• Females of childbearing potential (FCBP) must have a negative highly sensitive serum pregnancy test within 7 days of the first application of study treatment and they must agree to undergo a further pregnancy tests at monthly intervals and at the end of treatment visit <b>and</b> FCBP must either agree to use and be able to take highly effective contraceptive birth control methods (Pearl Index &lt; 1) during the course of the study and for at least 1 month after last application of study treatment. Complete sexual abstinence is acceptable as a highly effective contraceptive method only if the subject is refraining from heterosexual intercourse during the entire study treatment and at least one month after the discontinuation of study treatment and the reliability of sexual abstinence is in line with the preferred and usual lifestyle of the subject. A female subject following menarche is considered to be of childbearing potential unless she is naturally amenorrhoeic for <math>\geq 1</math> year without an alternative medical reason, or unless she is permanently sterile.</li> <li>• Males must agree to use condoms during the course of the trial and for at least 6 months after last administration of study drugs or practice complete abstinence from heterosexual intercourse.</li> <li>• Signed and dated informed consent before the start of any specific protocol procedures</li> </ul> <p>Patient's legal capacity to consent to study participation</p>
OUTCOME(S)	<p><b>Primary Endpoint:</b></p> <ul style="list-style-type: none"> <li>• Progression free survival (PFS)</li> </ul> <p><b>Secondary Endpoints:</b></p> <ul style="list-style-type: none"> <li>• Overall survival (OS)</li> <li>• Objective response rate (ORR)</li> <li>• Disease control rate (DCR)</li> <li>• Duration of study treatment</li> <li>• Type, incidence, causal relationship and severity of adverse events according to NCI CTCAE version 4.03</li> <li>• Quality of life as assessed by EORTC-QLQ-C30</li> <li>• Treatment with second-line chemotherapy as documented in the patient's medical file</li> </ul>
STUDY TYPE	<b>Multicenter randomized phase II</b>
STATISTICAL ANALYSIS	<p>Based on published phase III data for progression free survival for FOLFIRINOX (6.4 months) and Gemcitabine/nab-Paclitaxel (5.5 months) and the expected dropout rate (appr. 30%) 90 patients will be needed per arm (<math>\alpha = 0,1</math> &amp; <math>\beta = 0.2</math> –Hazard Ratio 0.65) to detect a difference in PFS between Gemcitabine/nab-Paclitaxel and the two investigational arms (B and C). Hence the hypotheses to be tested are:</p> <p style="text-align: center;"><math>H_0</math>: PFS (arm B) <math>\leq</math> PFS (arm A) <math>H_1</math>: PFS (arm B) <math>&gt;</math> PFS (arm A)</p> <p style="text-align: center;">and</p> <p style="text-align: center;"><math>H_0</math>: PFS (arm C) <math>\leq</math> PFS (arm A) <math>H_1</math>: PFS (arm C) <math>&gt;</math> PFS (arm A)</p> <p>Both pair of hypotheses will be tested with one-tailed <math>\alpha=0.067</math> and <math>\beta=0.2</math>. This leads to a total <math>\alpha</math> of one-tailed 0.1 for testing both pair of hypotheses. Given 118 required events for one pair of hypotheses and the expected dropout rate (appr. 30%) 90 patients will be needed per arm.</p>
SAMPLE SIZE	270 patients total
TRIAL DURATION	5 years



Pankreaskarzinom, palliative Therapie, 2nd-line**AIO-PAK-0216: Second line therapy with Nal-IRI after failure gemcitabine/nab-paclitaxel in advanced pancreatic cancer - predictive role of 1st line therapy – PREDICT**

AIO-Studie	
Studiennummer/-Code:	AIO-PAK-0216 - PREDICT
Status:	Aktiv rekrutierend
Rekrutierungszeitraum:	FPI März 2018 // Rekrutierung geplant auf 24 Monate
Anzahl initiiertes Zentren:	21 (inkl. der neu initiierten Zentren mit Ausblick im April)
Weitere Zentren:	Momentan nur Warteliste
Anzahl eingeschlossene Patienten:	1 von geplanten 270
Letzte Aktualisierung:	10. April 2018

EudraCT No.	2016-005147-17
National Coordinating Investigator	Prof. Dr. med. Manfred P. Lutz Internal Medicine Caritasklinikum St. Theresia Rheinstrasse 2, 66113 Saarbrücken Phone +49 681 406 1001 Fax +49 681 406 1003 m.lutz@caritasklinikum.de
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Study design	Open label, single arm, multicenter phase IIIb trial
Duration of study	Enrollment: 24 month total study duration 34 month (incl. follow-up)
Indication	Second-line treatment for advanced or metastatic pancreatic cancer
Target population	Patients with locally advanced or metastatic pancreatic cancer after failure of a gemcitabine/nab-paclitaxel 1 <sup>st</sup> -line treatment.
Total number of sites	35
Primary objective	Confirmation that longer Time-To-Treatment-Failure (TTF) during first-line treatment is predictive for the benefit of 2 <sup>nd</sup> line treatment with Nal-IRI combination chemotherapy
Secondary objectives	Secondary objectives of this study are: <ul style="list-style-type: none"> <li>• to generate additional efficacy and safety data for the 2<sup>nd</sup>-line treatment</li> <li>• to assess the Quality of Life and Patient Reported Outcomes during 2<sup>nd</sup>-line treatment</li> <li>• to assess the impact of the course of the 1<sup>st</sup>-line treatment on the outcome of the 2<sup>nd</sup>-line therapy</li> <li>• to explore the impact of physiological and molecular markers on the efficacy of the 2<sup>nd</sup>-line</li> </ul>
Planned sample size	N=270 total
Inclusion criteria	1. Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations

	<ol style="list-style-type: none"> <li>2. Clinical indication for a 2nd-line systemic therapy according to current standard-of-care.</li> <li>3. Age <math>\geq</math> 18 years at time of study entry</li> <li>4. Patients with histologically or cytologically confirmed pancreatic ductal adenocarcinoma</li> <li>5. Imaging of evaluable lesions within 2 weeks of inclusion (either sonography, X-ray, CT scans, MRI)</li> <li>6. ECOG performance status 0-2</li> <li>7. One line of systemic gemcitabine/Nab-paclitaxel therapy for advanced disease (irrespective of prior adjuvant therapy) OR Previous adjuvant gemcitabine/Nab-paclitaxel chemotherapy with documented progression less than 6 months after termination</li> <li>8. Detailed documentation of prior therapy (duration, dose-intensity, maximum toxicity, reason for discontinuation)</li> <li>9. Adequate blood count, liver-enzymes, and renal function:       <ul style="list-style-type: none"> <li>• neutrophil count <math>&gt; 1.5 \times 10^6/\text{mL}</math></li> <li>• Platelet count <math>\geq 100 \times 10^9/\text{L}</math> (<math>\geq 100,000</math> per <math>\text{mm}^3</math>)</li> <li>• AST (SGOT)/ALT (SGPT) <math>\leq 5 \times</math> institutional upper limit of normal</li> <li>• bilirubin <math>\leq 1.5 \text{ ULN}</math> (<math>&lt; 3 \times \text{ULN}</math> in patients with confirmed mechanical cholestasis)</li> <li>• Creatinine Clearance <math>\text{CLcr} \geq 30 \text{ mL/min}</math></li> </ul> </li> <li>10. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.</li> </ol>
Exclusion criteria	<p><b>Medical criteria:</b></p> <ol style="list-style-type: none"> <li>23. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to:       <ol style="list-style-type: none"> <li>(1) Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes</li> <li>(2) Premalignant hematologic disorders, e.g. myelodysplastic syndrome</li> <li>(3) Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment</li> <li>(4) Prior (<math>&lt; 3</math> years) or concurrent malignancy (other than biliary-tract cancer) which either progresses or requires active treatment. <b>Exceptions are:</b> basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial urinary bladder tumor [Ta, Tis and T1].</li> <li>(5) Pre-existing lung disease of clinical significance or with impact on performance status</li> <li>(6) History or clinical evidence of CNS metastases Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:           <ol style="list-style-type: none"> <li>b) are asymptomatic and</li> <li>c) have no requirement for steroids 6 weeks prior to start of study treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases</li> </ol> </li> <li>(7) Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy</li> <li>(8) Severe non-healing wounds, ulcers or bone fractures</li> <li>(9) Evidence of bleeding diathesis or coagulopathy</li> <li>(10) Major surgical procedures, except open biopsy, or significant traumatic injury within 28 days prior to start of study treatment, or anticipation of the need for major surgical procedure during the course</li> </ol> </li> </ol>

	<p>of the study except for surgery of central intravenous line placement for chemotherapy administration.</p> <p>(11) Known Gilbert-Meulengracht syndrome  (12) Known chronic hypoacusis, tinnitus or vertigo  (13) Bone marrow depression (e.g., after radiation therapy)  (14) Pernicious anemia and other megaloblastic anemias secondary to vitamin B12 deficiency  (15) Severe impairment of hepatic function  (16) Diarrhea</p> <p><b>Drug related criteria:</b>  24. Medication that is known to interfere with any of the agents applied in the trial.  25. Known dihydropyrimidine dehydrogenase (DPD) deficiency  26. History of hypersensitivity to any of the study drugs or any of the constituents of the products.  27. Any other efficacious cancer treatment except protocol specified treatment at study start.</p> <p><b>Safety criteria:</b>  28. Female subjects who are pregnant, breast-feeding or male/female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner]. Women of childbearing potential must have a negative pregnancy test (urine or serum <math>\beta</math>-HCG acc. to SOC) at screening.</p> <p><b>Methodological criteria:</b>  29. Any experimental pretreatment for advanced disease  30. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lives of previously used trial medication, whichever is longer  31. Previous enrollment in the present study (does not include screening failure).</p> <p><b>Regulatory and ethical criteria:</b>  32. Patient who might be dependent on the sponsor, site or the investigator  33. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p>
Investigational agents	<ul style="list-style-type: none"> <li>• Nal-IRI (MM-398, IRINOTECAN LIPOSOME)</li> <li>• 5-Fluorouracil (5-FU)</li> <li>• folinic acid</li> </ul> <p>Study medications will not be provided by the Sponsor and must be prescribed locally. The investigator will ensure that the study medication is used only in accordance with the protocol.</p>
Treatment schedule	<ul style="list-style-type: none"> <li>• Nal-IRI 80 mg/m<sup>2</sup> as a 1.5 hour infusion</li> <li>• 5-FU 2400 mg/m<sup>2</sup> as 46 hour infusion</li> <li>• Leucovorin 400 mg/m<sup>2</sup> as 0.5 hour infusion</li> <li>• all on Day 1 of each cycle; cycle q2w</li> </ul> <p>Treatment until progressive disease or intolerable toxicity or withdrawal of consent.</p>

	<p>Key study procedures (and routine procedures):</p> <ul style="list-style-type: none"> <li>• Clinical and toxicity evaluations before each new cycle; Q2W</li> <li>• Disease evaluation (imaging if applicable) after 4 cycles of CTx (Q8W)</li> <li>• QoL assessments Q4W; Assessment tools: EORTC QLQ-PAN26, QLQ-C30; EQ-5D-5L</li> <li>• Tumor tissue analysis at reference pathology</li> <li>• Serum sample for cell-free DNA mutational analysis Q4W</li> <li>• CA19-9 measurement Q2W</li> </ul>
Primary endpoint	<p>Time to Treatment Failure of second-line treatment (TTF2)</p> <p>Expected increase of the TTF2 by 50% in the cohort of patients with favorable TTF1 (TTF1 high: upper third of the patient population) as compared to patients with short TTF1 (TTF low: lowest third of the patient population)</p>
Secondary endpoints	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• AEs / SAEs</li> <li>• QoL [EORTC QLQ-PAN26, QLQ-C30; EQ-5D-5L</li> <li>• Evaluation of time to definitive deterioration of QoL (TDD)</li> <li>• Growth modulation index</li> </ul>
Exploratory objectives and endpoints	<ul style="list-style-type: none"> <li>• Time course of individual parameters of QoL during 2nd-line treatment</li> <li>• Correlation index of dose intensity of 1st-line treatment with TTF2</li> <li>• Correlation of reasons for termination of 1st-line (progression or toxicity) with TTF2</li> <li>• Correlation of BMI with TTF2</li> <li>• Comparison of treatment effect on QLQ-C30/Pan26 parameters with PROM (patient-related outcome measures)</li> <li>• Correlation of CA19-9 response with TTF2</li> <li>• Correlation of sequential cell-free DNA mutation levels with TTF2</li> <li>• Correlation of CA19-9 to TTF2 and OS Evaluate PROM as measure of treatment success</li> <li>• Comparison of QoL as measured by standard tools (i.e. EORTC QLQ-C30 or -PAN26 or EQ-5D-5L) with PROM</li> <li>• Compare variations and applicability of QLQ-C30/-PAN26 and PROM (Gerritsen et al. Europ J Cancer 57:68, 2016) in relation to treatment success</li> <li>• Sequential measure of cell-free DNA in correlation to imaging response at 6-8 weeks according to RECIST1.1 guidelines (if available)</li> <li>• Correlation of decrease in cell-free DNA to OS</li> <li>• Correlation of histology (collection of tumor blocks required) to cell-free DNA and TTF2/OS</li> <li>• Serum cell-free DNA analysis q4w and correlation with TTF2/OS/CA19-9</li> </ul>
Rationale Hypothesis	<p>Second-line nanoliposomal irinotecan (Nal-IRI) in combination with 5-FU/folinic acid increases median overall survival of patients with advanced pancreatic cancer from 4.2 months to 6.1 months as compared to 5-FU/folinic acid alone (Wang-Gillam et al., Lancet 387; 545-57: 2016), albeit with a considerable rate of grade 3/4 toxicities (e.g. 13% of grade 3/4 diarrhea and 14% fatigue).</p> <p>Exploratory subgroup analysis was unable to show a clear difference of treatment efficacy e.g. for sex, age, BMI, prior therapies or stage at diagnosis. However, the positive effect seemed to be more pronounced in patients with reduced performance status or with shorter time since diagnosis, a result which could not be easily explained and may be due to the limited patient number.</p> <p>In summary, it is currently unknown which patients profit most from 2<sup>nd</sup>-line treatment with Nal-IRI.</p> <p>It is also not known if 2<sup>nd</sup>-line treatment and its associated toxicities have an impact on symptom control or Quality of Life (QoL).</p>

	<p>Confounding factors for the efficacy of 2<sup>nd</sup>-line treatment have only rarely been examined in pancreatic cancer.</p> <p>In a subgroup analysis of the CONCO-003 trial (oxaliplatin/5-FU/FA compared to 5-FU/FA as second-line therapy after gemcitabine pretreatment), the hazard ratio for overall survival in favor of the investigational treatment barely reached significance for i) longer treatment duration during 1<sup>st</sup>-line (&gt; 6 months, HR 0.58, 95% CI 0.35-0.98), for ii) patients in slightly reduced performance status (KI 70-80%, HR 0.67, 95% CI 0.38-0.95), and iii) for metastatic disease. Other factors are not reported (Oettle et al. J Clin Oncol 32; 2423-29: 2014). Additional hypothesis can be derived from other tumor types.</p> <p>In soft tissue sarcoma, a good performance status predicts success of 2<sup>nd</sup>-line therapy with trabectedin (Penel et al. Ann Oncol 24:537-42, 2013). In this group, the growth modulatory index (GMI) reaches 1.33 (PS 0, p&lt;0.04), as compared to a GMI of 0.6 in the whole patient population. In addition, a high GMI was correlated with an increased response rate and with prolonged PFS.</p> <p>In advanced colorectal cancer, early progression during 1<sup>st</sup>-line treatment had a significantly negative effect on overall survival (Penichoux et al. Europ J Cancer 49; 1882-8, 2013), but this effect varied considerably between the type of treatment. It was more pronounced with an intensified regimen (FOLFOX, HR 18.0, 7.9-41.2) as compared to 5FU/FA (HR 7.7, 3.9-17.4) and was strongly dependent from the rate of severe toxicities.</p> <p>In summary, the success of first-line therapy seems to have a beneficial effect on the efficacy of 2<sup>nd</sup>-line treatment and on overall survival in soft tissue sarcoma as well as in advanced colorectal cancer. Relevant cofactors are toxicity and the performance status. There are no comparable analyses in pancreatic cancer.</p> <p><b>Research hypothesis:</b>  Patients profit from 2<sup>nd</sup>-line therapy with Nal-IRI if they also had a benefit from 1<sup>st</sup>-line treatment.  Benefit from treatment (either 1<sup>st</sup> or 2<sup>nd</sup>-line) will be defined as a patient specific Time-To-Treatment Failure (TTF) which is in the upper third of the distribution of TTF values of the studied population.</p>
Safety data	<ul style="list-style-type: none"> <li>• AEs, SAEs and treatment emergent adverse events according to CTCAE Version 4.03</li> <li>• Frequency of clinically significant abnormal laboratory parameters</li> </ul>
Sample size estimation and Statistical considerations	<ul style="list-style-type: none"> <li>• Confirm an increase of TTF2 by 50% in patients with favorable TTF1 ('highTTF1', i.e. the population with TTF1 in the upper third) as compared to the group with 'lowTTF1' (i.e. patients with TTF1 in the lowest third of the population) in patients pretreated with gemcitabine/Nab-Paclitaxel as 1<sup>st</sup>-line therapy for advanced disease.</li> <li>• Assumptions: The expected median TTF2 of the whole patient population is 2.3 months (95% CI 1.6-2.8), as derived from another 2<sup>nd</sup>-line trial with Nal-IRI/5-FU/FA (Napoli-1, Wang-Gillam et al. Lancet 387; 545-57: 2016). If the TTF2 in the 'lowTTF1' is assumed to reach 1.8 months, a calculated 50% increase would lead to a TTF2 of 2.7 months in the 'highTTF1' population.</li> <li>• Calculation – Log-Rank-Test: 156 events will be needed in 158 patients in the two compared groups to reach 80% power with a one-sided alpha of 0.05. Including 12% dropouts, this translates into 180 patients. Because only 2/3 of the patients are used for comparison (the 'lowTTF1' and 'highTTF1' population), this translates into a total number of n=270 (180 x 1.5) patients to be included into the trial.</li> </ul>
Study plan / time lines	First Patient In (FPI): Q4/2017

Last Patient In (LPI):	after approx. 24 month
Last Patient Last treatment (LPLT):	after approx. 29 month
End of follow-up period after LPI:	after approx. 34 month
Study report:	after approx. 40 month
Publication:	after approx. 42 month

### Pankreaskarzinom – palliative Therapie, 1st-line

**AIO-PAK-0114: Induction treatment with nab-paclitaxel/gemcitabine for first-line treatment of metastatic pancreatic cancer followed by either alternating application of gemcitabine monotherapy and nab-paclitaxel/gemcitabine or continuing application of nab-paclitaxel/gemcitabine: A randomized phase II study (ALPACA)**

<b>AIO-Studie</b>	
Studiennummer/-Code:	AIO-PAK-0114 - ALPACA
Status:	Aktiv rekrutierend
Rekrutierungszeitraum:	30 Monate (FPI 27.05.2016)
Anzahl initiiertes Zentren:	30
Weitere Zentren:	Momentan nur Warteliste
Anzahl eingeschlossene Patienten:	147 von 325 (57 randomisierte Patienten von 228 geplanten)
Letzte Aktualisierung:	10.04.2018

Study Type	Multicenter, open-label, randomized active-controlled phase II trial
Coordinating Investigator	Prof. Dr. Frank Kullmann Kliniken Nordoberfalz AG Klinikum Weiden, Söllnerstraße 16, 92637 Weiden E-Mail: frank.kullmann@kliniken-nordoberpfalz.ag
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Number of patients	A total of 325 patients will be enrolled to the trial. (228 randomized)
Study duration	<p><b>Accrual period:</b> The accrual period is estimated to last 30 months.</p> <p><b>Estimated treatment duration of the individual patient:</b> Treatment duration in the individual patient will differ; estimated average treatment duration will be 6 - 8 months.</p> <p><b>Duration of follow up after end of treatment:</b> Until death or the end of the study whichever is sooner and for at least 6 months or until death in each patient</p> <p><b>Estimated study duration:</b> 3.5 years from the first patient enrolled until the end of study</p> <p><b>Start of the study:</b> First patient First visit (FPFV): Date of the written informed consent by the first patient enrolled.</p> <p><b>End of the study:</b></p>



	Last Visit Last Patient (LPLV) will be the last follow-up visit of the last patient having received study drug.
Planned number of sites	Up to 30 trial centers in Germany This study is <u>not open</u> for new sites.
Background and Rationale	<p>In the MPACT trial nab-paclitaxel in combination with gemcitabine has been shown to significantly improve overall survival ([OS]; 8.5 vs. 6.6 months; median improvement of 2.1 months; <math>p &lt; 0.001</math>) compared to standard gemcitabine monotherapy in metastatic pancreatic adenocarcinoma. Progression-free survival ([PFS]; 5.5 vs. 3.7 months), objective response rate (23% compared to 7%), and time to treatment failure (5.1 vs. 3.6 months) evaluated as secondary endpoints likewise showed significant improvement. However, these results were less impressive than the results of the prior phase I/II trial by Hoff and coworkers, in which a median OS of 12.2 months and a median PFS of 7.9 months had been observed for patients with the identical nab-paclitaxel dosage (125 mg/m<sup>2</sup>). In the MPACT trial the median number of cycles applied was 3 (=3.9 months of treatment duration) in contrast to 6 cycles (= 6 months) in the phase I/II study, though for patients of all dosage levels (100, 125, or 150 mg/m<sup>2</sup>). This shorter treatment duration could have contributed to reduced overall survival.</p> <p>It is the rationale of the study to investigate whether improved overall tolerability that would subsequently prolong treatment duration and increase efficacy can be achieved by alternating treatment cycles of gemcitabine monotherapy followed by nab-paclitaxel/gemcitabine compared to standard continuing nab-paclitaxel/gemcitabine treatment cycles in patients having received 3 cycles of induction therapy with standard nab-paclitaxel/gemcitabine and by means of an additional improved toxicity monitoring and quality of life monitoring.</p> <p>The considerations for the justification of alternating treatment cycles of gemcitabine monotherapy followed by nab-paclitaxel/gemcitabine are as follows:</p> <p>The proof of principle of an alternating gemcitabine-based regime in untreated metastatic pancreatic cancer is given. Trouilloud et coworkers had shown in the FIRGEM phase II trial that alternating cycles of FOLFIRI.3 (CPT-11 [nanoliposomal irinotecan] plus folinic acid plus 5-FU and gemcitabine monotherapy improved rate of PFS at 6 months compared to gemcitabine monotherapy (48% versus 30%).</p> <p>Von Hoff et coworkers had reported that in preclinical studies in mice with human pancreatic cancer xenografts nab-paclitaxel alone and in combination with gemcitabine decreased the peritumoral desmoplastic stroma. The intratumoral concentration of gemcitabine was increased by 2.8 fold in nab-paclitaxel plus gemcitabine treated mice versus those receiving only gemcitabine. Peritumoral desmoplastic stromal depletion allowing the chemotherapeutics to reach the tumor more efficiently has been postulated as one contributing mode of action of nab-paclitaxel. Other preclinical experiments in mouse models of pancreatic cancer suggest that nab-paclitaxel may increase the intratumoral gemcitabine levels by decreasing the enzyme cytidine desaminase, the main gemcitabine metabolizing enzyme, thus blocking the break-down of gemcitabine in pancreatic cancer, increasing intratumoral levels of gemcitabine and supporting synergism of nab-paclitaxel and gemcitabine. Thus it is assumed that induction therapy with the standard combination will be sufficiently long for all patients to allow for a continued increased tumoral accumulation of active gemcitabine– even in those patients subsequently treated with the alternating therapy.</p>
Inclusion criteria	<ul style="list-style-type: none"> <li>• Adult patients (≥ 18 years of age)</li> <li>• Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Patients with islet cell neoplasms are excluded</li> <li>• Karnofsky performance status (KPS) ≥ 70%</li> <li>• At least one unidimensionally measurable lesion as assessed by CT-scan or MRI according to RECIST 1.1</li> <li>• Total bilirubin ≤ 1,5 x ULN. Patients with a biliary stent may be included</li> </ul>

	<p>provided that bilirubin level after stent insertion decreased to <math>\leq 1,5</math> x ULN and there is no cholangitis.</p> <ul style="list-style-type: none"> <li>• Adequate renal, hepatic and bone marrow function, defined as <ul style="list-style-type: none"> <li>- Calculated creatinine clearance <math>\geq 30</math> mL/min according to CKD-EPI formula</li> <li>- AST/GOT and/or ALT/GPT <math>\leq 2.5</math> x ULN and <math>\leq 5.0</math> x ULN in case of liver metastasis</li> <li>- Absolute neutrophil count (ANC) <math>\geq 1.5 \times 10^9/L</math></li> <li>- Haemoglobin <math>\geq 9</math> g/dL</li> <li>- Platelets <math>\geq 100 \times 10^9/L</math></li> </ul> </li> <li>• Females of childbearing potential (FCBP) must have a negative pregnancy test within 7 days of the first application of study treatment and they must agree to undergo further pregnancy tests before randomization and at the end of treatment visit <b>and</b> FCBP must either agree to use and be able to take effective contraceptive birth control measures (Pearl Index <math>&lt; 1</math>) or agree to practice complete abstinence from heterosexual intercourse during the course of the study and for at least 1 month after last application of study treatment. A female subject is considered to be of childbearing potential unless she is age <math>\geq 50</math> years and naturally amenorrhoeic for <math>\geq 2</math> years, or unless she is surgically sterile.</li> <li>• Males must agree not to father a child during the course of the trial and for at least 6 months after last administration of study drugs.</li> <li>• Signed and dated informed consent before the start of any specific protocol procedures.</li> </ul> <p>Patient's legal capacity to consent to study participation.</p>
Exclusion criteria	<ul style="list-style-type: none"> <li>• Missing histological or cytological confirmation of metastatic adenocarcinoma of the pancreas</li> <li>• Locally advanced pancreatic adenocarcinoma without metastases</li> <li>• Any previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. (Prior adjuvant chemotherapy with gemcitabine or fluoropyrimidine in curative intent is allowed if terminated more than 6 months before first application of study treatment. Previous palliative radiotherapy of bone metastases for alleviation of pain is permitted provided that irradiated bone metastases are no target lesions.)</li> <li>• Known brain metastase/brain metastases. Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients.</li> <li>• Pre-existing polyneuropathy <math>\geq</math> grade 2 according to CTCAE version 4</li> <li>• Medical history of interstitial lung disease (ILD) or pulmonary fibrosis</li> <li>• Patients with high cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year</li> <li>• Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus)</li> <li>• Any other severe concomitant disease or disorder, which could influence patient's ability to participate in the study and his/her safety during the study or interfere with interpretation of study results e.g. severe hepatic, renal, pulmonary, metabolic, or psychiatric disorders</li> <li>• Previous or concurrent tumor other than underlying tumor disease (pancreatic cancer) with the exception of cervical cancer in situ, adequately treated basal cell carcinoma or squamous cell carcinoma of the skin, superficial bladder tumors (Ta,Tis, and T1) or any curatively treated tumors <math>&gt; 5</math> years prior to enrolment</li> <li>• Hypersensitivity against nab-paclitaxel, gemcitabine, or any excipients of these drugs</li> <li>• Continuing abuse of alcohol, drugs, or medical drugs</li> <li>• Pregnant females, breast feeding females or females of childbearing potential unable to either perform adequate contraceptive measures or practice complete abstinence from heterosexual intercourse</li> <li>• Participation in any other clinical trial or treatment with any experimental drug within 28 days before enrolment to the study or during study participation</li> </ul>

	<p>until the end of treatment visit.</p>
<p>Treatment regimen</p>	<p><b>Induction treatment</b>                  All patients will be given:  <b>3 cycles nab-paclitaxel/gemcitabine; duration of each cycle 28 days</b>                  nab-paclitaxel 125 mg/m<sup>2</sup>, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle                  Patient with progression or unacceptable toxicity have to discontinue study treatment.                  After three cycles nab-paclitaxel/gemcitabine tumor evaluation is performed. Randomization in Arm A and Arm B will take place for all patients with at least stable disease (SD).</p> <p><b>Continuous treatment after randomization</b>  <b>Standard Arm A</b></p> <p>Patients randomized in Arm A will receive <b>continuing application of nab-paclitaxel/gemcitabine treatment cycles</b> until progression or unacceptable toxicity.                  Duration of each cycle is 28 days and comprises:                  nab-paclitaxel 125 mg/m<sup>2</sup>, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle</p> <p><b>Experimental Arm B</b></p> <p>Patients randomized in Arm B will receive <b>alternating application of gemcitabine monotherapy and nab-paclitaxel/gemcitabine treatment cycles</b> until progression or unacceptable toxicity, starting with a treatment cycle of gemcitabine. Duration of each cycle irrespective of treatment cycle with GEM or with nab-paclitaxel/gemcitabine is 28 days.</p> <p><b>Gemcitabine treatment cycle:</b>                  Gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle</p> <p><b>nab-paclitaxel/gemcitabine treatment cycle:</b>                  nab-paclitaxel 125 mg/m<sup>2</sup>, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m<sup>2</sup> as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle</p> <p>At discontinuation of study treatment (standard or experimental arm) due to progression patients with a good performance status are encouraged to receive a non-neurotoxic combination of a fluoropyrimidine. In the presence of a reduced performance status treatment with a mono fluoropyrimidine may be recommended. However, this further second-line treatment is not part of the study protocol and at investigator's discretion.</p> <pre>                 graph LR                 START((START)) --&gt; Induction[3 cycles Nab-P / GEM]                 Induction --&gt; Randomisation((Randomisation 1:1))                 Randomisation --&gt; EndTreatment[End of treatment if PD]                 Randomisation --&gt; StandardArmA[Standard Arm A]                 Randomisation --&gt; ExperimentalArmB[Experimental Arm B]                 StandardArmA --&gt; S1[Nab-P / GEM]                 S1 --&gt; S2[Nab-P / GEM]                 S2 --&gt; S3[Nab-P / GEM]                 S3 --&gt; S4[Nab-P / GEM]                 S4 --&gt; S4_PD[Continuation until PD]                 ExperimentalArmB --&gt; E1[GEM]                 E1 --&gt; E2[Nab-P / GEM]                 E2 --&gt; E3[GEM]                 E3 --&gt; E4[Nab-P / GEM]                 E4 --&gt; E4_PD[Continuation until PD]                 </pre> <ul style="list-style-type: none"> <li>GEM = gemcitabine; Nab-P = nab-paclitaxel, PD = progression</li> </ul>
<p>Statistical and analytical plan and methodology</p>	<p>Standard statistical methods will be applied for analyzing this study. The primary goal is to derive a point estimate and an associated 80% confidence interval with a pre-specified precision for the overall survival treatment hazard ratio of alternating treatment cycles of gemcitabine monotherapy followed by nab-paclitaxel/gemcitabine relative to standard nab-paclitaxel/gemcitabine treatment cycles following induction treatment. A Cox-proportional hazards model will be</p>

	applied.
Endpoints	<p><u>Primary endpoint:</u> Overall survival determined from time of randomization until date of death</p> <p><u>Secondary endpoints:</u> <i>Efficacy variables:</i></p> <ul style="list-style-type: none"> <li>• Progression-free survival as time from randomization to objective tumor progression or death from any cause</li> <li>• Overall response rate according to RECISTv1.1 determined from first application of induction treatment</li> <li>• Disease control rate according to RECISTv1.1) determined from first application of induction treatment</li> <li>• Quality of life as determined with EORTC QLQ-C30 determined from randomization</li> </ul> <p><i>Safety variables:</i></p> <ul style="list-style-type: none"> <li>• Type, incidence, and severity of adverse events according to NCI CTCAE version 4 with explicit consideration of any neurotoxicity</li> <li>• Duration of treatment without toxicity leading to permanent discontinuation</li> </ul> <p>Functional assessment of neurotoxicity (with FACT taxane score)</p>
Additional exploratory endpoints	<p><b>Efficacy and safety during induction phase:</b></p> <ul style="list-style-type: none"> <li>• Overall response rate (according to RECISTv1.1) during induction phase</li> <li>• Disease control rate (according to RECISTv1.1) during induction phase</li> <li>• Overall survival during induction phase</li> <li>• Progression-free survival during induction phase</li> <li>• Duration of treatment during induction phase</li> <li>• Type, incidence, and severity of adverse events according to NCI CTCAE version 4 with explicit consideration of any neurotoxicity during induction phase</li> <li>• FACT taxane score during induction phase</li> <li>• Quality of Life as determined with EORTC QLQ-C30 during induction phase</li> </ul> <p><b>Efficacy and safety in patients treated with alternating or continuing nab-paclitaxel/ gemcitabine treatment cycles after randomization and all non-randomized patients with nab-paclitaxel/gemcitabine induction treatment:</b></p> <ul style="list-style-type: none"> <li>• OS determined from first application of induction treatment</li> <li>• PFS determined from first application of induction treatment</li> <li>• ORR (according to RECISTv1.1)</li> <li>• DCR (according to RECISTv1.1)</li> <li>• Type, incidence, and severity of adverse events according to NCI CTCAE version 4 with explicit consideration of any neurotoxicity</li> </ul>
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Pankreaskarzinom, palliative Therapie: Phase-I Studie**AIO-PAK-0117: Phase I feasibility study of *nab*-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer and cholestatic hyperbilirubinemia (PANCHO)****AIO-Studie**

Studiennummer/-Code: AIO-PAK-0117 - PANCHO

Status: in Vorbereitung

Rekrutierungszeitraum: 2018 – 2021 (geplant)

Weitere Zentren: sind aktuell leider nicht möglich

Letzte Aktualisierung: April 2018

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Study design	This is a multicenter, open-label, non-randomized, non-comparative dose-escalation Phase I study with 3 parallel dose finding cohorts
Anticipated start date	Q3/2018
Duration of study	~ 44 months Accrual period: 38 month Simultaneous recruitment start for the 3 different cohorts
Indication	Metastatic pancreatic adenocarcinoma and cholestatic hyperbilirubinemia not previously treated for metastatic disease
Total number of sites	4-5
Primary objective	To determine safety and feasibility and the maximum tolerated dose (MTD) of <i>nab</i> -paclitaxel in combination with gemcitabine in first line patients with advanced pancreatic cancer and cholestatic hyperbilirubinemia.
Primary endpoint	Determination of the Maximum Tolerated Dose (MTD) by recording dose limiting toxicities (DLT) in each tested dose level in all three Bilirubin cohorts. DLTs will be identified by observing frequency and severity of specific adverse events.
Secondary objectives and endpoints	To evaluate further efficacy data for the combination of <i>nab</i> -paclitaxel in combination with gemcitabine: <ol style="list-style-type: none"> <li>1. Tumor response according to RECIST 1.1</li> <li>2. Progression-free survival (PFS)</li> <li>3. Overall Survival (OS)</li> <li>4. Ca19-9 response</li> <li>5. Change in hyperbilirubinemia</li> <li>6. QoL (EORTC QLQ-C30 and Pan26), (Q-Twist)</li> <li>7. Treatment associated change of pts. nutritional status</li> </ol>
Exploratory objectives and endpoints	Correlative research and biomarker assessments: <ul style="list-style-type: none"> <li>• SPARC/CXCR4/p53/KRAS/BRAF/BRCA,</li> <li>• Immune cell infiltration,</li> <li>• Subtype expression (IPMN/AC)</li> </ul>

	on primary [and refractory] sampled tissue.
Planned sample size	<p>Maximum N=60 patients (incl. drop outs)</p> <p>Cohort A: max. 12 pts</p> <p>Cohort B: max. 18 pts</p> <p>Cohort C: max. 24 pts</p> <p>Maximum numbers per dose cohort always refer to evaluable subjects.</p>
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>2. Age <math>\geq</math> 18 years at time of study entry</li> <li>3. Histological or cytological documentation of adenocarcinoma of an adenocarcinoma of the pancreas</li> <li>4. Metastatic disease not amenable to surgical resection with curative intent</li> <li>5. No prior chemotherapy for metastatic disease</li> <li>6. Measurable disease, defined as at least one unidimensional measurable lesion on a CT scan as defined by RECIST 1.1</li> <li>7. Performance-Status according to Karnofsky-Scale <math>\geq</math> 70%</li> <li>8. Life expectancy of at least 3 months</li> <li>9. Adequate bone marrow, renal, and hepatic function: <ul style="list-style-type: none"> <li>• Absolute neutrophil count (ANC) <math>\geq</math> 1,500/mm<sup>3</sup></li> <li>• Platelets <math>\geq</math> 100,000/mm<sup>3</sup></li> <li>• Hemoglobin <math>\geq</math> 8.0 g/dL</li> <li>• Bilirubin <math>\geq</math> 1.5 x ULN <math>\leq</math> 10 x ULN due to cholestasis measured 3 days after drainage (if possible)</li> </ul> <p>Bilirubin level must be decreasing after drainage.</p> </li> <li>10. Women of childbearing potential and male subjects must agree to use adequate contraception for the duration of study participation and up to 3 months (90 days) following completion of therapy. Females of childbearing potential who are sexually active with a non-sterilized male partner must use highly effective methods contraception from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product.</li> <li>11. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: <math>\geq</math> 60 years old and no menses for <math>\geq</math> 1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a pregnancy test performed at a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment.</li> <li>12. In the assessment of the investigator, patient is able to comply with study requirements.</li> <li>13. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.</li> </ol>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Hyperbilirubinaemia successfully treatable with internal or external drainage of the choledochus</li> <li>2. Active infection &gt; Grad 2 NCI-CTCAE V4.03</li> <li>3. Serious systemic disease: uncontrolled hypertension or hyperglycaemia, hypoglycaemia, congestive heart failure NYHA III – IV, symptomatic coronary heart disease, uncontrolled cardiac arrhythmia &gt; grade II</li> <li>4. Hepatic transaminases elevation &gt; 5xULN</li> <li>5. Albumin &lt; 2.0 mg/dL</li> <li>6. GFR &lt; 30 mL/min</li> </ol> <p>International Normalized Ratio (INR) &gt; 2.0 or prolongation of the activated partial prothrombin time (aPTT) &gt; 2 x ULN</p> <ol style="list-style-type: none"> <li>7.</li> <li>8. Uncontrolled diabetes type I or II</li> <li>9. Need of immuno-suppressive therapy (e. g. pts after transplantations)</li> </ol> <p>Subject uses medication known to be strong inducers of CYP3A4 and CYP2C8</p> <ol style="list-style-type: none"> <li>10.</li> </ol>

	<p>11. Severe non-healing wounds, ulcers or bone fractures</p> <p>12. Hypersensitivity against <i>nab</i>-paclitaxel, gemcitabine, or any of the constituents of the products</p> <p>13. Female subjects who are pregnant, breast-feeding or intent to become pregnant.</p> <p>14. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results</p> <p>15. Participation in another clinical study with an investigational product during the last 30 days before inclusion</p> <p>16. Previous enrollment in the present study (does not include screening failure).</p> <p>17. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p>
Investigational agent	<ul style="list-style-type: none"> <li>• <i>Nab</i>-paclitaxel</li> <li>• Gemcitabine</li> </ul>
Treatment plan and schedule	<p><b>General treatment regimen:</b>  <i>Nab</i>-Paclitaxel X* mg/m<sup>2</sup>, 30min, i.v., d1, 8, 15  Gemcitabine X* mg/m<sup>2</sup>; 30min, i.v., d1, 8, 15  Cycle length is 28 days (4 weeks).  * Dose depending on dose level and bilirubin cohort</p> <p><b>Dose escalation design adapted to hyperbilirubinemia.</b>  Three parallel cohorts:</p> <ul style="list-style-type: none"> <li>• 1 cohort with bilirubin <math>\geq 1.5 \times \text{ULN} \leq 3.0 \times \text{ULN}</math> (<b>Cohort A</b>)</li> <li>• 1 cohort with bilirubin <math>&gt; 3.0 \times \text{ULN} \leq 5.0 \times \text{ULN}</math> (<b>Cohort B</b>)</li> <li>• 1 cohort with bilirubin <math>&gt; 5.0 \times \text{ULN} \leq 10.0 \times \text{ULN}</math> (<b>Cohort C</b>)</li> </ul> <p>If drainage is possible bilirubin will be measured after drainage and should be decreasing to indicated successful drainage.  Bilirubin levels which determine Cohort allocation during screening assessments must be measured no earlier than 48 hours before administration of first dose of study medication. [Re-testing of bilirubin levels to determine/ascertain eligibility is permitted max. 2 times] .  Bilirubin will be measured again before each administration of chemotherapy (d1, d8, d15 of each cycle), but only the first value (during screening) leads to inclusion decision in respective cohort.</p> <p><b>Dose levels to be tested:</b></p> <ul style="list-style-type: none"> <li>• Level 3: 125 mg/m<sup>2</sup> <i>nab</i>-paclitaxel followed by 1000 mg/m<sup>2</sup> gemcitabine weekly, i.v., 30 min.</li> <li>• Level 2 (starting dose for A): 100 mg/m<sup>2</sup> <i>nab</i>-paclitaxel followed by 800 mg/m<sup>2</sup> gemcitabine weekly, i.v., 30 min.</li> <li>• Level 1 (starting dose for B): 75 mg/m<sup>2</sup> <i>nab</i>-paclitaxel followed by 600 mg/m<sup>2</sup> gemcitabine weekly, i.v., 30 min.</li> <li>• Level 0 (starting dose for C): 50 mg/m<sup>2</sup> <i>nab</i>-paclitaxel followed by 600 mg/m<sup>2</sup> gemcitabine weekly, i.v., 30 min. [dose level will only be tested in cohort C]</li> </ul> <p><b>Definition of Dose Limiting Toxicities (DLTs):</b></p> <ul style="list-style-type: none"> <li>• Every grade 3 or 4 non-hematologic toxicity with the exception of nausea, vomiting (and bilirubin in cohort B and C)</li> <li>• Grade 4 thrombocytopenia or grade 3 thrombocytopenia with concomitant bleeding</li> <li>• Grade 4 neutropenia for more than 7 days or febrile neutropenia</li> </ul> <p>Grading according to Common Toxicity Criteria or Adverse Events; NCI-CTCAE Version 4.03</p>

If the occurrence of DLT toxicity is probably not drug related (e.g. result of a comorbidity or progression of cancer), the investigator do seek advice from the CI for further guidance.

**Modified 3+3 dose finding strategy:**

- No appearance of DLT in 3 pts during cycle 1, then additional 3 pts with higher dose level will be recruited
- At least one patient with DLT in 3 pts during cycle 1, the cohort must be expanded to 6 pts
- If there is an appearance of DLT in 1 out of 6 pts during cycle 1, next pts will be recruited in higher dose level
- If there is an appearance of DLT in at least 2 of 6 pts during cycle 1 the maximum tolerated dose is either estimated as the next lower dose level or depending on starting dose level no MTD can be established.
- **Cohort A modification:** If there is an appearance of DLT in at least 2 of 6 pts at dose level 2 (starting dose for this cohort), than 3(+3) pts will be treated with next lower dose level (level 1); if there is an appearance of DLT in at least 2 of 6 pts at dose level 1 no new pts are allowed to be treated with dose level 0. That is, no formal MTD for this dose cohort will be established.
- **Cohort B modifications:** If there is an appearance of DLT in at least 2 of 6 pts at dose level 1 no new pts are allowed to be treated with dose level 0. That is, no formal MTD for this dose cohort will be established.
- **Cohort C modifications:** In order to give maximum chance to patients in Cohort C to benefit from *nab*-Paclitaxel/Gemcitabine combination therapy, for each of the 3-6 pts that started with dose level 0, the dose of *nab*-paclitaxel for these pts must be adjusted to 75 mg/m<sup>2</sup> from c2/d1 onwards [intra-subject dose escalation] if the following applies: a) no DLT in cycle 1 and b) common inclusion criteria (except billirubin) are fulfilled on day 1 cycle 2. If there is an appearance of DLT in at least 2 of 6 pts treated at dose level 0 no maximum tolerated dose will be determined for this cohort

After the MTD has been established patients may continue further treatment with either the established MTD or an individually tolerated dose.

**Safety- Intra-subject dose modification plan**

Doses will be reduced for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity.

Toxicities will be graded using the NCI-CTCAE Version 4.03.

A maximum of two dose reductions are permitted according to the criteria below. If a toxicity requiring dose modification occurs in a patient who started at dose level 0, or following the first (for a patient who started at dose level 1) or the second (for a patient who started at dose level ≥2) dose reduction of either drug, further treatment should be discontinued.

Dose Level	<i>nab</i> -PAC Dose (mg/m <sup>2</sup> )	Gemcitabine Dose (mg/m <sup>2</sup> )
Level 3	125	1000
Level 2	100	800
Level 1	75	600
Level 0	50	600



	<table border="1"> <tr> <td><b>If more than 2 dose reductions required</b></td> <td>Discontinue treatment</td> <td>Discontinue treatment</td> </tr> </table>	<b>If more than 2 dose reductions required</b>	Discontinue treatment	Discontinue treatment									
<b>If more than 2 dose reductions required</b>	Discontinue treatment	Discontinue treatment											
Rationale	<p>Many patients with pancreatic cancer present with hyperbilirubinemia at time of diagnosis. This is in most cases caused by the obstruction of the bile duct by the tumor itself. The patients are treated with a stent in order to reduce cholestasis. Nevertheless, cholestasis cannot be resolved completely in all patients leading to continuously elevated bilirubin levels. Currently no valid treatment options in pancreatic cancer pts with hyperbilirubinemia due to cholestasis exist. <i>Nab</i>-paclitaxel and gemcitabine has been approved for metastatic pancreatic cancer patients in 2013. But the SmPC states that treatment with <i>nab</i>-paclitaxel and gemcitabine is not recommended in patients with ULN of bilirubin &gt; 1.5 ULN due to insufficient data. This phase I study aims to evaluate the MTD of <i>nab</i>-paclitaxel and gemcitabine in metastatic pancreatic cancer patients with elevated bilirubin levels due to cholestasis despite appropriate stenting to establish a safe treatment option for these patients.</p> <p><b>References:</b></p> <ol style="list-style-type: none"> <li>1) A Phase II Trial of nab-Paclitaxel as Second-line Therapy in Patients With Advanced Pancreatic Cancer. Hosein PJ et al; Am J Clin Oncol. 2012 Feb 2</li> <li>2) Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine, von Hoff et al., The New England Journal of Medicine, 2013</li> <li>3) Current version of SmPC Abraxane</li> <li>4) Patients with Advanced Pancreatic Cancer and Hyperbilirubinaemia: Review and German Expert Opinion on Treatment with nab-Paclitaxel plus Gemcitabine, Oncology Research and Treatment, Vogel et al, 2015</li> </ol>												
Interim analyses	<p>According to the standard 3+3 dose finding strategy, a DLT assessment will be performed after the first cycle of each dose level (patient cohorts of n=3) and the frequency of DLTs determined. Based on the results the dose for the consecutive patient cohort will either be escalated (0/3 DLTs), repeated (1/3 DLTs) or de-escalated (&gt;1/3 DLTs). The exact escalation and de-escalation strategy depends on the patient cohort/starting dose level.</p>												
Safety data	<p>All safety variables of classical phase I trials, measurements of AEs, SAEs and DLTs</p>												
Sample size estimation and statistical analysis considerations	<p>No formal sample size calculation is required for this study. A modified 3+3 dose finding design (intra-subject dose escalation permitted in cohort C) will be adopted with a maximum of 4 distinct dose-levels to be evaluated. Each dose-level will be tested on a minimum of three and a maximum of 6 patients. Hence, the maximum number of enrolled subjects to be evaluated is <b>n=54</b>.</p> <p>Subjects withdrawn from the study will not be replaced, unless the investigator can <u>unequivocally ascertain</u> that the reasons for withdrawal of a patient are personal and have no medical motivation (e.g. burden of treatment, adverse events, lack of efficacy) and withdrawal/drop-out occurred during the first dosing cycle. The maximum number of subjects (i.e drop-outs) to be replaced due to the aforementioned condition is limited to n=6. The maximum number of study subjects to be enrolled and treated is <b>N=60</b>.</p> <p>The MTD will be the dose for which the frequency of DLTs is &lt;33%.</p> <p>All secondary efficacy, safety and QoL endpoints will be analyzed descriptively.</p>												
Study plan/ Timelines	<table> <tr> <td>First Patient In (FPI):</td> <td>Q3/2018</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 38 months</td> </tr> <tr> <td>Last Patient Last Visit (LSO):</td> <td>after approx. 44 months</td> </tr> <tr> <td>End of follow-up period after LSO:</td> <td>after approx. 44 months</td> </tr> <tr> <td>Study report:</td> <td>after approx. 50 months</td> </tr> <tr> <td>Publication:</td> <td>after approx. 53 months</td> </tr> </table>	First Patient In (FPI):	Q3/2018	Last Patient In (LPI):	after approx. 38 months	Last Patient Last Visit (LSO):	after approx. 44 months	End of follow-up period after LSO:	after approx. 44 months	Study report:	after approx. 50 months	Publication:	after approx. 53 months
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Study report:	after approx. 50 months												
Publication:	after approx. 53 months												

**AIO-PAK-0217: Gemcitabin und nab-Paclitaxel in Kombination mit Afatinib, einem oralen irreversiblen Blocker der ErbB-Familie, bei Patienten mit metastasiertem Pankreaskarzinom: eine klinische Phase Ib Studie (AFFECT-Trial)**

**AIO-Studie**

Studiennummer/-Code:	AIO-PAK-0217 - AFFECT-Trial
Status:	in Rekrutierung
Rekrutierungszeitraum:	2016 - 2018
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

<b>Eudra-CT Nummer</b>	2015-004065-86
<b>Leiter der klinischen Prüfung</b>	Prof. Dr. Volker Heinemann
<b>Sponsor</b>	Klinikum der Universität München-Großhadern Ludwig-Maximilians-Univ. München Marchioninstr. 15 81377 München
<b>Indikation</b>	Erstlinientherapie des metastasierten Adenokarzinoms des Pankreas
<b>Studienzentren</b>	3 Studienzentren in Deutschland
<b>Hintergrund und Rationale</b>	<p>Das duktales Adenokarzinom des Pankreas (PDAC) bleibt eine nahezu immer tödlich verlaufende Erkrankung. Obwohl signifikante Fortschritte beim Verständnis der zugrunde liegenden Molekularbiologie des Pankreaskarzinoms gemacht wurden, haben diese Fortschritte nicht zu substantiell besseren Behandlungen geführt. In besorgniserregender Weise steigt die Zahl der Fälle von Pankreastumoren beständig und das Pankreaskarzinom wird bis 2030 von allen durch Karzinome bedingten Todesfällen die zweithäufigste Todesursache sein.</p> <p>Entsprechend werden für Patienten mit Pankreaskarzinom dringend neue Therapiestrategien benötigt.</p> <p>Kürzlich hat sich die Kombination von Gemcitabin und <i>nab</i>-Paclitaxel verglichen mit der alleinigen Gabe von Gemcitabin als überlegen erwiesen (Gesamtüberleben [OS] 8,7 Monate in der <i>nab</i>-Paclitaxel/Gemcitabin Gruppe gegenüber 6,6 Monaten in der Gemcitabin Gruppe; Hazard-Ratio für Tod 0,72; 95% Konfidenzintervall 0,62 bis 0,83; <math>p &lt; 0,001</math>).</p> <p>Infolgedessen wird diese Kombinationstherapie jetzt als neue Behandlungsoption für Patienten mit metastasiertem Pankreaskarzinom eingeschätzt und sollte bei zukünftigen Studien als Basistherapie eingesetzt werden.</p> <p>Präklinische Studien legen für den ErbB Signalweg eine bedeutsame Rolle bei der Pathogenese des Pankreaskarzinoms nahe. Entsprechend scheint eine zielgerichtete Therapie der Tyrosinkinase Rezeptoren der ErbB-Familie eine vielversprechende Option zu sein, um das Behandlungsergebnis bei Patienten mit Pankreaskarzinom zu verbessern.</p> <p>Die Gabe des selektiven reversiblen EGFR Tyrosinkinase Inhibitors Erlotinib zusätzlich zu Gemcitabin hat das progressionsfreie Überleben und Gesamtüberleben bei Patienten mit metastasiertem Pankreaskarzinom signifikant verbessert. Allerdings betrug der Unterschied in der Wirkung beim Median der Überlebenszeit in absoluten Werten zwischen den beiden Studienarmen (Erlotinib und Gemcitabin gegenüber nur Gemcitabin) weniger als einen halben Monat.</p> <p>Afatinib ist ein selektiver, potenter und irreversibler Blocker der ErbB</p>

	<p>Familie. Im Unterschied zu Erlotinib bindet Afatinib kovalent an alle Homo- und Heterodimere, die von den Mitgliedern der ErbB Protein Familie EGFR (ErbB1), HER2 (ErbB2), ErbB3 und ErbB4 gebildet werden und blockiert irreversibel die Signalgebung über diese Rezeptoren. Afatinib wird oral einmal täglich verabreicht. Präklinische Studien legen nahe, dass die Gabe von Afatinib eine größere Wirksamkeit im Hinblick auf die Hemmung des Tumorwachstums hat als die Gabe von Erlotinib. Für die Afatinib Monotherapie besteht eine Marktzulassung für die Behandlung des lokal fortgeschrittenen oder metastasierten nicht kleinzelligen Lungenkarzinoms (NSCLC) mit aktivierenden EGFR Mutationen in einer Dosis von bis zu 50 mg einmal täglich.</p> <p>In einer Phase I Studie zur Sicherheit und Verträglichkeit von Afatinib in Kombination mit Gemcitabin in Patienten mit fortgeschrittenen soliden Tumoren betrug die maximal tolerierte Dosis (MTD) 40 mg Afatinib (kontinuierlich einmal täglich verabreicht) zusammen mit 1000 mg/m<sup>2</sup> Gemcitabin an Tag 1 und Tag 8 eines 21 Tage dauernden Zyklus. Dabei traten in der diesbezüglichen Kohorte keine dosislimitierenden Toxizitäten auf. Deshalb wird in einer anderen noch laufenden Phase II Studie des Sponsors zur Behandlung des metastasierten Pankreaskarzinoms eine Dosis von 40 mg kontinuierlich oral einmal täglich verabreichtem Afatinib in Kombination mit 1000 mg/m<sup>2</sup> Gemcitabin an Tag 1, Tag 8 und Tag 15 eines 28 Tage dauernden Zyklus gegenüber einer Monotherapie mit 1000 mg/m<sup>2</sup> Gemcitabin geprüft.</p> <p>Da mit Gemcitabin/<i>nab</i>-Paclitaxel eine neue zugelassene Behandlungsoption für das metastasierte Pankreaskarzinom zur Verfügung steht, sollte die MTD für Afatinib in Kombination mit Gemcitabin/<i>nab</i>-Paclitaxel bestimmt werden, die dann die empfohlene Dosis für zukünftige Phase II Studien sein wird.</p>
<b>Primäres Studienziel</b>	Das primäre Studienziel ist, die MTD von Afatinib in Kombination mit Gemcitabin/ <i>nab</i> Paclitaxel zu ermitteln. Die ermittelte MTD wird als empfohlene Phase II Dosis dienen (RP2D).
<b>Sekundäres Studienziel</b>	Beurteilung der Sicherheit von Afatinib in Kombination mit Gemcitabin/ <i>nab</i> -Paclitaxel
<b>Exploratives Studienziel</b>	Beurteilung der Wirksamkeit von Afatinib in Kombination mit Gemcitabin/ <i>nab</i> -Paclitaxel
<b>Primärer Endpunkt</b>	<ul style="list-style-type: none"> <li>• MTD von Afatinib in Kombination mit Gemcitabin/<i>nab</i>-Paclitaxel</li> </ul>
<b>Sekundäre Endpunkte</b>	<p><b>Variablen für Sicherheit:</b></p> <ul style="list-style-type: none"> <li>• Dauer der Studienbehandlung</li> <li>• Art, Inzidenz und Schwere von unerwünschten Ereignissen nach NCI CTCAE Version 4.03</li> </ul>
<b>Explorative Endpunkte</b>	<p><b>Variablen für Wirksamkeit:</b></p> <ul style="list-style-type: none"> <li>• Objektive Ansprechrate (ORR)</li> <li>• Progressionsfreies Überleben (PFS)</li> <li>• Gesamtüberleben (OS)</li> </ul>
<b>Studiendesign</b>	Interventionelle multizentrische, offene, Phase Ib Studie. Um die MTD zu ermitteln wird das standardmäßig eingesetzte „3+3“ Design benutzt, d.h. die MTD wird die höchste Dosisstufe sein, bei der bei ≤ 1 von 6 Patienten eine dosis-limitierende Toxizität (DLT) auftritt. Die DLT wird nur im ersten Zyklus bestimmt.
<b>Einschlusskriterien</b>	<ol style="list-style-type: none"> <li>1. Erwachsene Patienten im Alter von ≥ 18 Jahren und ≤ 75 Jahren</li> <li>2. Histologisch (nicht zytologisch) bestätigte Diagnose eines metastasierten duktales Adenokarzinoms des Pankreas (PDAC) [Stadium IV nach UICC TNM Klassifikation Auflage 7 von 2009: jedes T, jedes N, M1]</li> <li>3. Keine Möglichkeit für eine chirurgische Resektion oder Bestrahlung</li> </ol>

	<p>in kurativer Intention</p> <ol style="list-style-type: none"> <li>4. Wenigstens eine unidimensional messbare Tumorkläsion (nach RECIST 1.1)</li> <li>5. ECOG Performance Status 0 - 1</li> <li>6. Lebenserwartung von wenigstens 3 Monaten</li> <li>7. Adäquate Leber-, Nieren- und Knochenmarksfunktion, definiert als:       <ul style="list-style-type: none"> <li>○ Absolute Zahl der Neutrophilen <math>\geq 1,5 \times 10^9/L</math></li> <li>○ Hämoglobin <math>\geq 9 \text{ g/dL}</math></li> <li>○ Thrombozyten <math>\geq 100 \times 10^9/L</math></li> <li>○ Gesamtbilirubin <math>\leq 1,5 \times</math> obere Grenze des Normalwertes. Patienten mit einem Gallengangsstent dürfen eingeschlossen werden, sofern der Bilirubinspiegel nach dem Einsetzen des Stents auf <math>\leq 1,5 \times</math> obere Grenze des Normalwertes sinkt und keine Cholangitis vorliegt.</li> <li>○ AST/GOT und/oder ALT/GPT <math>\leq 2,5 \times</math> obere Grenze des Normalwertes oder im Fall von Lebermetastasen <math>\leq 5 \times</math> obere Grenze des Normalwertes)</li> <li>○ Serumkreatinin im Normalbereich oder Kreatinin-Clearance berechnet nach der CKD-EPI Formel <math>\geq 60 \text{ mL/min/1,73 m}^2</math> bei Patienten mit einem Serumkreatininspiegel oberhalb oder unterhalb des Normalwertes des Prüfzentrums</li> </ul> </li> <li>8. Akzeptable Gerinnungswerte definiert als Prothombinzeit (oder INR) und PTT <math>\leq 1,5 \times</math> obere Grenze des Normalwertes</li> <li>9. Stabile/abnehmende Schmerzsymptome unter Schmerzmedikation oder keine Schmerzen innerhalb der letzten 2 Wochen vor erster Gabe der Studienmedikation (nach Angaben und Einschätzung des Patienten)</li> <li>10. Bei gebärfähigen Frauen muss ein negativer hochsensibler Schwangerschaftstest im Serum im Zeitraum von 7 Tagen vor erster Gabe der Studienbehandlung vorliegen und sie müssen einverstanden sein, sich weiteren Schwangerschaftstests in monatlichen Abständen und am Ende der Behandlung zu unterziehen <b>und</b> gebärfähige Frauen müssen einwilligen und in der Lage sein, während des Verlaufs der Studie und wenigstens einen Monat nach letzter Gabe der Studienmedikation hochwirksame Methoden zur Schwangerschaftsverhütung (Pearl Index <math>&lt; 1</math>) anzuwenden oder aber einwilligen, vollständige Enthaltbarkeit von jedem heterosexuellen Geschlechtsverkehrs im genannten Zeitraum zu praktizieren. Eine weibliche Person nach der Menarche wird als gebärfähig eingeschätzt, sofern sie nicht seit wenigstens einem Jahr natürlicherweise ohne Vorliegen alternativer medizinischer Gründe eine Amenorrhoe hat und sofern sie nicht permanent unfruchtbar ist.</li> <li>11. Männer müssen einwilligen, während der Dauer der Studie und wenigstens 6 Monate nach letzter Gabe der Studienmedikation Kondome beim Geschlechtsverkehr zu verwenden oder aber vollständige Enthaltbarkeit von jedem heterosexuellen Geschlechtsverkehr zu praktizieren.</li> <li>12. Unterschriebene und datierte Einwilligungserklärung vor dem Beginn jeglicher studienspezifischer Maßnahmen</li> <li>13. Einwilligungsfähigkeit des Patient in die Studienteilnahme</li> </ol>
<b>Ausschlusskriterien</b>	<ol style="list-style-type: none"> <li>1. Lokal fortgeschrittenes PDAC ohne Metastasen</li> <li>2. Vorliegen von Ascites</li> <li>3. Bekannte Hirnmetastasen. Bei Patienten mit entsprechenden Symptomen sind bildgebende Untersuchungen des Gehirns zum Ausschluss von Hirnmetastasen erforderlich, nicht aber bei asymptomatischen Patienten.</li> <li>4. Vorherige palliative Chemotherapie oder eine andere systemische palliative Tumortherapie zur Behandlung eines metastasierten PDAC.</li> </ol>

	<ol style="list-style-type: none"> <li>5. Vorherige Behandlung mit Gemcitabin <b>mit Ausnahme</b> einer Behandlung mit Gemcitabin als Monotherapie in einem adjuvanten Setting (nach einer potentiell kurativen R0 oder R1 Resektion) <b>und</b> nur sofern die adjuvante Gemcitabin Mono-Chemotherapie mindestens 6 Monate vor Studieneinschluss beendet wurde</li> <li>6. Vorherige Strahlentherapie des PDAC</li> <li>7. Vorherige gegen die ErbB Familie zielgerichtete Therapie des PDAC (z.B. Erlotinib, Cetuximab, Trastuzumab, Lapatinib)</li> <li>8. Jegliche größere chirurgische Maßnahme innerhalb der letzten 4 Wochen vor Studieneinschluss</li> <li>9. Klinisch signifikante Verschlechterung des Performance Status innerhalb von 2 Wochen vor beabsichtigter erster Gabe der Studienmedikation (nach Anamnese)</li> <li>10. Schwere tumorbedingte Kachexie und/oder bekannter Gewichtsverlust von &gt; 15% innerhalb eines Monats vor Studieneinschluss</li> <li>11. Vorbestehende Polyneuropathie <math>\geq</math> Grad 2 nach CTCAE Version 4.03</li> <li>12. LDH &gt; 2,5 x obere Grenze des Normalwertes</li> <li>13. Signifikante (<math>\geq</math> 20%) Abnahme des Serumalbuminspiegels innerhalb von 2 Wochen vor beabsichtigter erster Gabe der Studienmedikation (nach Anamnese)</li> <li>14. Gastrointestinale Erkrankungen, die die Absorption der Studienmedikation störend beeinflussen könnten und gastrointestinale Erkrankungen, die mit Diarrhoe als Hauptsymptom einhergehen (z.B. Morbus Crohn, Malabsorption) sowie chronische Diarrhoe jeglicher Ätiologie von CTCAE Version 4.03 Grad <math>\geq</math> 2</li> <li>15. Anamnese einer interstiellen Lungenerkrankung (ILD) oder Lungenfibrose oder schweren COPD</li> <li>16. Leberzirrhose Child-Pugh mit Ausnahme einer von Klasse A</li> <li>17. Bekannte Koagulopathie oder Blutgerinnungsstörung</li> <li>18. Anamnese von Bindegewebserkrankungen (e.g. Lupus, Sklerodermie, Arteritis nodosa)</li> <li>19. Andere schwere Begleiterkrankung oder Gesundheitsstörung, welche die Fähigkeit des Patienten, an der Studie teilzunehmen oder seine/ihre Sicherheit während der Studie oder die Auswertung der Studienergebnisse störend beeinflussen könnte, wie z.B. eine aktive Infektion, unkontrollierte Hypertonie, klinisch signifikante kardiovaskuläre Erkrankung wie cerebraler vaskulärer Insult (<math>\leq</math> 6 Monate vor Studienstart), Myokardinfarkt (<math>\leq</math> 6 Monate vor Studienstart), instabile Angina, Herzinsuffizienz <math>\geq</math> NYHA Funktionsklasse 2, schwere Herzrhythmusstörungen, die medikamentös behandelt werden müssen, metabolische Dysfunktion, schwere Nierenerkrankungen</li> <li>20. Andere maligne Tumorerkrankung als das PDAC innerhalb der letzten 5 Jahre vor Studienstart, mit Ausnahme eines adäquat behandelten Carcinoma in situ der Zervix, eines Basalioms oder Plattenepithelkarzinoms der Haut.</li> <li>21. Überempfindlichkeit auf Afatinib, <i>nab</i>-Paclitaxel oder Gemcitabin, oder auf sonstige Bestandteile der Zubereitung oder auf Substanzen mit ähnlicher chemischer oder biologischer Zusammensetzung</li> <li>22. Fortgesetzter Alkohol- oder Drogen- oder Medikamentenmissbrauch</li> <li>23. Schwangere oder stillende Frauen sowie gebärfähige Frauen, die nicht in der Lage sind, entweder hochwirksame Verhütungsmaßnahmen anzuwenden oder aber vollständige Enthaltensamkeit von jeglichem heterosexuellem Geschlechtsverkehr zu praktizieren.</li> <li>24. Gleichzeitige oder kürzliche (innerhalb von 4 Wochen vor erster Gabe der Studienbehandlung) Behandlung mit einer experimentellen Substanz oder Teilnahme an einer interventionellen klinischen Studie</li> </ol>
<b>Behandlungsregime</b>	Um die MTD zu ermitteln, wird ein standardmäßig eingesetztes „3+3“ Design angewandt, das heißt die MTD wird die höchste der geprüften

	<p>Dosisstufen sein, bei welcher bei <math>\leq 1</math> von 6 Patienten eine DLT auftritt. Die Patienten werden mit verschiedenen Dosisstufen von Afatinib in Kombination mit <i>nab</i>-Paclitaxel und Gemcitabin behandelt, die in der folgenden Tabelle aufgelistet sind. Es wird bei den Patienten der ersten Kohorte mit der Dosisstufe 0 als der Startdosisstufe begonnen.</p> <table border="1" data-bbox="443 389 1326 580"> <thead> <tr> <th>Dosisstufe</th> <th>Afatinib</th> <th><i>Nab</i>-paclitaxel</th> <th>Gemcitabin</th> </tr> </thead> <tbody> <tr> <td>Dosisstufe +1</td> <td>40 mg</td> <td>125 mg/m<sup>2</sup> KOF</td> <td>1000 mg/m<sup>2</sup> KOF</td> </tr> <tr> <td>Dosisstufe 0 = Startdosisstufe</td> <td>30 mg</td> <td>125 mg/m<sup>2</sup> KOF</td> <td>1000 mg/m<sup>2</sup> KOF</td> </tr> <tr> <td>Dosisstufe -1</td> <td>30 mg</td> <td>100 mg/m<sup>2</sup> KOF</td> <td>800 mg/m<sup>2</sup> KOF</td> </tr> <tr> <td>Dosisstufe -2</td> <td>30 mg</td> <td>75 mg/m<sup>2</sup> KOF</td> <td>600 mg/m<sup>2</sup> KOF</td> </tr> </tbody> </table> <p>28 Tage werden als ein Zyklus definiert. Afatinib wird kontinuierlich oral einmal täglich eingenommen. Es darf wenigstens 3 Stunden vor der Einnahme und wenigstens 1 Stunde nach der Einnahme der Afatinib-Tabletten keine Nahrung aufgenommen werden. <i>Nab</i>-Paclitaxel wird als intravenöse Infusion über 30 Minuten verabreicht, gefolgt von einer 30-minütigen intravenösen Infusion von Gemcitabin; jeweils an Tag 1, Tag 8, Tag 15 eines jeden Zyklus von 28 Tagen. Falls die vorgesehene Dosis von <i>nab</i>-Paclitaxel/Gemcitabin am Tag 1 nicht wie geplant verabreicht werden konnte oder die Gabe versäumt wurde, wird der betreffende Zyklus solange als noch nicht begonnen eingestuft, bis die für Tag 1 vorgesehene Dosis von <i>nab</i>-Paclitaxel/Gemcitabin tatsächlich verabreicht wird, selbst wenn die Behandlung mit Afatinib fortgesetzt wird. Der Zyklus mit Afatinib in Kombination mit <i>nab</i>-Paclitaxel und Gemcitabin wird alle 28 Tage bis zum Eintritt von Progression oder nicht akzeptabler Toxizität mit der Dosisstufe der jeweiligen Kohorte wiederholt, es sei denn, dass unerwünschte Ereignisse eine weitere Dosisreduktion erforderten.</p>	Dosisstufe	Afatinib	<i>Nab</i> -paclitaxel	Gemcitabin	Dosisstufe +1	40 mg	125 mg/m <sup>2</sup> KOF	1000 mg/m <sup>2</sup> KOF	Dosisstufe 0 = Startdosisstufe	30 mg	125 mg/m <sup>2</sup> KOF	1000 mg/m <sup>2</sup> KOF	Dosisstufe -1	30 mg	100 mg/m <sup>2</sup> KOF	800 mg/m <sup>2</sup> KOF	Dosisstufe -2	30 mg	75 mg/m <sup>2</sup> KOF	600 mg/m <sup>2</sup> KOF
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<p><b>Statistisch analytischer Plan und Methodik</b></p>	<p>In der „Full Analysis Population“ sind alle Patienten, die wenigstens eine Dosis der Studienmedikation Afatinib oder <i>nab</i>-Paclitaxel oder Gemcitabin erhalten haben, erfasst, dieses Patientenkollektiv ist identisch mit der „Safety Population“.</p> <p>Das „Full Analysis Set“ wird herangezogen für die meisten sekundären Parameter für Wirksamkeit und Sicherheit, die beurteilt werden sollen. Das primäre Studienziel der Sicherheitsanalyse wird sein, die DLTs während des ersten Zyklus zu ermitteln, um die MTD zu bestimmen. Für die Ermittlung der MTD sind die folgenden Patienten auswertbar: Bei den Patienten muss entweder eine DLT im ersten Zyklus vor dem Beginn des 2. Zyklus aufgetreten sein <b>oder</b> sie müssen wenigstens 80% der Afatinib Dosis und 60% der <i>nab</i>-Paclitaxel und Gemcitabin- Dosis ihrer jeweiligen Dosisstufe im Zyklus 1 erhalten haben ohne dass eine DLT aufgetreten ist.</p> <p>Falls es vor dem Schließen der Datenbank als notwendig erachtet wird, kann eine per Protokoll Analyse in der Per-Protokoll Population durchgeführt werden, in die nur geeignete Patienten eingeschlossen werden. Kriterien für die Auswählbarkeit werden im Statistischen Analysenplan festgelegt, der die statistische Auswertung ausführlich beschreibt.</p> <p>Die Sicherheitsdaten, die analysiert werden, umfassen die Exposition für die Studienmedikamente Afatinib, <i>nab</i>-Paclitaxel und Gemcitabin (Dosisstufe und Applikationsfrequenz per Zyklus, Behandlungsdauer), Art, Inzidenz und Schwere von unerwünschten Ereignissen, Laborwerte und ECOG-Punktzahl. Deskriptive Übersichtstabellen werden für alle Safety Parameter erstellt.</p> <p>Eine Interimsanalyse der Studiendaten ist nicht vorgesehen.</p>																				
<p><b>Fallzahl</b></p>	<p>Der Algorithmus der einzuschließenden Patienten folgt einem standardmäßig eingesetzten „3+3“ Design, bei welchem eine modifizierte</p>																				

	Fibonacci Sequenz Anwendung findet. Es wird geschätzt, dass maximal 18 Patienten benötigt werden, um die MTD von Afatinib in Kombination mit Gemcitabin/ <i>nab</i> -Paclitaxel zu ermitteln. Die geplante Fallzahl basiert nicht auf einer Fallzahlberechnung.
<b>Studiendauer</b>	<p><i>Rekrutierungszeit:</i> Die Rekrutierungszeit wird auf 12 Monate geschätzt.</p> <p><i>Geschätzte Behandlungsdauer des einzelnen Patienten:</i> Die Behandlungsdauer für den einzelnen Patienten kann differieren, die geschätzte durchschnittliche Behandlungsdauer beträgt 6 Monate.</p> <p><i>Dauer des Follow up nach Beendigung der Behandlung:</i> Bis zum Tod oder bis zur Visite am Ende der Behandlung des letzten Patienten, je nachdem, was früher eintritt.</p> <p><i>Geschätzte Studiendauer:</i> 1,5 Jahre gerechnet vom ersten eingeschlossenen Patienten bis zum Ende der Studie</p> <p><i>Studienbeginn:</i> Erste Studienvisite des ersten Patienten: Datum der unterschriebenen Einverständniserklärung durch den ersten eingeschlossenen Patienten Geplant Q3/2016</p> <p><i>Studienende:</i> Letzte Studienvisite des letzten Patienten ist die Studienvisite am Ende der Behandlung des letzten Patienten Geplant Q3/2018</p>
Anzahl eingeschlossene Patienten	Stand 06/04/2018: 11 von maximal 18; (3+3 Design)

Pancreatic Ductal Adenocarcinoma / metastatic disease (stage IV)

**AIO-PAK-0118: A multi-center, phase I/II study of sequential epigenetic and immune targeting in combination with nab-Paclitaxel/Gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. (SEPION)**

**AIO-Studie**

Studiennummer/-Code:	AIO-PAK-0118 / SEPION-Trial
Status:	in Vorbereitung
Rekrutierungszeitraum:	2018 – 2020
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	12.04.2018

APPLICANT/ COORDINATING INVESTIGATOR / CONTACT	Prof. Dr. med. Jens Siveke Dep. of Medical Oncology and Division of Solid Tumor Translational Oncology West German Cancer Center University Hospital Essen Hufelandstr. 55, 45147 Essen Phone: +49 201 723-3704 Fax: +49 201 723 6725 E-mail: jens.siveke@uk-essen.de
SPONSOR	GWT-TUD GmbH Freiberger Str. 33, 01067 Dresden Phone : +49 351 259 33190 carsta.koehler@gwt-online.de
CONDITION	Patients with metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (stage IV) and no prior chemotherapy for stage IV disease.
OBJECTIVE(S)	<p><b>Primary objective(s)</b></p> <p>The primary objective of the study, including the dose escalating part (Part 1a/Phase I), the dose expansion part (Part 1b/Phase I) as well as the consolidation part (Part 2/Phase II), is to determine the safety and tolerability of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine, followed by sequential immune targeting with PD-L1 blockade in combination with low-dose Lenalidomide in patients with advanced PDAC (Part 1 and 2). Moreover, in the dose escalating part of the study (Part 1a/Phase I), the recommended dose for expansion (RDE) and dose-limiting toxicity (DLT) of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine will be identified.</p> <p><b>Secondary objective(s)</b></p> <ul style="list-style-type: none"> <li>→ to assess ORR, CA19-9 response and disease control rate (=1st DCR after 3 cycles), progression free survival (PFS) and overall survival (OS) in patients treated at the recommended dose and regimen of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine (Part 1a and Part 1b)</li> <li>→ to show a promising clinical activity (refer to 4.2.2) of the selected epigenetic and chemotherapeutic targeting approach from part 1a with regard to the disease control rate (Part 1b/Phase I)</li> <li>→ to assess 2<sup>nd</sup> ORR, 2<sup>nd</sup> CA19-9 response and 2<sup>nd</sup> DCR (after start of Part 2), PFS and OS in patients treated with Durvalumab and Lenalidomide as consolidation treatment (Part 2)</li> </ul>



	<p>→ to assess OS in all patients treated at the recommended dose and regimen</p> <p>→ to characterize the molecular (genetic, transcriptional, epigenetic) and immune properties of PDAC before and 4 weeks after treatment initiation</p> <p><b>Exploratory Translational Sub-studies</b></p> <ol style="list-style-type: none"> <li>1. Exploratory analyses on tumor biopsy samples may include but will not be limited to: Genetic, epigenetic and expression profiling of tumor cells and immune phenotyping before and after therapy initiation including next generation sequencing (NGS)-based DNA/RNA-seq, genome-wide methylation profiling, immune cells infiltrate characterization (e.g. CD8, CD4, Treg, Macrophages and DC), immune phenotyping (e.g. interferon-stimulating genes such as IFI16, IFI27, IFI44, IFI44L, MX1 and OASL; induction of endogenous retroviral sequences (=ERVs) such as Syncytin-1-3, ERV-3, env-K, env-H and env-Fc1-2) by epigenetic treatment.</li> <li>2. An exploratory objective of this study is to evaluate biomarkers in liquid biopsies, including but not limited to tracking oncogenic mutations such as KRAS in cell free DNA (ctDNA analysis), cytokines, chemokines, circulating receptors or ligands, other immune-related biomarkers (e.g. interleukin 2, interferon-<math>\gamma</math>) and immuno-phenotyping (e.g. CD8, CD4, Treg, Macrophages).</li> </ol>
INTERVENTION(S)	<p>The dose escalation part of the study will employ a standard 3 + 3 design to test safety and tolerability of histone deacetylases (HDAC) inhibition with Romidepsin (Arm A), DNA methyltransferases (DNMT) inhibition with Azacitidine (Arm B) or both agents (Arm C) in combination with nab-Paclitaxel/Gemcitabine (<b>part 1a</b>). Study treatment is given until intolerable toxicity for a maximum of 3 cycles as defined in the protocol. Treatment will escalate until the recommended dose for expansion (RDE) is identified. In the event that dose level 1 has 2 dose-limiting toxicities (DLT) the dose will be reduced and a dose level -1 will be included.</p> <p>DLT, defined as any of the following toxicities occurring during treatment cycle 1 of a respective dose level and regarded to be related to the studied drug combination. Common terminology criteria for adverse events (CTCAE) 4.03 will be used to assess toxicities:</p> <ul style="list-style-type: none"> <li>- absolute neutrophil count <math>&lt; 0.5 \times 10^9/L</math> for <math>\geq 7</math> days</li> <li>- platelets <math>&lt; 25 \times 10^9/L</math> for <math>\geq 7</math> days (severe thrombopenia)</li> <li>- CTCAE grade <math>\geq 3</math> non-hematologic toxicity related to study treatment despite adequate therapy</li> <li>- Drug-related, non-remitting CTCAE grade 2 or unexpected toxicity may be declared a DLT after thorough consultation between the investigator and the sponsor</li> </ul> <p>For the dose expansion part (<b>part 1b</b>) of the study, one of the treatment arms (Arm C over B over A) will be continued using a Simon Two-stage design to a maximum of 35 patients. Selection of the expansion arm will be as follows in case of successful determination of the RDE: arm C preferred over arm B over arm A. In case of no determination of RDE in arm C, arm B will be preferred over arm A. In case of no determination of RDE in arm B, arm A will be selected.</p> <p>All patients from <b>part 1a and 1b</b> will be treated for a total of three cycles and will then enter the second part of the study in case of disease control, but still measurable disease (partial response [PR], stable disease [SD]). In case of intolerable toxicity, patients will deescalate to a lower dose level as defined in the protocol.</p> <p>Because of our aim to study a consolidation concept in the second part of the study, a sufficient number of patients with controlled disease after 3 cycles of therapy is needed based on the statistical considerations. Thus, in addition to the patients undergoing part 1a (Dose escalation) and part 1b (Dose Expansion), patients treated with nab-Paclitaxel/Gemcitabine alone</p>

	<p>will be additionally recruited in this study (so-called "standard arm"). The number of patients in the standard group may vary on the recruited number of patients in Parts 1a and 1b (total target number of patients for Part 1 including standard group = 75), so that 41 patients will be available for Part 2 given a presumed 60% DCR after 3 cycles in part 1 and a drop-out rate of 10%.</p>
<p>KEY EXCLUSION CRITERIA</p>	<p><b>Principal exclusion criteria</b></p> <ol style="list-style-type: none"> <li>1. Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse event from agents administered more than 4 weeks earlier;</li> <li>2. Patients may not be receiving any other investigational agents;</li> <li>3. Patients who have previously received Romidepsin, Azacitidine, Lenalidomide or Durvalumab;</li> <li>4. Patients with untreated or uncontrolled brain metastases or leptomeningeal disease;</li> <li>5. Presence of other active illnesses;</li> <li>6. Any known cardiac abnormalities such as:       <ul style="list-style-type: none"> <li>• Congenital long QT syndrome</li> <li>• QTc interval <math>\geq</math> 500 milliseconds;</li> </ul> </li> <li>7. Myocardial infarction within 6 months of C1D1. Subjects with a history of myocardial infarction between 6 and 12 months prior to C1D1 who are asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event may participate;</li> <li>8. Other significant EKG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min);</li> <li>9. Symptomatic coronary artery disease (CAD), e.g., angina Canadian Class II-IV (see Appendix III). In any patient in whom there is doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present;</li> <li>10. Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix IV) and/or known ejection fraction <math>&lt;</math>40% by MUGA or <math>&lt;</math>50% by echocardiogram and/or magnetic resonance imaging (MRI);</li> <li>11. A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter defibrillator (AICD);</li> <li>12. Concomitant use of any drug known to prolong QT interval;</li> <li>13. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole);</li> <li>14. Patients with human immunodeficiency virus (HIV), hepatitis B or C (requirement for screening);</li> <li>15. Patients with any other medical or psychological condition deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results;</li> <li>16. Diagnosis of immunodeficiency or any condition that requires systemic steroid therapy or other forms of immunosuppressive therapy;</li> <li>17. Prior thromboembolic events;</li> <li>18. History of other malignancies, except:       <ul style="list-style-type: none"> <li>• Malignancy treated with curative intent and with no known active disease present for <math>\geq</math>2 years before the first dose of study drug and felt to be at low risk for recurrence by investigator.</li> <li>• Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.</li> <li>• Adequately treated carcinoma in situ without current evidence of disease (all treatment of which should have been completed 6 months prior to randomization).</li> <li>• Any uncontrolled active systemic infection;</li> </ul> </li> </ol>

	<p>19. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk;</p> <p>20. History of stroke or intracranial hemorrhage within 6 months prior to enrollment;</p> <p>21. History of interstitial lung disease, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis;</p> <p>22. Unable to swallow oral medication or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction;</p> <p>23. Concomitant use of warfarin or other Vitamin K antagonists;</p> <p>24. Known hypersensitivity to any study drug;</p> <p>25. Unwilling or unable to participate in all required study evaluations and procedures. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information;</p> <p>26. Pregnant females, breast feeding females or females of childbearing potential unable to perform adequate contraceptive measures or practice complete abstinence from heterosexual intercourse;</p> <p>27. Subject is an employee of GWT-TUD GmbH.</p>
KEY INCLUSION CRITERIA	<p><b>Principal inclusion criteria</b></p> <p>1. Patients must have histologically confirmed PDAC;</p> <p>2. Patients must have metastatic disease (stage IV) and not received prior chemotherapy for Stage IV disease;</p> <p>3. Patients must not have received the following drugs before: Azacitidine, Romidepsin, any checkpoint-inhibitor or immunomodulating agents such as IMiDs (Lenalidomide);</p> <p>4. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with response evaluation criteria in solid tumors (RECIST) criteria v. 1.1;</p> <p>5. Male or female, age <math>\geq 18</math> years;</p> <p>6. Eastern Cooperation Oncology Group (ECOG) performance status 0 or 1;</p> <p>7. Patients must have normal organ and marrow function as defined below:</p> <ul style="list-style-type: none"> <li>• Leukocytes <math>\geq 2,500/\text{mcl}</math></li> <li>• Absolute neutrophil count <math>\geq 1,500/\text{mcl}</math></li> <li>• Platelets <math>\geq 100,000/\text{mcl}</math></li> <li>• Haemoglobin <math>\geq 8 \text{ g/dL}</math></li> <li>• Total bilirubin <math>&lt; 2 \text{ mg/dL}</math></li> <li>• Aspartate aminotransferase/alanine aminotransferase (AST/ALT) (SGOT/SGPT) <math>\leq 2.5 \times</math> upper limit of normal (ULN) and <math>\leq 5</math> in the case of liver metastasis</li> <li>• Serum creatinine <math>\leq 1.5 \text{ mg/dL}</math> or calculated creatinine clearance <math>&gt; 60 \text{ mL/min}</math></li> </ul> <p>8. Patients must be recovered from the effects of any prior surgery;</p> <p>9. Ability to provide written informed consent and to understand and comply with the requirements of the study;</p> <p>10. All subjects must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study treatment;</p> <p>11. All subjects must agree not to share medication;</p> <p>12. Females of childbearing potential (FCBP) must:</p> <ul style="list-style-type: none"> <li>• Understand the potential teratogenic risk to the unborn child</li> <li>• Understand the need and agree to utilize two reliable forms of contraception simultaneously without interruption for at least 28 days before starting study drug, while participating in the study (including dose interruptions), and for at least 90 days after study treatment discontinuation</li> <li>• Understand and agree to inform the investigator if a change or stop of method of contraception is needed</li> <li>• Be capable of complying with effective contraceptive measures (refer to appendix 17.VI).</li> <li>• Be informed and understand the potential consequences of pregnancy and the need to notify her study doctor immediately if</li> </ul>

	<p>there is a risk of pregnancy.</p> <ul style="list-style-type: none"> <li>• Understand the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test.</li> <li>• Understand the need and accept to undergo pregnancy testing based on the frequency outlined in this protocolacknowledges that she understands the hazards Lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of Lenalidomide.</li> <li>• Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.</li> <li>• Males must understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP.</li> <li>• Males must agree to use a latex condom during any sexual contact with FCBP while participating in the study and for 90 days following discontinuation from this study, even if he has undergone a successful vasectomy.</li> <li>• Males must also agree to refrain from donating semen or sperm while on the study drugs and for 90 days after discontinuation from this study treatment.</li> <li>• Males must agree not to father a child during the course of the trial and for at least 6 months after last administration of study drugs.</li> </ul> <p>13. A female subject is considered to be of childbearing potential unless she is age <math>\geq</math> 50 years and naturally amenorrhoe for <math>\geq</math> 1 year, or unless she is surgically sterile.</p>
OUTCOME(S)	<p><b>Primary endpoint(s)</b></p> <p>The primary endpoint is the determination of the maximal tolerated dose (MTD) and RDE for the dose escalating part (Part 1a/Phase I), the dose expansion part (Part 1b/Phase I) as well as the consolidation part (Part 2/Phase II) of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine, followed by sequential immune targeting with PD-L1 blockade in combination with low-dose Lenalidomide in patients with advanced PDAC (Part 1 and 2).</p> <p><b>Secondary endpoint(s)</b></p> <p>The secondary endpoints are defined as:</p> <p>Part 1:</p> <ul style="list-style-type: none"> <li>→ Overall response rate (ORR)</li> <li>→ CA19-9 Response</li> <li>→ Disease-control rate (DCR) at 3-month</li> <li>→ Overall survival (OS)</li> <li>→ Translational endpoints</li> </ul> <p>Part 2:</p> <ul style="list-style-type: none"> <li>→ Overall response rate (ORR)</li> <li>→ CA19-9 Response</li> <li>→ DCR at 3-month and 6-month</li> <li>→ Overall survival (OS)</li> <li>→ Translational endpoints</li> </ul>
STUDY TYPE	<p>This will be an interventional, multicenter, phase I/II clinical study of sequential epigenetic and immune targeting in combination with nab-Paclitaxel/Gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. The study will be accompanied by a broad translational research project with several aims.</p>

STATISTICAL ANALYSIS	<p><u>Descriptive analyses</u></p> <p>Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by treatment group. Frequency tables for categorical data will be provided. Medical history findings will be summarized using MedDRA terms.</p> <p><u>Safety examinations</u></p> <p>Individual listings of AEs will be provided. The incidence of treatment-emergent AEs and drug-related AEs, respectively, will be summarized by treatment using MedDRA terms. All AEs starting or worsening after first study drug administration up to 30 days after last study drug administration will be considered as treatment-emergent.</p> <p>In summary, the trial design is based on the following assumptions:</p> <ul style="list-style-type: none"> <li>• The experimental therapy in part 1b would be rated as insufficiently active, if the true DCR at &gt; 12 weeks is 60% or lower, considered to be futile.</li> <li>• The experimental therapy would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true DCR amounted to 83% or more.</li> <li>• Probability to accept the experimental therapy as promising (&gt; 83% DCR) with respect to efficacy, in spite of a true DCR of ≤ 60%: 0.05 (type I error)</li> <li>• Probability to reject the experimental therapy as not sufficiently efficient (≤ 60%), although the true DCR is promising (&gt; 83%): 0.1 (type II error, corresponding to a power of 90%).</li> </ul> <p>For the part 2 (consolidation treatment after three cycles of nab-Paclitaxel/Gemcitabine-based therapy with or without additional epigenetic treatment) sample size is based on continued safety evaluation and evaluation of (subsequent) overall response rate (ORR). ORR is defined using modified RECIST 1.1 as the proportion of subjects with a response defined as confirmed CR or confirmed PR ≥ 16 weeks. Only patients with at least stable disease (SD by RECIST 1.1) and still measurable lesions will proceed from Part 1 to Part 2 of this study.</p>
SAMPLE SIZE	<p>Up to 75 patients are planned to be enrolled. The sample size is based on disease control rate and ORR and these calculations are made without adjusting for multiplicity.</p> <p>Because of our aim to study a consolidation concept in the second part of the study, a sufficient number of patients with controlled disease after 3 cycles of therapy is needed based on the statistical considerations. Thus, in addition to the patients undergoing part 1a (Dose escalation) and part 1b (Dose Expansion), patients treated with nab-Paclitaxel/Gemcitabine alone will be additionally recruited in this study (so-called “standard arm”). The number of patients in the standard group may vary on the recruited number of patients in Parts 1a and 1b (total target number of patients for Part 1 including standard group = 75), so that 41 patients will be available for Part 2 given a presumed 60% DCR after 3 cycles in part 1 (Goldstein 2015) and a drop-out rate of 10%.</p> <p>According to these parameters, and using the variant out of the class of optimal two-stage designs by SIMON (1989), that leads to the lowest maximum number of patients required (optimal approach), n = 13 patients have to be recruited in the first stage. The experimental combination will be rejected, if only 8 or less of these patients fulfill the criterion of clinical benefit. In the second step, further patients will be recruited up to a total number of 35 cases. A clinical benefit finding in 25 or more out of these will allow to reject the hypothesis of insufficient efficacy. The final conclusion of the trial will depend on the definite DCR (and its confidence interval) as well as the complete information on type, frequency and severity of toxicities.</p>

TRIAL DURATION	<p><b>For the individual patient:</b></p> <p>About 3 months induction part, thereafter 12 months follow-up beginning after start of the stage 2 consolidation therapy and up to 2 years for AEs and SAEs.</p> <p><b>Planned study schedule</b></p> <table border="0"> <tr> <td>First Patient First Visit</td> <td>Q3/2018</td> </tr> <tr> <td>Last Patient First Visit</td> <td>Q2/2020</td> </tr> <tr> <td>Last Patient End of Trial</td> <td>Q1/2021</td> </tr> <tr> <td>Last Patient Last Follow Up</td> <td>Q1/2022</td> </tr> <tr> <td>Final Study report</td> <td>Q1/2023</td> </tr> </table>	First Patient First Visit	Q3/2018	Last Patient First Visit	Q2/2020	Last Patient End of Trial	Q1/2021	Last Patient Last Follow Up	Q1/2022	Final Study report	Q1/2023
First Patient First Visit	Q3/2018										
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Last Patient Last Follow Up	Q1/2022										
Final Study report	Q1/2023										
PARTICIPATING CENTERS	8-10										

Metastasiertes Adenokarzinom des Pankreas, Zweit- u. Drittlinie

**AIO-PAK-0116: A health service research study to investigate survival of metastatic pancreatic cancer patients after sequential chemotherapy: An AIO phase II cross over trial (PANTHEON)**

**AIO-Studie**

Studiennummer/-Code: AIO-PAK-0116 - PANTHEON  
 Status: in Vorbereitung  
 Rekrutierungszeitraum: 2017 – 2021 (geplant)  
 Weitere Zentren: sind sehr erwünscht  
 Letzte Aktualisierung: Apri 2018

Study Type	Open label, randomized, sequential cross-over phase II study
Verantwortlicher Studienleiter nach AMG	Prof. Dr. med. Helmut Oettle, Praxis und Tagesklinik Friedrichstr. 53, 88045 Friedrichshafen Telefon: +49 7541 289956-0, FAX.: +49 7541 289950-10 E-Mail: helmut.oettle@charite.de
Kontaktadresse/ Kontaktperson:	AIO-Studien-gGmbH, Dr. Aysun Karatas Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 8145 344 31, Fax +49 30 3229 329 26 info@aio-studien-ggmbh.de
Studienziele/ Objectives	<p><u>Primäres Studienziel:</u> To assess efficacy of second and third-line therapies (OFF vs. FOLFIRI) in a sequential cross-over design in patients pretreated with nab-paclitaxel/gemcitabine first-line. The primary objective will be the demonstration of non-inferiority of FOLFIRI treatment regime compared to OFF with regard to progression-free-survival during 2<sup>nd</sup>-line therapy.</p> <p><u>Sekundäre Studienziele:</u> Assessment of safety and feasibility of the sequential cross-over treatment approach for advanced treatment lines in PDAC</p>

Patientenzahl Number of patients	Geplant: 204 Patienten Bereits eingeschlossen: 2 (05.04.2018)
Rekrutierungszeitraum	Start Q4 2017 Last Patient In: approx. Q1 2021
Haupt-Einschlusskriterien Key inclusion criteria	<ol style="list-style-type: none"> <li>14. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>15. Age <math>\geq</math> 18 years at time of study entry</li> <li>16. Irresectable adenocarcinoma of the pancreas previously treated in the palliative setting with gemcitabine and <i>nab</i>-paclitaxel (Abraxane<sup>®</sup>)</li> <li>17. Adequately documented recurrence and disease status after/under 1<sup>st</sup> line (Best response, duration of treatment, time to progression, preexisting PNP and other side effects)</li> <li>18. Radiologically confirmed disease progression during 1<sup>st</sup>-line therapy and measurable reference cancer site(s) as defined by RECIST1.1</li> <li>19. Randomization and start of 2<sup>nd</sup>-line treatment possible within 4 weeks after radiologically documented disease progression during 1<sup>st</sup>-line therapy</li> <li>20. ECOG performance status 0-2</li> <li>21. No prior radiotherapy</li> <li>22. Adequate blood count, liver-enzymes, and renal function: <ul style="list-style-type: none"> <li>• Absolute neutrophil count (ANC) <math>\geq</math> <math>1.5 \times 10^9/L</math> (<math>&gt; 1500</math> per <math>mm^3</math>)</li> <li>• Platelet count <math>\geq</math> <math>100 \times 10^9/L</math> (<math>&gt;100,000</math> per <math>mm^3</math>)</li> <li>• AST (SGOT)/ALT (SGPT) <math>&lt;</math> <math>2.5 \times</math> institutional upper limit of normal unless liver metastases are present, in which case it must be <math>&lt;</math> <math>5 \times</math> ULN</li> <li>• Serum creatinine <math>\geq</math> CL60 mL/min calculations according to local standard</li> <li>• Bilirubin <math>&lt;</math> 3 ULN</li> </ul> </li> <li>23. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: <math>\geq</math>60 years old and no menses for <math>\geq</math>1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.</li> <li>24. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.</li> </ol>
Haupt-Ausschlusskriterien / Key exclusion criteria	<ol style="list-style-type: none"> <li>1. Serious cardiovascular disease (eg, unstable coronary artery disease or myocardial infarction within 3 months of study start)</li> <li>2. Preexisting polyneuropathy (PNP) <math>\geq</math> grade 3 [National Cancer Institute Common Toxicity Criteria grade 3 or 4 sensory or motor neuropathy]</li> <li>3. Prior or concurrent malignancy (other than pancreatic cancer) which either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin</li> <li>4. History of DPD deficiency</li> <li>5. Morbus Gilbert</li> <li>6. History of hypersensitivity to any of the study drugs or any of the constituents of the products</li> <li>7. Medication that is known to interfere with any of the agents applied in the trial.</li> <li>8. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year)</li> </ol>

	<p>9. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results</p> <p>10. Any medical condition that contraindicates dosing with any of the IMPs or constitutes a safety risk for the patient including but not limited to:</p> <ol style="list-style-type: none"> <li>a) chronic inflammatory bowel disease and/or bowel obstruction.</li> <li>b) active uncontrolled infection</li> <li>c) clinically significant bleeding or bleeding diathesis</li> <li>d) clinically significant stomatitis</li> <li>e) active ulceration of the gastrointestinal tract</li> </ol> <p>11. Previous enrollment or randomization in the present study (does not include screening failure).</p> <p>12. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>13. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p>
<p>Therapieschema Scheme of therapy</p>	<p>The OFF-regimen is an established second line treatment for adenocarcinoma of the pancreas.</p> <p>For the 5-FU/Irinotecan regimen, there is no formal comparison of the different regimen available. In order to ensure comparability, a schedule similar to the OFF regimen was chosen.</p> <p>OFF:</p> <ul style="list-style-type: none"> <li>• 5-FU 2000 mg/m<sup>2</sup> as 24 hour infusion + Na folinic acid 200 mg/m<sup>2</sup> on D1, 8, 15, 22 Oxaliplatin 85 mg/m<sup>2</sup> on D8, 22</li> <li>• 3 weeks rest after D22;</li> <li>• Cycle q42d</li> </ul> <p>FOLFIRI (all on day 1)</p> <ul style="list-style-type: none"> <li>• Irinotecan 180 mg /m<sup>2</sup></li> <li>• 5-FU 400 mg/m<sup>2</sup> (bolus) + 2400 mg/m<sup>2</sup> as 46 hour infusion</li> <li>• Na folinic acid 200 mg/m<sup>2</sup></li> <li>• Cycle q2w</li> </ul> <p>Treatment until progressive disease or intolerable toxicity or withdrawal of consent. Treatment cross-over is only permitted after radiologically confirmed progression during 2<sup>nd</sup>-line treatment.</p> <p>Key study procedures (and routine procedures):</p> <ul style="list-style-type: none"> <li>• Tumor assessment according to standard of care q10w</li> <li>• Routine tumormarker assessments</li> <li>• Neurotoxicity assessments</li> </ul>
<p>Rationale</p>	<p>The prognosis of patients with locally advanced or metastatic pancreatic cancer after failure of first line treatment is dismal. In the era of gemcitabine monotherapy as standard of care, the OFF-regimen was the only approach with a proven overall survival benefit leading to an improvement in median OS of about two months.</p> <p>Nowadays, the combination of gemcitabine and nab-paclitaxel has been approved for first line treatment based on a similar improvement of OS. So far,</p>

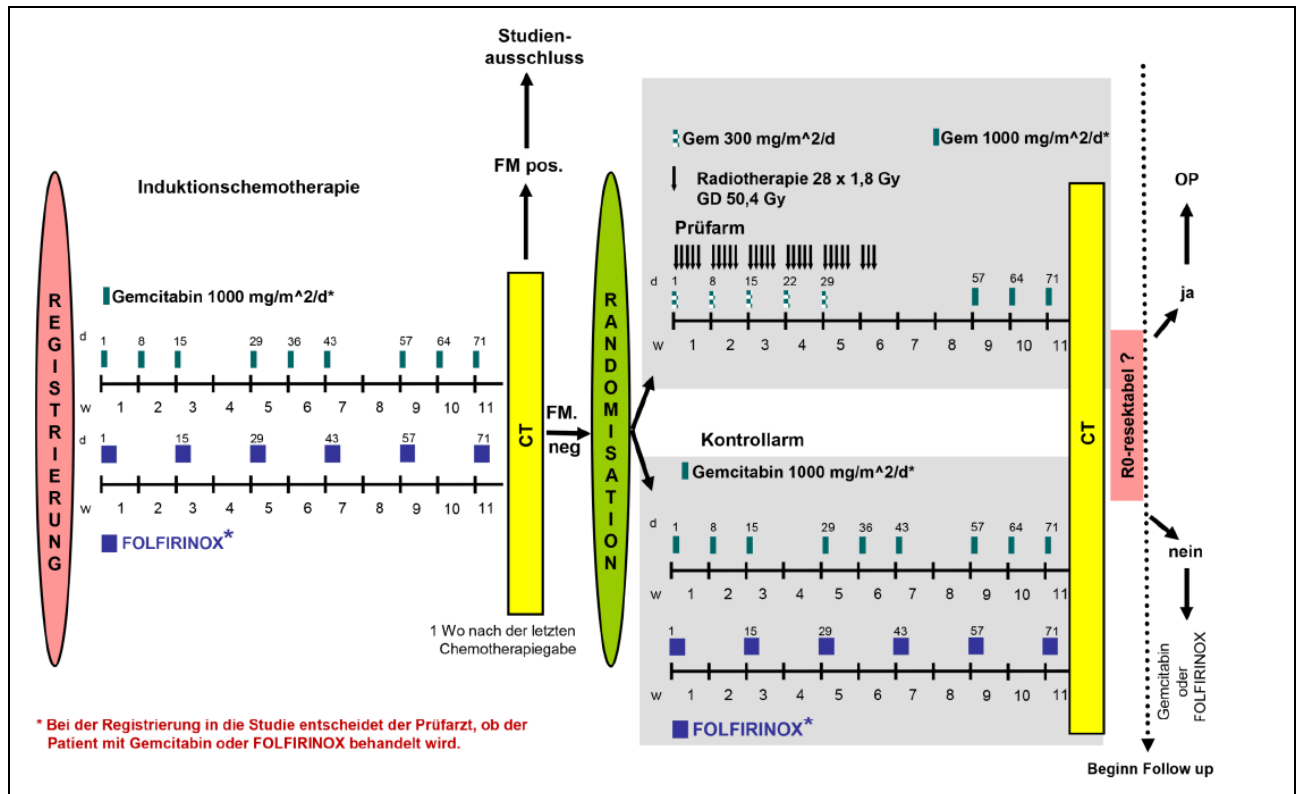


	<p>no second line treatment has been formally evaluated following this regimen. Due to the neurotoxicity which is immanent to both nab-paclitaxel and oxaliplatin, concerns exist regarding the feasibility of the two regimen when given sequentially directly one after another.</p> <p>Irinotecan has been evaluated in combination with 5-FU in a number of phase II-trials. Furthermore, the intensive four drug combination of FOLFIRINOX has been shown to be superior to Gemcitabine in first line treatment.</p> <p>We assume, that both OFF and FOLFIRI are active regimen in pretreated pancreatic cancer, that both a non cross-resistant and can be given sequentially in a part of the patients as second and third line treatment to selected patients.</p>
Statistik (optional)	<p>Sample size estimation: It is hypothesized that OFF and FOLFIRI chemotherapy show similar efficacy with regard to PFS in 2<sup>nd</sup>-line treatment of patients with metastatic PDAC. The test hypothesis is formulated to demonstrate non-inferiority of FOLFIRI treatment compared to OFF.</p> <p>Under the proportional hazards assumption, the hazard ratio <math>HR = h_{\text{FOLFIRI}} / h_{\text{OFF}}</math> is constant across time.</p> <p>For a given non-inferiority margin <math>HR_0=1.5</math> (the maximum ratio of clinical insignificance; <math>PFS_{\text{OFF}} = 3</math> month, <math>PFS_{\text{FOLFIRI}} = 2</math> month), the statistical hypotheses tested are:</p> $H_0 : HR \geq HR_0 \text{ vs. } H_1 : HR < HR_0$ <p>A non-inferiority Log-Rank test with an overall sample size of <b>N=204</b> subjects (102 in the OFF group and 102 in the FOLFIRI group) achieves 80.1% power at a one-sided <math>\alpha=0.025</math> significance level to detect a non-inferiority hazard ratio of 1.5 when the actual hazard ratio is an equivalence hazard ratio of 1.0 and the OFF group hazard rate is <math>h_{\text{OFF}}=0.23</math> (<math>PFS_{\text{OFF}}=3</math> month).</p> <p>Total Follow-up is 40 month (second-line treatment) of which subject accrual (entry) occurs in the first 36 month.</p> <p>The accrual pattern across time is assumed to be uniform. The proportion dropping out of each study group is 0.004 subjects per month (equals a total study drop-out of 16%).</p> <p>In order to analyse the primary endpoint <b>191 events</b> need to be observed.</p>

Local begrenztes, inoperables Pankreaskarzinom**Randomisierte Phase-III-Studie zum Stellenwert einer Radiochemotherapie nach Induktionschemotherapie beim lokal begrenzten, inoperablen Pankreaskarzinom: Chemotherapie gefolgt von Radiochemotherapie im Vergleich zur alleinigen Chemotherapie (CONKO-007)****AIO-assoziierte Studie**

Studiennummer/-Code:	CONKO-007
Status:	in Rekrutierung
Rekrutierungszeitraum:	2013 – 2019
Weitere Zentren:	derzeit nur mit Warteliste
Letzte Aktualisierung	April 2018

Kurztitel	CONKO-007, EudraCT-Nr.: 2009-014476-21
Art der Studie	Phase-III
Studienleiter nach AMG	Prof. Dr. Rainer Fietkau Universitätsklinikum Erlangen, Strahlenklinik
Kontaktadresse/ Kontaktperson:	Dr. Dorota Lubgan Universitätsklinikum Erlangen, Strahlenklinik Universitätsstr. 27, 91054 Erlangen Tel.: 09131-85-33968 Fax: 09131/85-33996 E-Mail: st-studiensekretariat@uk-erlangen.de
Studienziele/ Objectives	<u>Primäres Studienziel:</u> <ul style="list-style-type: none"> <li>• Gesamtüberlebenszeit</li> </ul> <u>Sekundäre Studienziele:</u> <ul style="list-style-type: none"> <li>• Tumorfremie Überlebenszeit</li> <li>• Rate an lokoregionären Rezidiven bzw. Progressionsrate</li> <li>• Rate an Fernmetastasen</li> <li>• Akute und chronische Toxizität der RCT</li> <li>• Lebensqualität</li> <li>• Remissionsraten</li> <li>• Häufigkeit des Erreichens einer Resektion nach Chemotherapie oder Radiochemotherapie</li> <li>• Häufigkeit des Erreichens einer R0-Resektion nach Chemotherapie oder Radiochemotherapie</li> </ul>
Zielparameter/ Objectives	Geprüft wird die Fragestellung, ob beim inoperablen, nicht metastasierten Pankreaskarzinom nach einer Induktionschemotherapie mit drei Zyklen Gemcitabin bzw. 6 Zyklen FOLFIRINOX durch eine zusätzliche Radiochemotherapie im Vergleich zu einer alleinigen Chemotherapie eine Verbesserung der Prognose erreicht werden kann.
Patientenzahl	Geplant: 830 Patienten Bereits eingeschlossen: 350
Rekrutierungszeitraum	Q1 2013-Q1 2019 (verlängert)
Weitere teilnehmende Zentren erwünscht?	keine weiteren Zentren mehr möglich Ursprünglich 24 Zentren geplant, 52 Zentren eröffnet (Stand 09.04.2018)



Metastasiertes Pankreaskarzinom, Retrospektive Analyse**AIO-YMO/PAK-0515: Histopathologische, molekulargenetische und klinische Charakterisierung von Patienten mit isolierten Lungenmetastasen eines Pankreaskarzinoms.**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/PAK-0515
Status:	retrospektiv
Rekrutierungszeitraum:	2016 - 2019
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018
Art der Studie Study Type	Retrospektive Analyse
Kontaktadresse/ Kontaktperson:	Dr. Kruger / Prof. Böck (Verantwortlicher Studienleiter nach AMG) Comprehensive Cancer Center Medizinische Klinik und Poliklinik III Hämatologie und Onkologie Klinikum der Universität München, Campus Großhadern Marchioninistraße 15, 81377 München
Die Synopse finden ist zu finden unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologists!	

Registerstudie**AIO-YMO/PAK-0215 Eine multizentrische Registerstudie zur Erfassung klinischer, epidemiologischer und biologischer Parameter beim duktalem Adenokarzinom des Pankreas (PDAC, PaCaReg)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/PAK-0215 - PDAC, PaCaReg
Status:	Einschluss des 1. Patienten steht unmittelbar bevor
Rekrutierungszeitraum:	Geplanter Start Q2/2018
Weitere Zentren:	bitte wenden Sie sich ggfs. an die Studienleitung
Letzte Aktualisierung	April 2018
Studienleitung	Dr. med. Thomas Ettrich Universitätsklinikum Ulm, Klinik für Innere Med. I 89081 Ulm, Tel. 0731-500 44774, thomas.ettrich@uniklinik-ulm.de Mentoring <i>Investigator</i> : Univ.-Prof. Dr. Thomas Seufferlein Universitätsklinikum Ulm, Klinik für Innere Medizin I
Die Synopse finden ist zu finden unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologists!	

## Arbeitsgruppe Supportive Therapie

### Therapie der tiefen Venenthrombose/Lungenarterienembolie bei Patienten mit aktiver Tumorerkrankung

#### **AIO-SUP-0115/ass. : Rivaroxaban in the treatment of venous thrombembolism (VTE) in cancer patients – a randomized phase III study (CONKO-011)**

##### AIO-assoziierte Studie

Studiennummer/-Code: AIO-SUP-0115/ass (CONKO-011)

Status: in Rekrutierung

Rekrutierungszeitraum: 2015 – 2019

Weitere Zentren: sind erwünscht

Letzte Aktualisierung April 2018

Study Type	Phase-III
Principal investigator	Prof. Dr. med. Hanno Riess Charité – Universitätsmedizin Berlin, Charité Centrum für Tumormedizin CONKO-Studiengruppe Augustenburger Platz 1, 13353 Berlin
Study coordinator	PD Dr. med. Marianne Sinn CONKO-Studiengruppe, Augustenburger Platz 1, 13353 Berlin Tel: +49 -030 450-553222, Fax +49-030 450-553959 conko-studien@charite.de
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Tel: +49 30 814534431; Fax: +49 30 322932926 info@aio-studien-ggmbh.de
Study Objectives	<p><u>Primary objective:</u></p> <ul style="list-style-type: none"> <li>• Patient's treatment satisfaction / quality of life measured with the anti-clot treatment scale (ACTS Burden)</li> </ul> <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> <li>• Newly diagnosed and objectively confirmed acute venous thromboembolism</li> <li>• Active malignancy</li> <li>• Life expectancy of at least 6 months</li> <li>• Performance-Status according to Karnofsky Performance Scale <math>\geq 70</math> %</li> <li>• Patient's compliance and geographical situation allowing an adequate follow up, especially the willingness to visit the study center regularly for at least 3 months after randomization</li> <li>• platelets <math>\geq 100.000</math> /<math>\mu</math>l, INR <math>&lt; 1.5</math>, PTT <math>&lt; 40</math> sec.</li> <li>• written informed consent of the patient prior to any procedure in connection with the study</li> </ul>
Zielparameter/ Objectives	Patient-reported treatment satisfaction (convenience) with Rivaroxaban in the treatment of acute VTE in cancer patients in comparison with the standard treatment with low molecular weight heparin (LMWH) after 3 months of anticoagulant treatment
Number of patients	A total of 450 patients will be randomized in a 1:1 ratio Currently randomized patients: 159 (March 2018)
Anticipated start date	November 2015
Study Centers	Number of sites total: approx.: 40
More centres?	Yes

Key inclusion criteria	<ul style="list-style-type: none"> <li>• Newly diagnosed and objectively confirmed acute venous thromboembolism</li> <li>• Active malignancy</li> <li>• Life expectancy of at least 6 months</li> <li>• Performance-Status according to Karnofsky Performance Scale <math>\geq</math> 70 %</li> <li>• Patient's compliance and geographical situation allowing an adequate follow up, especially the willingness to visit the study center regularly for at least 3 months after randomization</li> <li>• Platelets <math>\geq</math> 100.000 /<math>\mu</math>l, INR &lt; 1.5, PTT &lt; 40 sec.</li> <li>• written informed consent of the patient prior to any procedure in connection with the study</li> <li>• male and female patients with an age of at least 18 years</li> </ul>
Key exclusion criteria	<ul style="list-style-type: none"> <li>• therapeutic anticoagulation 96h prior to study treatment</li> <li>• known allergic reactions against the study drugs or the substances included therein</li> <li>• known conditions associated with high risk of bleeding, known history of hemorrhagic diathesis</li> <li>• acute clinically relevant bleeding in the last 2 weeks</li> <li>• any history of spontaneous major/cerebral bleeding</li> <li>• history of HIT II</li> <li>• pregnant or breast-feeding women. Women of child-bearing potential must have a negative pregnancy test performed &lt; 7 days prior to start of the treatment</li> <li>• severe renal insufficiency (GFR &lt; 30 ml/min)</li> <li>• liver disease with coagulation impairment, including Child B and C cirrhosis/acute medical illness</li> <li>• treatment of the underlying cancer with experimental therapies (in Germany not approved)</li> </ul>
Scheme of therapy	<p><b>Arm A:</b> Rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily</p> <p><b>Arm B:</b> LMWH in therapeutic dosage (1–2x daily s.c.) according to standards of the individual study center, using licensed dosages, e.g.</p> <ul style="list-style-type: none"> <li>• Enoxaparin 1 mg/kg BW twice daily</li> <li>• Tinzaparin 175 I.E./kg BW once daily</li> <li>• Dalteparin 200 I.E./kg BW once daily</li> </ul>
Criteria for evaluation	As scheduled for the actual antitumoral treatment
Study rationale	<p>Cancer is one of the major risk factors for venous thromboembolism (VTE) and VTEs are relevant complications in the management and treatment of tumor patients.</p> <p>Low molecular weight heparin (LMWH) became the standard of care in the therapy of cancer patients with VTE (AWMF 2010, ACCP 2012). Recurrence of symptomatic VTE under treatment ranges between 7 % and 12 % in former studies. Consistent data are available for Dalteparin (CLOT), Tinzaparin (LITE) and Enoxaparin (CANTHANOX) (Lee 2003, Hull 2006, Meyer 2002). However, prolonged therapy with subcutaneously applied LMWH is inconvenient and not well accepted by the patients. Numerous practical limitations make the use of NMH in clinical practice challenging. It has to be expected that anticoagulant therapy with an orally applied drug is better tolerated by cancer patients than subcutaneous treatment. In this context it is important to realize that patient's reported treatment satisfaction in general is higher under Rivaroxaban compared to standard anticoagulation treatment (Bamber, thrombosis and haemostasis 2011).</p> <p>The EINSTEIN DVT trial (Bauersachs 2010) included more than 3400 patients comparing Rivaroxaban versus Enoxaparin/vitamin K antagonist (Enox/VKA) in patients with symptomatic deep vein thrombosis. In both treatment groups, patients with active cancer were not excluded. 118 (6.8 %) patients in the Rivaroxaban group and 89 (5.2 %) in the Enox/VKA group had cancer. For the subgroup of cancer patients treated with Rivaroxaban, the rate of recurrence</p>

	<p>was 3.4 %, indicating a good efficacy of Rivaroxaban in the treatment of deep vein thrombosis. The rate of relevant bleeding complications was comparable to those of the CLOT study (Rivaroxaban 14.4 %, Dalteparin 14 %).</p> <p>In the EINSTEIN PE trial (Büller 2012) investigating patients with pulmonary embolism, 221 patients with active cancer were included [114 (5.7 %) Rivaroxaban and 109 (4.5%) Enox/VKA]. The rate of recurrence was even lower than in the EINSTEIN DVT (1.8%), relevant bleeding complications were comparable (12.3%).</p> <p>In conclusion, in cancer patients with VTE, Rivaroxaban may be an as effective and just as safe treatment compared with the standard treatment with LMWH. Furthermore a better acceptance by the patients may lead to a better treatment adherence and effectiveness. In the EINSTEIN trials the Anti-Clot Treatment Scale (ACTS) was used as the primary measure of treatment satisfaction, but no data specific for cancer patients that suffered from a thromboembolic event are available so far. Therefore, a study backing up these hypotheses is urgently warranted.</p>
Statistics	<p>To demonstrate a greater patient-reported satisfaction with Rivaroxban in comparison to the standard treatment with low molecular weight heparin (LMWH) after 3 months, the anti-clot treatment scale (ACTS) will be used to measure ACTS burden and benefits. The clinical significance of any observed group mean difference will be interpreted in terms of its equivalent effect size, calculated as mean difference/standard deviation of difference. Clinical significance is assumed at a conservative effect size of at least 0.3 or higher.</p> <p>Drop out - i.e. due to tumor or treatment associated complications - is estimated to be about 10%. Lost to follow up is estimated to be less than 1%.</p>

## Arbeitsgruppe Thorakale Onkologie

### AIO-TRK-0216: An open-label, multicenter, phase I dose-escalation trial of EGF816 and trametinib in patients with non-small cell lung cancer and acquired EGFR p.T790M positive resistance to 1<sup>st</sup> or 2<sup>nd</sup> generation EGFR TKI therapy (EATON)

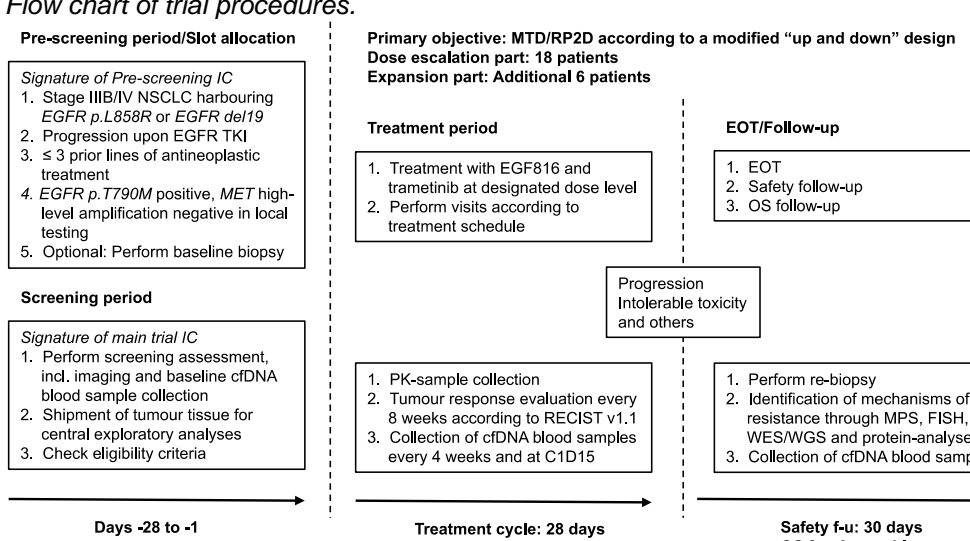
#### AIO-Studie

Studiennummer/-Code:	AIO-TRK-0216 - EATON
Status:	in Vorbereitung
Rekrutierungszeitraum:	2018 – 2019 (geplant)
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Principal Investigator	Prof. Dr. Jürgen Wolf, University Hospital of Cologne, Kerpener Str. 62, 50937 Cologne, Germany
Study sponsor	University Hospital of Cologne, Kerpener Str. 62, 50937 Cologne, Germany
Primary indication	Patients with advanced non-small cell lung cancer harbouring sensitizing <i>EGFR</i> mutations ( <i>EGFRdel19</i> or <i>EGFR p.L858R</i> ) with progression upon treatment with 1 <sup>st</sup> or 2 <sup>nd</sup> generation EGFR TKI and acquired resistance mutation <i>EGFR p.T790M</i>
Trial design	Phase I, dose escalation, genetically pre-selected, international, multicentre, open-label
Trial rationale	<p>Mechanisms of resistance to 3<sup>rd</sup> generation EGFR TKIs recently have been described to be different from those triggering resistance to 1<sup>st</sup> and 2<sup>nd</sup> generation EGFR TKIs. Mechanisms described so far in preclinical models and biopsies involve <i>EGFR p.C797S</i>, <i>HER2</i> amplification, <i>MET</i> amplification and others. Multiple mechanisms of activation of the RAS/RAF/MEK pathway, among them, acquired activating mutations in <i>NRAS</i> and <i>KRAS</i> as well as amplifications and gain of copy number of <i>KRAS</i>, <i>MAPK1</i> and <i>NRAS</i> have been described to contribute to acquired resistance [Eberlein et al., 2015; Ercan et al., 2012; Sharifnia et al., 2014; Thress et al., 2015].</p> <p>Preclinical models have also shown that activation of the RAS/MEK pathway results in reduced EGFR dependency, which can be overcome by inhibition of MEK [Tricker et al., 2015]. We thus hypothesize that combined inhibition of EGFR and MEK may restore sensitivity to EGFR inhibition in patients with acquired RAS/MEK activation and may as well prolong the acquisition of RAS/MEK mediated resistance to 3<sup>rd</sup> generation EGFR TKIs.</p>
Summary of the study strategy and aims	<p>The population of interest for this trial is defined by patients with NSCLC harbouring the sensitizing <i>EGFR</i> mutation <i>del19</i> or <i>p.L858R</i> who develop resistance to treatment with EGFR TKIs. The detection of the <i>EGFR p.T790M</i> resistance mutation in the rebiopsy tumour tissue is mandatory. High level amplification of <i>MET</i> however may not be detected. <i>EGFR</i> mutation status is assessed locally by DNA sequencing (e.g. Sanger sequencing, massively parallel sequencing). <i>MET</i> status will be assessed locally by FISH.</p> <p>The aim of the trial is to identify the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) for a continuous treatment with EGF816 and trametinib.</p> <p>The recommendations for dose level escalations will be based on an “up and down” design proposed by Storer, 1989. The dose limiting toxicity (DLT) period comprises the first 28 days of treatment with EGF816 and trametinib at the designated dose level (Cycle 1).</p> <p>Preliminary efficacy data of EGF816 and trametinib in the trial population will be generated according to RECIST v1.1.</p> <p>Throughout the study blood samples will be collected to monitor cell free plasma DNA (cfDNA).</p>



	Patients who develop resistance upon treatment with the study drugs will undergo a rebiopsy to identify potential mechanisms of resistance.
Primary objective	1. To assess the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) of a combination treatment of EGF816 and trametinib
Primary endpoint	1. Incidence of dose limiting toxicities (DLTs)
Secondary objectives	1. To characterize the safety of EGF816 in combination with trametinib 2. To characterize the tolerability of EGF816 in combination with trametinib 3. To assess the preliminary clinical efficacy of EGF816 in combination with trametinib 4. To define PK variables of the combination treatment
Secondary endpoints	1. Incidence, severity and grading of AEs and SAEs 2. Dose interruptions, reductions and dose intensity 3. Objective response rate (ORR), progression free survival (PFS), duration of response (DOR) and disease control rate (DCR), overall survival (OS) according to investigators assessed RECIST v1.1 4. Plasma concentration vs time profiles - plasma PK parameters of EGF816 and trametinib
Exploratory objectives	1. To analyse pre-treatment samples for multiple cancer related genes in order to assess potential predictive markers for response and resistance 2. To determine mechanisms of primary and acquired resistance to a combination treatment of EGF816 and trametinib in post-treatment samples 3. To assess the value of cell-free plasma DNA (cfDNA) for assessment of predictive molecular markers of response and resistance and for monitoring those under therapy 4. To evaluate the value of conditionally reprogrammed tumour cells (CRCs) established from tumour biopsies (baseline or upon progression) of fresh tissue for the analysis of molecular resistance mechanisms and drug sensitivity assessment in selected centres
Exploratory endpoints	1+2. Massively parallel sequencing (MPS), FISH, phospho-immunoblots of pre-treatment tumour samples and progression tumour samples, and whole exome or genome sequencing if possible 3. MPS of cfDNA at baseline, during treatment and at progression 4. CRCs will be made at the Department of Translational Genomics and the Institute of Pathology of the University Hospital of Cologne according to the established protocols.
Patient number calculations and statistics	Dose level escalation will be based on a modified traditional cumulative 3+3 dose (C33D) design, i.e. the "up and down" "Design D" proposed by [Storer, 1989]: Starting with the first dose level (dose level 1: 100 mg EGF816 QD + 1 mg trametinib QD) groups of 3 patients will be treated. Escalation occurs if no DLTs or other toxicities $\geq$ Grade 2, that to the discretion of the sponsor fulfil the criteria of a DLT, are seen. De-escalation will be necessary if more than one patient exhibits such an event. If only a single patient has toxicity as described above, then the next group of three patients is treated at the same dose level. At a first stage, 18 (6 $\times$ 3) patients will be treated and evaluated. Based on these data, the "virtual MTD" (product of daily doses of EGF816 and trametinib in mg) is estimated by inverse prediction at 1/3 from exact logistic regression (with 95% confidence interval). At a second stage, 6 further patients (2 $\times$ 3) will be treated on the highest (already investigated) dose level (i.e. the actual MTD) equal or below the virtual MTD (extension cohort). No formal statistical sample size calculation was performed for this trial. A total number of 24 patients will be treated.

<p>Treatment regimen and dose levels</p>	<p>Patients will receive continuous doses of EGF816 and trametinib at the designated dose levels.</p> <p>The starting dose of EGF816 will be 100 mg QD. The dose will be escalated by 50.0% in dose level 3.</p> <p>The starting dose of trametinib will be set at 1.0 mg daily. Dose levels will be increased from the previous dose by 50.0% (dose level 2) and 33.3% (dose level 4).</p> <p><b>Dose levels and treatment regimen</b></p> <table border="1" data-bbox="430 443 1098 656"> <thead> <tr> <th>Dose level</th> <th>EGF816 daily dose (mg, QD)</th> <th>trametinib daily dose (mg, QD)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>100</td> <td>1.0</td> </tr> <tr> <td>2</td> <td>100</td> <td>1.5</td> </tr> <tr> <td>3</td> <td>150</td> <td>1.5</td> </tr> <tr> <td>4</td> <td>150</td> <td>2.0</td> </tr> </tbody> </table>	Dose level	EGF816 daily dose (mg, QD)	trametinib daily dose (mg, QD)	1	100	1.0	2	100	1.5	3	150	1.5	4	150	2.0
Dose level	EGF816 daily dose (mg, QD)	trametinib daily dose (mg, QD)														
1	100	1.0														
2	100	1.5														
3	150	1.5														
4	150	2.0														
<p>Molecular analyses</p>	<p>Adenocarcinoma patients progressing on 1<sup>st</sup> or 2<sup>nd</sup> generation EGFR TKI will be re-biopsied for local <i>EGFR p.T790M</i> and <i>MET</i> amplification testing (baseline sample).</p> <p><i>EGFR</i> status will be determined by single gene sequencing (e.g. Sanger sequencing) or massively parallel sequencing (MPS). <i>MET</i> status will be determined by fluorescence in-situ hybridisation (FISH). High level <i>MET</i> amplification is defined as a tumour fulfilling the following criteria:</p> <p>a) a <i>MET/CEN7</i> ratio <math>\geq 2.0</math> or b) an average <i>MET</i> gene copy number per cell of <math>\geq 6.0</math> or c) <math>\geq 10\%</math> of tumour cells containing <math>\geq 15</math> <i>MET</i> signals [Schildhaus et al., 2015].</p> <p>After inclusion into the trial, pre-treatment biopsy tumour samples of all patients will be sent to NGM for massively parallel sequencing, FISH and phospho-protein analysis by immunohistochemistry to determine cancer related aberrations that may predict response or resistance to the combination treatment of EGF816 and trametinib.</p> <p>At baseline, during the course of treatment and at progression, blood samples will be collected and sent to NGM for analysis of circulating cfDNA by MPS.</p> <p>At progression according to RECIST, an optional rebiopsy will be scheduled to determine mechanisms of acquired resistance to the combination treatment of EGF816 and trametinib. Tumour specimens will be analysed centrally by MPS and FISH (NGM).</p> <p>In selected centres fresh-frozen and vital cell biopsies will be collected at baseline and progression for phospho-protein analyses, WES or WGS as well as for the establishment of functional CRC models.</p>															
<p>Summary of trial procedures</p>	<p><b>Flow chart of trial procedures.</b></p>  <p><b>Pre-screening period/Slot allocation</b></p> <p><i>Signature of Pre-screening IC</i></p> <ol style="list-style-type: none"> <li>1. Stage IIIB/IV NSCLC harbouring <i>EGFR p.L858R</i> or <i>EGFR del19</i></li> <li>2. Progression upon EGFR TKI</li> <li>3. <math>\leq 3</math> prior lines of antineoplastic treatment</li> <li>4. <i>EGFR p.T790M</i> positive, <i>MET</i> high-level amplification negative in local testing</li> <li>5. Optional: Perform baseline biopsy</li> </ol> <p><b>Screening period</b></p> <p><i>Signature of main trial IC</i></p> <ol style="list-style-type: none"> <li>1. Perform screening assessment, incl. imaging and baseline cfDNA blood sample collection</li> <li>2. Shipment of tumour tissue for central exploratory analyses</li> <li>3. Check eligibility criteria</li> </ol> <p><b>Primary objective: MTD/RP2D according to a modified "up and down" design</b>  <b>Dose escalation part: 18 patients</b>  <b>Expansion part: Additional 6 patients</b></p> <p><b>Treatment period</b></p> <ol style="list-style-type: none"> <li>1. Treatment with EGF816 and trametinib at designated dose level</li> <li>2. Perform visits according to treatment schedule</li> </ol> <p><b>EOT/Follow-up</b></p> <ol style="list-style-type: none"> <li>1. EOT</li> <li>2. Safety follow-up</li> <li>3. OS follow-up</li> </ol> <p><b>Progression Intolerable toxicity and others</b></p> <ol style="list-style-type: none"> <li>1. PK-sample collection</li> <li>2. Tumour response evaluation every 8 weeks according to RECIST v1.1</li> <li>3. Collection of cfDNA blood samples every 4 weeks and at C1D15</li> </ol> <ol style="list-style-type: none"> <li>1. Perform re-biopsy</li> <li>2. Identification of mechanisms of resistance through MPS, FISH, WES/WGS and protein-analyses</li> <li>3. Collection of cfDNA blood sample</li> </ol> <p><b>Days -28 to -1</b>      <b>Treatment cycle: 28 days</b>      <b>Safety f-u: 30 days OS f-u: 3-monthly</b></p> <p>Before signing the Main Trial Informed Consent a slot for participation in the trial should have been allocated for the individual patient. A patient for whom a slot for participation has been requested should be able to start treatment within the next 28 days and presumably fulfil the eligibility criteria. In patients who are undergoing rebiopsy after signature of the Main Trial IC fresh frozen tissue will preferentially</p>															

	<p>be collected. Patients whose tumour harbour an <i>EGFR</i> p.T790M mutation and no high level <i>MET</i> amplification at local testing will be eligible for screening for the main trial.</p> <p>The screening period (d -28 to -1) will only start, once a slot has been allocated to the patient by the sponsor and after the signing of the Main Trial Informed Consent. After the screening period and if the patient meets eligibility criteria, treatment will start at the designated dose level and drug administration schedule. Patients will be treated on a continuous schedule of EGF816 and trametinib. Treatment cycles are defined as 28 days (4 weeks) for the purpose of scheduling procedures and evaluation.</p> <p>Tumour response evaluation will be performed by CT and/or MRI scans every 8 weeks and assessed according to RECIST v1.1.</p> <p>Treatment will be conducted until disease progression, occurrence of intolerable toxicity, withdrawal of IC or treatment discontinuation at the discretion of the investigator.</p> <p>At progression a biopsy should be collected to determine potential mechanisms of acquired resistance (<i>Section 11.3</i>).</p> <p>At baseline, throughout the trial treatment and at progression blood samples will be collected for analysis of circulating cfDNA by MPS.</p> <p>Treatment beyond progression will be allowed after approval by the PI, as long as the patient clinically derives benefit from the treatment.</p>
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Written informed consent must have been obtained prior to any screening procedures.</li> <li>2. Patients (male or female) <math>\geq 18</math> years of age.</li> <li>3. Histologically documented, locally advanced or recurrent (stage IIIB who are not eligible for combined modality treatment) or metastatic (stage IV) non-small cell lung cancer.</li> <li>4. Presence of at least one measurable lesion according to RECIST v.1.1.</li> <li>5. ECOG performance status <math>\leq 2</math></li> <li>6. Patients must have NSCLC harbouring <i>EGFR</i> p.L858R or <i>EGFR</i> del19.</li> <li>7. Archival biopsy sample, defined as a sample being obtained after or during progression upon the last anti-cancer treatment. No consecutive line of treatment must have been given after collection of the rebiopsy and inclusion into this trial. If an archival rebiopsy fulfilling these criteria is not available, patients must be suitable and willing to undergo baseline biopsy according to the local institution's guidelines (newly obtained biopsy).</li> <li>8. <i>EGFR</i> p.T790M mutation must have been detected by local testing in the tumour sample fulfilling the requirements of inclusion criterion 7.</li> <li>9. Documented progression of disease according to RECIST v1.1 while on continuous treatment with 1st or 2nd <i>EGFR</i> TKI (e.g. erlotinib, gefitinib or afatinib).</li> </ol>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. History of allergic reactions or hypersensitivity to one of the study drugs or to any component of the study drugs.</li> <li>2. Prior treatment with any investigational agent known to inhibit <i>EGFR</i> (mutant or wild-type) or any 3<sup>rd</sup> generation <i>EGFR</i> TKI</li> <li>3. Prior treatment with any agent known to inhibit MEK/ERK or other mediators of KRAS pathway.</li> <li>4. Prior treatment with more than 3 lines of antineoplastic therapy in the advanced setting including <i>EGFR</i> TKI treatment.</li> <li>5. Patients with high level <i>MET</i> amplification in the archival or newly obtained biopsy sample as determined by local testing</li> <li>6. Patients with brain metastases. However, if radiation therapy and/or surgery has been completed at least 4 weeks prior to screening for the trial and evaluation by CT (with contrast enhancement) or MRI at study baseline demonstrates the disease to be stable and if the patient remains asymptomatic and off steroids, then patients with brain metastases may be enrolled.</li> <li>7. Patients with presence or history of carcinomatous meningitis.</li> <li>8. Any acute or chronic medical, mental or psychological condition, which in the opinion of the investigator would not permit the patient to participate or complete the study or understand the patient information</li> <li>9. History of hepatitis B (HBV) or hepatitis C (HCV) or positive result in mandatory testing for acute or chronic hepatitis B or hepatitis C</li> <li>10. Known HIV infection or history of HIV infection independent from the cellular</li> </ol>

	<p>immune status</p> <ol style="list-style-type: none"> <li>11. Patients who receive any continuous, long term immunosuppressive treatment, including long term treatment with steroids at immunosuppressive doses at the time of study entry</li> <li>12. Patients who underwent bone marrow or solid organ transplantation, including patients who do not receive any immunosuppressive treatment.</li> <li>13. Presence or history of any other primary malignancy other than NSCLC within 5 years prior to enrolment into the trial. Except from this: Adequately treated basal or squamous cell carcinoma of the skin or any adequately treated in situ carcinoma</li> <li>14. Any of the following within 6 months prior to first trial drug administration: Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure (&gt; NYHA II), uncontrolled hypertension, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack</li> <li>15. Aortic valve stenosis with mean gradient <math>\geq 25</math> mmHg and aortic valve area of <math>\leq 1.5</math> cm<sup>2</sup></li> <li>16. Any other cardiac valve abnormality of more than mild degree/stage</li> <li>17. Left ventricular ejection fraction (LVEF) of &lt; 50 %</li> <li>18. Atrial fibrillation of any Grade or ongoing cardiac dysrhythmias of CTCAE Grade <math>\geq 2</math>, including corrected QTcF prolongation of &gt; 480 ms, history of congenital long QT-syndrome or Torsades de Pointes</li> <li>19. History of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED)</li> <li>20. Unable or unwilling to swallow tablets or capsules</li> <li>21. Patients with impaired gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of EGF816 (e.g., ulcerative diseases, uncontrolled nausea, vomiting diarrhoea, or malabsorption syndromes)</li> <li>22. Patients have received anticancer treatment within the following time frames prior to the first dose of study treatment:       <ol style="list-style-type: none"> <li>a. Conventional cytotoxic chemotherapy: <math>\leq 4</math> weeks (<math>\leq 6</math> weeks for nitrosoureas, mitomycin-C and suramin)</li> <li>b. Biological therapy (e.g., antibodies, excluding PD-1 or PD-L1 antibodies): <math>\leq 4</math> weeks</li> <li>c. PD-1/PD-L1 antibodies (e.g., nivolumab, pembrolizumab): <math>\leq 5</math> half-times</li> <li>d. Non-cytotoxic anti-cancer therapeutic (e.g., tyrosine kinase inhibitors): <math>\leq 5</math> half-times or <math>\leq 1</math> weeks (whichever is longer)</li> <li>e. Other investigational agent: <math>\leq 4</math> weeks</li> <li>f. Radiation therapy (excluding palliative radiation, e.g., of bone metastases): <math>\leq 4</math> weeks</li> <li>g. Major surgery (excluding minor surgical interventions, e.g., vascular device implantation): <math>\leq 2</math> weeks</li> </ol> </li> <li>23. Laboratory values as listed below, that cannot be corrected to normal limits within screening :       <ol style="list-style-type: none"> <li>a. Absolute Neutrophil Count (ANC) &lt; <math>1.5 \times 10^9/L</math></li> <li>b. Haemoglobin (Hb) &lt; 9 g/dL</li> <li>c. Platelets (PLT) &lt; <math>100 \times 10^9/L</math></li> <li>d. Total bilirubin &gt; <math>1.5 \times</math> upper limit of normal (ULN). For patients with confirmed Gilbert's disease total bilirubin &gt; <math>2.5 \times</math> ULN</li> <li>e. AST and/or ALT &gt; <math>3 \times</math> ULN</li> <li>f. AST and/or ALT &gt; <math>5 \times</math> ULN in patients with liver involvement</li> <li>g. Serum creatinine &gt; <math>1.5 \times</math> ULN</li> <li>h. Measured or calculated creatinine clearance <math>\leq 45</math> mL/min</li> <li>i. Serum amylase and/or lipase CTCAE Grade &gt; 2</li> <li>j. Potassium, magnesium, phosphorus, total calcium (corrected from serum albumin) &gt; ULN</li> </ol> </li> <li>24. Patients receiving treatment with any medication that are known to be       <ol style="list-style-type: none"> <li>a. Strong inhibitors or inducers of CYP3A4/5</li> <li>b. Substrates of CYP2D6 with narrow therapeutic index</li> <li>c. and that cannot be discontinued at least 7 days prior to the first dose of the study drugs.</li> </ol> </li> <li>25. Patients with a history of or presence of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis</li> <li>26. Pregnancy or breastfeeding/nursing women</li> </ol>
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	<p>27. Women of child-bearing potential unless they use highly effective methods of contraception during treatment and for 7 days after withdrawal of study treatment</p> <p>28. Sexually active males unless they use a condom during intercourse for the time of study treatment and for three months after the withdrawal of study treatment.</p>
Trial duration / timelines	<p>Inclusion first patient (FPFV): 04/2018</p> <p>Inclusion last patient: 01/2020</p> <p>Last patient last visit (LPLV): 01/2021</p>

### Metastasiertes NSCLC ohne Treibermutationen

#### **AIO-TRK-0115: A Phase II Randomized, Double-Blind, Placebo-Controlled Study of Pembrolizumab Maintenance Following First-Line Platinum Based Chemotherapy in Patients with Metastatic Squamous - Non-Small Cell Lung Cancer (sNSCLC) (PRIMUS)**

#### AIO-Studie

Studiennummer/-Code:	AIO-TRK-0115 - PRIMUS
Status:	in Rekrutierung
Rekrutierungszeitraum:	2015 - 2019
Weitere Zentren:	in Abhängigkeit vom weiteren Studienverlauf
Letzte Aktualisierung	April 2018

Principal Investigator	Prof. Dr. Martin Reck LungenClinic Grosshansdorf, Wöhrendamm 80, 22927 Großhansdorf
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany Phone: +49-30-322932931, Fax: +49-30-322932926 info@aio-studien-ggmbh.de
Study design	Randomized, double-blind, placebo-controlled study
Indication	Metastatic squamous non-small cell lung cancer
Countries Total number of sites	Germany About 15 sites
Primary objective	To investigate the efficacy of Pembrolizumab vs. placebo in terms of progression-free survival in patients with metastatic squamous, non-small cell lung cancer.
Secondary objectives	To evaluate tumor response, survival, tolerability and safety as well as quality of life of patients receiving Pembrolizumab
Planned sample size	65 patients per treatment arm, 130 patients total
Number of patients	30 randomized patients (04/2018)
Target population	Patients with metastatic squamous NSCLC and disease control following first-line platinum-based chemotherapy
Inclusion Criteria	<p>15. Male or female patient, age <math>\geq</math> 18 years</p> <p>16. Signed informed consent</p> <p>17. Ability to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and</p>

	<p>examinations</p> <ol style="list-style-type: none"> <li>18. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1</li> <li>19. At least one measurable tumor lesion according to RECIST 1.1</li> <li>20. Histologically or cytologically confirmed diagnosis of stage IV (AJCC Version 7) squamous non-small cell lung carcinoma</li> <li>21. Complete response, partial response or stable disease after at least 2 cycles of first-line chemotherapy with cisplatin or carboplatin</li> <li>22. Last administration of platinum based first-line chemotherapy <math>\geq 3</math> weeks and <math>\leq 8</math> weeks prior first dose of study treatment</li> <li>23. Tumor specimen available for central PD-L1 testing. Tumor specimen must be a tumor block not pre-cut slides.</li> <li>24. Adequate bone-marrow and organ function: <ol style="list-style-type: none"> <li>a. Absolute neutrophil count <math>\geq 1.5 \times 10^9/L</math> and</li> <li>b. Thrombocytes <math>\geq 100 \times 10^9/L</math> and</li> <li>c. Hemoglobin <math>\geq 9</math> g/dL</li> <li>d. INR <math>\leq 1.5</math> and PTT <math>\leq 1.5</math> x upper limit during the last 7 days before therapy</li> <li>e. Bilirubin <math>&lt; 1.5</math> x ULN and</li> <li>f. AST (GOT) and ALT (GPT) <math>&lt; 3</math> x ULN (5 x ULN in case of liver metastases)</li> <li>g. Creatinine <math>\leq 1.5</math> x ULN or creatinine clearance <math>\geq 45</math> mL/min (after first line chemotherapy)</li> </ol> </li> <li>25. In female patients of childbearing potential (i.e. did not undergo surgical sterilization – hysterectomy, bilateral tubal ligation, or bilateral oophorectomy - and is not post-menopausal for at least 24 consecutive months), a negative pregnancy test at screening</li> <li>26. Female patients of childbearing potential and male patients with female partners of childbearing potential must agree to use 2 adequate barrier methods of contraception during study treatment and for 120 days after last administration of study drug</li> </ol>
Exclusion Criteria	<ol style="list-style-type: none"> <li>19. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to treatment start. It is permissible that a patient participates in a follow-up phase of any previous study.</li> <li>20. Patient received systemic steroid therapy within three days prior to the first dose of study treatment (however an upper limit 10mg prednisolone or prednisolone equivalent is acceptable) or received any other form of immunosuppressive medication</li> <li>21. History of allogeneic tissue/solid organ transplant</li> <li>22. History of pneumonitis or interstitial lung disease that has required oral or i.v. steroids</li> <li>23. Radiotherapy of target lesion <math>\leq 28</math> days prior first dose of study treatment</li> <li>24. Major surgery <math>\leq 28</math> days prior first dose of study treatment</li> <li>25. Minor surgery (e.g. venous catheter) <math>\leq 24</math> hours prior first dose of study treatment</li> <li>26. Cardiovascular or cerebrovascular disease of clinical relevance: e.g. acute myocardial infarction or stroke during the last 6 months, unstable angina, relevant and unstable dysrhythmia (controlled TAA allowed).</li> <li>27. Severe wound healing disorders, active ulcer ventriculi/duodenal ulcer, bone fracture</li> <li>28. Known active HBV, HCV or HIV infection</li> <li>29. Has any other active infection requiring systemic therapy.</li> <li>30. Patients with active tuberculosis</li> <li>31. Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-Programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically</li> </ol>

	<p>targeting T-cell co-stimulation or checkpoint pathways)</p> <p>32. Female patient pregnant or breastfeeding, or expecting to conceive or father children during the study and through 120 days after last administration of study drug</p> <p>33. Indications of a neurological or other disease, which may influence the feasibility of the study or may seriously disturb tolerability</p> <p>34. A diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 3 days prior to the first dose of trial treatment.</p> <p>35. Patient has had a prior monoclonal antibody, which does significantly interfere with the immune system or which does have a systemic therapeutic impact on the tumor within 4 weeks prior to study Day 1.</p> <p>36. Patient has not recovered (i.e., <math>\leq</math> Grade 1 or at baseline) from side effects due to agents administered more than 4 weeks earlier. [Subjects with <math>\leq</math> Grade 2 neuropathy are an exception to this criterion and may qualify for the study.]</p> <p>37. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.</p> <p>38. Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.</p> <p>39. Has received a live vaccine within 30 days prior to the first dose of trial treatment.</p> <p>40. Has known hypersensitivity to pembrolizumab or any of its insipients.</p> <p>41. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p>
Investigational Medicinal Product	Pembrolizumab 200 mg fixed Placebo
Treatment schedule after randomization	<p><b>Arm A:</b> Pembrolizumab 200 mg every three weeks until disease progression (maximum 2 years)</p> <p><b>Arm B:</b> Placebo i.v. every three weeks until disease progression (maximum 2 years)</p>
Primary endpoint	<ul style="list-style-type: none"> <li>• Progression-free-survival (RECIST 1.1)</li> </ul>
Secondary endpoints	<ul style="list-style-type: none"> <li>• Overall response rate</li> <li>• Overall survival</li> <li>• PD-L1 expression in tumor samples</li> <li>• Tolerability and safety</li> <li>• Quality of life (FACT-L, LCSS)</li> </ul>
Randomization procedure	Permuted block randomization will be applied to guarantee balanced group numbers.

Scientific rationale	<p>Survival in stage IV NSCLC is still disappointing despite recent advantages in systemic treatment. Chemotherapy with cisplatin and gemcitabine represents one standard of care. To date, especially in sNSCLC, targeted therapies are lacking. Immunotherapy by blocking the PD-1/ PD-L1 pathway has shown promising results independent from histology in early clinical studies. The blockade of PD-1 is of specific interest in the area of maintenance following previous reduction of tumor burden by induction chemotherapy due to its specific mode of action.</p> <p>Specific interest should be drawn to the potential correlation between PD-L1 expression and efficacy of Pembrolizumab.</p>
Interim analysis	No interim analysis is planned for this study.
Statistical considerations and sample size calculation	<p><b>Sample Size Estimation:</b></p> <p>With a total number of 112 events (progressions or deaths), a log-rank test for testing superiority of progression-free survival with a 5% one-sided significance level will have 80% power to reject the null-hypothesis if the true median progression-free survival times in patients treated with placebo and Pembrolizumab are 2.5 and 4 months, respectively. Assuming exponential distribution of PFS, this treatment effect translates to a treatment-specific hazard ratio of 0.625. With a recruitment rate of 7.3 patients per month and a lost-to-follow-up rate of 5% per year, the required number of events can be expected to be observed within a study duration of roughly 35 months with a maximum of 130 randomized patients.</p> <p><b>Statistical Analysis Outline:</b></p> <p>An observed cases approach will be applied, and missing data will not be imputed. A significance level of 10% two-sided (corresponding to 5% one-sided) will generally be applied. Efficacy analysis will primarily be evaluated within the per-protocol analysis group.</p> <p>PFS and OS will be analyzed descriptively using the Kaplan-Meier method and compared between groups with a Cox-regression with the factors study site and treatment. The prognostic value of PD-L1 will be analyzed using a Cox-regression with the factor study site and PD-L1, both within each treatment group and overall with the additional factor treatment.</p> <p>Adverse Events and Serious Adverse Events will be summarized overall and by severity; 90% confidence intervals for event rates will be calculated.</p>
Translational research	<p>PD-L1 expression will be assessed on tumor tissues of both patient groups (Arm A and Arm B)</p> <p>In addition to PD-L1 analysis on tumor samples, whole blood samples (20 ml) will be collected in consenting patients of both patient groups before first administration of study drug, after cycle 2 and after progression to assess changes in circulating markers in the course of the therapy.</p>
Study plan	<p>FPI: Q4/2015</p> <p>LPI: after approx.48 month Q4/2019</p> <p>Duration of treatment: approximately 7 months</p> <p>Follow up period for the last patient: 10 months after EOT</p> <p>LPLV: Q2/2021</p> <p>Study report: Q3/2019</p>
Further sites required?	Depends on actual recruitment



Metastatic non-small cell lung cancer (NSCLC)**AIO-YMO/TRK-0416: DURvalumab (MEDI4736) in frail and elderly Patients with metastatic NSCLC (DURATION)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/TRK-0416 - DURATION
Status:	In Rekrutierung
Rekrutierungszeitraum:	Q4 2017 – Q1 2020
Weitere Zentren:	vollständig
Letzte Aktualisierung	April 2018

Study design	Open label, treatment stratified and randomized phase II study
National Coordinating Investigator	Dr. med. Jonas Kuon Internistische Onkologie der Thoraxtumoren, Thoraxklinik – Universität Heidelberg Röntgenstrasse 1, 69126 Heidelberg, Germany jonas.kuon@med.uni-heidelberg.de  <b>Mentoring Investigator:</b> Univ.-Prof. Dr. Michael Thomas, Thoraxklinik at Heidelberg University Hospital E-mail: michael.thomas@med.uni-heidelberg.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, Fax +49 30 322932926 info@aio-studien-ggmbh.de
Die vollständige Synopse ist zu finden unter den Kurzprotokollen der Young-Medical Oncologists!	

Metastatic adenocarcinoma of the lung (non-squamous NSCLC), second line and beyond**AIO-YMO/TRK-0415: Fostering efficacy of anti – PD-1 – treatment: Nivolumab plus radiotherapy in advanced NSCLC (FORCE)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/TRK-0415 - FORCE
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Study Type	Open-label, randomized Phase-II
Coordinating investigator (LKP)	Dr. med. Farastuk Bozorgmehr Department of Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital Röntgenstrasse 1, 69126 Heidelberg, Germany Phone: +49 6221 396-1301, Fax: +49 6221 396-1302 E-mail: farastuk.bozorgmehr@med.uni-heidelberg.de  <b>Mentoring Investigator:</b> Univ.-Prof. Dr. Michael Thomas, Thoraxklinik at Heidelberg University Hospital E-mail: michael.thomas@med.uni-heidelberg.de
Die vollständige Synopse ist zu finden unter den Kurzprotokollen der Young-Medical Oncologists!	

NSCLC und SCLC second line**AIO-TRK-0116: Eine Phase II-Studie mit Nivolumab in Kombination mit Ipilimumab zur Evaluierung der Sicherheit und Wirksamkeit im rezidierten Lungenkrebs und zur Evaluierung von Biomarkern welche für das Ansprechen auf Immuncheckpointinhibition prädiktiv sind (BIOLUMA)****AIO-Studie**

Studiennummer/-Code:	AIO-TRK-0116 - BIOLUMA
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Kurztitel	BIOLUMA: <u>B</u> iomarker für Nivolumab und Ipilimumab und Evaluierung der Kombinationstherapie bei Patienten mit Lungenkrebs
Sponsor	Universität zu Köln, Albertus-Magnus-Platz, 50923 Köln, Deutschland Vertreten durch: Prof. Dr. Jürgen Wolf, Medizinische Klinik I, Centrum für Integrierte Onkologie (CIO), Uniklinik Köln, Kerpener Strasse 62, 50937 Köln, Germany
Indikation	<u>Kohorte 1</u> : Nicht-kleinzelliges Lungenkarzinom, Adenokarzinom (AD-NSCLC) Patienten mit lokal fortgeschrittenem oder metastasiertem Adenokarzinom der Lunge erhalten nach Versagen einer Platin-haltigen Erstlinientherapie eine Zweitlinientherapie mit Nivolumab bis zum Tumorprogress und anschließend die Kombinationstherapie aus Nivolumab und Ipilimumab. <u>Kohorte 2</u> : Kleinzelliges Lungenkarzinom (SCLC) Patienten mit kleinzelligem Lungenkarzinom in frühen oder fortgeschrittenen Stadien erhalten nach Versagen einer Platin-haltigen Erstlinientherapie eine Zweitlinientherapie mit der Kombination aus Nivolumab und Ipilimumab über vier Zyklen und anschließend eine Nivolumab-Monotherapie bis zum Tumorprogress.
Studienmedikation	(I) Nivolumab (II) Ipilimumab
Konzept der Studie	Der monoklonale IgG4-Antikörper Nivolumab, der gegen den Checkpointrezeptor PD-1 gerichtet ist, zeigt bemerkenswerte therapeutische Aktivität sowohl beim NSCLC, als auch beim SCLC. Selbst bei deutlich vorbehandelten Patienten werden beeindruckende Ansprechraten mit teilweise langanhaltendem Ansprechen erreicht. Kürzlich konnten zwei Phase III-Studien bei Patienten mit rezidiertem Adeno- und Plattenepithelkarzinom der Lunge ein verbessertes Gesamtüberleben um etwas drei Monate mit Nivolumab im Vergleich zur Standard-Chemotherapie zeigen. Aufgrund dieser Studienergebnisse erfolgte in den USA und in Europa die Zulassung für Nivolumab im rezidierten NSCLC <sup>1,2</sup> . Allerdings machen Ansprechraten von rund 20% auch deutlich, dass ein hoher Bedarf an genauere Charakterisierung der Ansprecher vor Einleitung der Therapie und Identifizierung von Biomarkern besteht. Darüber hinaus müssen therapeutische Strategien zur Verbesserung der therapeutischen Aktivität von Nivolumab entwickelt werden. Kombinationstherapien könnten eine attraktive Strategie sein, um die Rate und Dauer der antitumoralen Immunantwort auf Checkpointblockade zu erhöhen. Die PD-L1 Immunhistochemie (PD-L1 IHC) wurde als potentieller prädiktiver Biomarker in mehreren Immuntherapiestudien beim NSCLC untersucht. Über die PD-L1 IHC können Patienten identifiziert werden, die eine höhere Wahrscheinlichkeit haben, auf PD-1-Blockade anzusprechen und die längerfristig von dieser Therapie profitieren. Allerdings eignet sich die PD-L1 IHC derzeit nicht zur Selektion von Patienten, die nicht auf die Therapie ansprechen <sup>1,3</sup> . Zudem haben frühe Studien gezeigt, dass die PD-L1 IHC zwar

	<p>beim malignen Melanom eine Wertigkeit bezüglich der Frage besitzt, welche Patienten von einer Kombinationstherapie mit Nivolumab und Ipilimumab profitieren können<sup>4</sup>, aber dies gilt vermutlich eher nicht bei Patienten mit SCLC<sup>5</sup>. Daher wird der klinische Wert der PD-L1 IHC derzeit kontrovers diskutiert.</p> <p>BIOLUMA ist eine multizentrische, nicht-randomisierte Phase II-Studie bei Patienten mit AD-NSCLC und SCLC nach Versagen einer Platin-haltigen Erstlinientherapie. Patienten mit NSCLC erhalten Nivolumab bis zum Tumorprogress und anschließend eine Kombinationstherapie mit Nivolumab und Ipilimumab. Patienten mit SCLC erhalten vier Zyklen einer Kombinationstherapie mit Nivolumab und Ipilimumab und im Anschluss eine Monotherapie mit Nivolumab. Der primäre Endpunkt der Studie ist für beide Kohorten die Ansprechrate der Kombinationstherapie.</p> <p>Ein weiterer Fokus der Studie liegt auf dem besseren Verständnis der biologischen Mechanismen, die dem Ansprechen auf Checkpointblockade zugrunde liegen. Es erfolgt eine umfassende Analyse von frisch gefrorenen sowie in Formalin fixierten Tumorproben, von peripherem Blut und des Mikrobioms. Die Gewinnung der Proben erfolgt vor Beginn der Studientherapie in beiden Kohorten, sowie zum Zeitpunkt des Tumorprogresses unter der Nivolumab-Monotherapie vor Einleitung der Kombinationstherapie aus Nivolumab und Ipilimumab in Kohorte 1, bzw. nach Komplettierung der vier Zyklen der Kombinationstherapie vor Fortführung mit Nivolumab als Monotherapie in Kohorte 2. Die Durchführung der Rebiopsien ist obligat, eine optionale Rebiopsie ist im Falle eines Tumorprogresses bei Ende der Studientherapie vorgesehen (Siehe Abbildung 1 und 2).</p> <p>Die Charakterisierung der Tumorzellen und des Tumormikromilieus erfolgt histologisch und immunhistochemisch. Die Rolle von spezifischen somatischen Mutationen und der Mutationslast wird mittels DNA-Sequenzierung (whole genome oder whole exome sequencing), Transkriptom-Sequenzierung (RNAseq), der Prädiktion von Neoepitopen und der Erstellung eines Modells zur HLA-Prozessierung erfolgen. Zelluläre und lösliche Bestandteile des Blutes werden mittels FACS und ELISA untersucht. Die Zusammensetzung der Darmflora wird mittels Tiefensequenzierung analysiert. Diese Untersuchungen sollen zum Verständnis der zu Grunde liegenden immunologischen Mechanismen bei Wirksamkeit und Unwirksamkeit der Checkpointblockade beitragen, und dazu dienen, weiterführende prädiktive Biomarker zu identifizieren und Hypothesen für weitere Studien zu generieren.</p>
Studientyp	<p>Eine multizentrische, nicht-randomisierte Phase II-Studie zur Evaluierung der Sicherheit und Wirksamkeit der Kombinationstherapie aus Nivolumab und Ipilimumab bei Patienten mit rezidiviertem AD-NSCLC und SCLC mit daran angeschlossenem explorativem Biomarkerprogramm zur Analyse von mononukleären Zellen des peripheren Blutes, Tumorgewebe und dem Mikrobiom.</p>
Studiendesign	<p>BIOLUMA ist eine multizentrische, nicht-randomisierte Phase II-Studie bei erwachsenen Männern und Frauen mit rezidiviertem oder progredientem lokal fortgeschrittenem oder metastasiertem Adenokarzinom der Lunge (AD-NSCLC) zur Evaluierung der Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab bei Nivolumab-refraktären Patienten (Kohorte 1) und zur Evaluierung der Ansprechrate von Nivolumab in Kombination mit Ipilimumab bei Patienten mit rezidiviertem kleinzelligem Lungenkarzinom (SCLC) in frühen oder fortgeschrittenen Tumorstadien (Kohorte 2).</p> <p>Im Rahmen des diagnostischen Programms werden Tumorbiopsate analysiert. Tumorgewebe wird in Kohorte 1 vor Therapieeinleitung und nach Progress unter Nivolumab-Monotherapie vor Hinzunahme von Ipilimumab gewonnen und in Kohorte 2 nach Komplettierung der vier Gaben Nivolumab/Ipilimumab vor der anschließenden Therapiefortsetzung mit Nivolumab als Monotherapie. Eine optionale Rebiopsie ist für den Fall eines Tumorprogresses in Therapiephase B für Kohorte 1 vorgesehen (siehe Abbildung 1) und am Ende der Studientherapie bei Tumorprogress in Therapiephase A oder B für Kohorte 2 (siehe Abbildung 2). Ein Teil des Tumorbiopsates wird in Paraffin eingebettet; der andere Teil dient als frisch</p>

	<p>gefrorenes Tumormaterial zur DNA- (whole genome/ whole exome) und RNA-Sequenzierung. Archivierte, in Paraffin-eingebettete Tumorproben werden zur Kompletttierung der Daten ebenfalls untersucht.</p> <p>Weiterhin werden die Expression von PD-L1/ PD-L2, die Immunzellinfiltration, die Immunantwort-bezogene Expression von Genen, Treibermutationen und die Mutationslast mittels IHC, FISH, Genomsequenzierung, RNA-Sequenzierung und Nanostring-Analysen untersucht, sowie eine umfassende bioinformatische Modelleerstellung durchgeführt. Darüber hinaus werden vor Therapieeinleitung und während der Therapie Blutproben zur FACS-Analyse und Stuhlproben zur Analyse des Mikrobioms gewonnen.</p>
Primäre Zielsetzung	<p><u>Kohorte 1:</u> Erhebung der Ansprechrate der Kombinationstherapie aus Nivolumab und Ipilimumab nach Tumorprogress unter Nivolumab-Monotherapie bei Patienten mit rezidiviertem AD-NSCLC in der Zweitlinientherapie.</p> <p><u>Kohorte 2:</u> Erhebung der Ansprechrate der Kombinationstherapie aus Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC in der Zweitlinientherapie.</p>
Primärer Endpunkt	<p><u>Kohorte 1:</u> Die nach RECIST 1.1 durch den Prüfer erhobene Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab nach Tumorprogress unter Nivolumab-Monotherapie bei Patienten mit rezidiviertem AD-NSCLC.</p> <p><u>Kohorte 2:</u> Die nach RECIST 1.1 durch den Prüfer erhobene Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC.</p>
Sekundäre Zielsetzungen	<ul style="list-style-type: none"> <li>• Erhebung der Wirksamkeit der Nivolumab-Monotherapie und der Kombinationstherapie mit Nivolumab und Ipilimumab</li> <li>• Charakterisierung der Sicherheit und Tolerabilität der Nivolumab-Monotherapie und der Kombinationstherapie mit Nivolumab und Ipilimumab</li> <li>• Beurteilung des prädiktiven Wertes der PD-L1- und PD-L2-Positivität der Tumorzellen für das Ansprechen auf die Nivolumab-Monotherapie und Kombinationstherapie mit Nivolumab und Ipilimumab</li> <li>• Korrelation von Mutationslast und Neoepitop-Signaturen mit dem klinischen Therapieansprechen</li> </ul>
Sekundäre Endpunkte	<ul style="list-style-type: none"> <li>• OS, PFS, DCR und DOR unter der Nivolumab-Monotherapie und unter der Kombinationstherapie mit Nivolumab und Ipilimumab</li> <li>• Inzidenz und Schweregrad von unerwünschten Ereignissen (UEs) und schwerwiegenden unerwünschten Ereignissen (SUEs) unter der Nivolumab-Monotherapie und unter der Kombinationstherapie mit Nivolumab und Ipilimumab</li> </ul> <p>Alle Biomarker-bezogenen sekundären Endpunkte werden sowohl für die Nivolumab-Monotherapie, als auch für die Kombinationstherapie mit Nivolumab und Ipilimumab erhoben:</p> <ul style="list-style-type: none"> <li>• Prädiktiver Wert der PD-1/PD-L2-Positivität der Tumorzellen vor der Studientherapie für ORR, DCR, PFS, OS, TTR und DOR (Grenzwerte <math>\geq 1\%</math>, <math>\geq 5\%</math>, <math>\geq 10\%</math>, <math>\geq 25\%</math> und <math>\geq 50\%</math>)</li> <li>• Korrelation der PD-L1/PD-L2/PD-1-Positivität der Tumor-assoziierten Immunzellen vor der Studientherapie mit ORR, DCR, PFS, OS, TTR und DOR</li> <li>• Prädiktiver Wert der Zusammensetzung des Immunzellinfiltrates vor der Studientherapie für ORR, DCR, PFS, OS, TTR und DOR</li> <li>• Prädiktiver Wert von zusätzlichen ko-inhibitorischen Molekülen für ORR, DCR, PFS, OS, TTR und DOR</li> <li>• Prädiktiver Wert der RNA-Expression von PD-L1 und PD-L2 für ORR, DCR, PFS, OS, TTR und DOR</li> <li>• Prädiktiver Wert der Tumormutationslast und der vorherberechneten</li> </ul>

	Neoepitope für das klinische Therapieansprechen.
Explorative Zielsetzungen	<ul style="list-style-type: none"> <li>• Beschreibung von Immunsystem-assoziierten Expressionsprofilen in Tumorbiopsaten und Korrelation mit dem klinischen Verlauf</li> <li>• Beschreibung der Zusammensetzung des Immunzellinfiltrates in Tumorbiopsaten und Korrelation mit dem klinischen Verlauf</li> <li>• Beschreibung der Zusammensetzung der Immunzellpopulationen im peripheren Blut vor, während und nach der Studientherapie und Korrelation mit dem klinischen Verlauf</li> <li>• Korrelation von Veränderungen des C-reaktiven Proteinwertes und der Leukozytenzahl mit dem klinischen Verlauf</li> <li>• Beschreibung der Zusammensetzung des Mikrobioms vor, während und nach der Studientherapie und Korrelation mit dem klinischen Verlauf</li> <li>• Charakterisierung der molekularen Heterogenität der Tumorzellen in den Biopsaten</li> <li>• Korrelation des genetischen Subtyps (definiert nach gezielt behandelbaren Mutationen) mit dem klinischen Verlauf</li> <li>• Korrelation von bekannten Treibermutationen mit dem klinischen Verlauf</li> </ul> <p>Die folgenden Analysen werden sowohl an Tumorbiopsaten durchgeführt, welche vor der Therapie gewonnen wurden, als auch an Biopsaten, welche im Rahmen des Tumorprogresses gewonnen wurden, und, soweit zutreffend, an Proben des peripheren Blutes:</p> <ul style="list-style-type: none"> <li>• Analyse der Mutationslast mittels DNA-Sequenzierung (Whole Genome Sequencing oder, je nach DNA-Gehalt der Biopsate, Whole Exome Sequencing)</li> <li>• Charakterisierung der Transkriptom-Expression mittels Whole Transcriptome Sequencing (RNAseq)</li> <li>• Muster der Infiltrate von Immunzellsubpopulationen mittels IHC</li> <li>• Proteinexpression von PD-L1 und PD-L2, mRNA-Expression und Muster der Immunzellsubpopulationen</li> <li>• Immunzellinfiltrat im Tumormikromilieu und Verhältnisse der Immunzellpopulationen im peripheren Blut</li> <li>• Evaluierung der Funktionsveränderung von T-Zellen des peripheren Blutes mittels Analyse von Aktivierungsmarkern und Änderungen der Zytokinlevel</li> <li>• Erstellung eines umfassenden Modells zur Tumorimmunogenität und zu Mechanismen der Umgehung einer Immunantwort über die Zusammenführung von Histopathologie, Immunhistochemie, Genomik, Neoepitop-Prädiktion und Neoepitop-Expression</li> </ul>
Statistische Analysen	<p><u>Kohorte 1:</u> Die Studie folgt einem "one-stage A'Hern design" mit Ansprechverhältnissen (das heißt ORR der Kombinationstherapie) <math>\pi_0 = 0.075</math> und <math>\pi_1 = 0.2</math>, <math>\alpha = 0.1</math> und <math>\beta = 0.2</math>. Demnach werden 33 evaluierbare Patienten benötigt. Die Nullhypothese <math>H_0: \pi \leq 0.1</math> ist verworfen, wenn mindestens 5 von 33 Patienten ansprechen<sup>6</sup>.</p> <p>Unter der Annahme einer Ausfallrate von 5% aufgrund von Therapieabbruch in Therapiephase A<sup>2</sup> und einer erneuten Ausfallrate von 35% in Therapiephase B<sup>5</sup> müssen etwa 53 Patienten (das heißt <math>\approx 33/0.95/0.65</math>) eingeschlossen werden.</p> <p>Unter der Annahme einer Ausfallrate der Rebiopsie vor Einleitung der Therapiephase B von 25% aufgrund von klinischer Verschlechterung, sind etwa 53 Patienten ausreichend, um eine Anzahl von 40 Tumorbiopsaten sowohl im Rahmen der Screeningperiode, als auch nach Versagen der Nivolumab-Monotherapie zu erhalten.</p> <p>In jedem Falle wird die Rekrutierung solange erfolgen, bis 33 Studienpatienten für die Analyse des primären Endpunktes evaluierbar sind UND von 40 Patienten <u>evaluierbare</u> Rebiopsien im Rahmen des Screenings, sowie nach Versagen der Nivolumab-Monotherapie vor Einleitung der Therapiephase B gewonnen wurden.</p> <p>Die statistischen Methoden sind überwiegend deskriptiv, so auch die Methodik für Raten, Verhältnisse, zusammenfassende Statistik (Durchschnitt,</p>

	<p>Standardabweichung und Perzentile (0, 25, 50, 75, 100) für regelmäßige Variablen; Anzahl und Prozent für qualitative Variablen) und Ereigniszeitanalyse (Schätzung nach Kaplan-Meier, konkurrierende Risikomodelle). Zur Verbesserung der Interpretation der Daten werden Konfidenzintervalle berechnet. Die prädiktive Funktion von Biomarkern (einzeln und in Kombination) wird über Regressionsanalysen und Analyse von ROC-Kurven ermittelt.</p> <p>Die Subgruppenanalysen erfolgen nach PD-L1-Positivität (ja/nein), Geschlecht und Therapieansprechen unter Nivolumab (primäre/sekundäre Resistenz).</p> <p><u>Kohorte 2:</u> Analog zu Kohorte 1.</p>
Haupteinschlusskriterien	<ul style="list-style-type: none"> <li>• Kohorte 1: Zweitlinientherapie für Patienten mit histologisch oder zytologisch gesichertem, fortgeschrittenem Adenokarzinom der Lunge im Stadium IIIB/IV mit Tumorprogress nach Platin-haltiger Erstlinientherapie. Patienten, die eine adjuvante oder neoadjuvante Therapie, oder eine definitive Radiochemotherapie erhalten haben und innerhalb von sechs Monaten nach Vollendung der Therapie ein Rezidiv oder einen Tumorprogress mit Stadium IIIB/IV erleiden, sind zur Teilnahme berechtigt.</li> <li>• Kohorte 2: Zweitlinientherapie für Patienten mit histologisch oder zytologisch gesichertem SCLC in frühem oder fortgeschrittenem Stadium mit Tumorprogress nach Platin-haltiger Erstlinientherapie.</li> </ul> <p>Die folgenden Einschlusskriterien gelten für die Kohorte 1 und 2:</p> <ul style="list-style-type: none"> <li>• Unterschriebene und datierte Patienteneinwilligung, welche vor jeglicher Studien-spezifischen Maßnahme eingeholt werden muss und welche zuvor von einer unabhängigen Ethikkommission genehmigt wurde</li> <li>• Männliche oder weibliche Patienten <math>\geq 18</math> Jahre</li> <li>• Eastern Cooperative Oncology Group (ECOG) Performance Status von 0-1</li> <li>• Studienpatienten müssen bereit sein, mindestens zwei Tumorbiopsien durchführen zu lassen (Baseline und vor Einleitung der Therapiephase B)</li> <li>• Der jeweilige Prüfarzt muss den Studienpatienten für fähig erachten, zwei Tumorbiopsien durchführen zu lassen (Baseline und bei Einleitung der Therapiephase B)</li> <li>• Mindestens eine nach RECIST 1.1 auswertbare Tumorerläsion im CT oder MRT. Zielläsionen können in einer zuvor bestrahlten Region liegen, wenn ebendort ein Tumorprogress nach Vollendung der Bestrahlung dokumentiert wurde</li> <li>• Patienten mit ZNS-Metastasen dürfen an der Studie teilnehmen, wenn diese behandelt wurden und die Patienten für mindestens 28 Tage vor Verabreichung der ersten Studienmedikation ihren neurologischen Ausgangsstatus wieder erreicht haben (davon ausgenommen sind verbleibende Symptome, die mit der Therapie in Zusammenhang stehen). Zusätzlich darf keine Therapie mit Corticosteroiden mehr notwendig sein, bis auf eine stabile oder abnehmende Dosis von täglich <math>\leq 10</math> mg Predisonäquivalent.</li> </ul>
Hauptausschlusskriterien	<ul style="list-style-type: none"> <li>• Patienten mit Plattenepithelkarzinom der Lunge</li> <li>• Betrifft nur die Kohorte 1: aktivierende EGFR-Mutation oder ALK-Translokation</li> <li>• Mehr als eine vorhergehende Chemotherapielinie beim fortgeschrittenen NSCLC</li> <li>• Vorliegen eines medizinischen Zustandes, der mit signifikant erhöhtem Risiko für Blutungskomplikationen im Rahmen der Tumorbiopsie einhergeht (z.B. bekannte Koagulopathie, therapeutische Antikoagulation)</li> <li>• Aktive Hirn- oder leptomeningeale Metastase. Patienten mit Hirnmetastasen kommen für den Studieneinschluss in Frage, wenn die Metastase behandelt wurde und im MRT vier Wochen nach Abschluss der Therapie, sowie innerhalb von 28 Tagen vor Beginn der Studienmedikation kein Progress nachzuweisen ist. Außerdem darf für</li> </ul>

	<p>mindestens zwei Wochen vor Studientherapiegabe keine Notwendigkeit einer systemischen Therapie mit Corticosteroiden &gt; 10 mg Prednisonäquivalent täglich bestehen</p> <ul style="list-style-type: none"> <li>• Aktuell vorliegende, oder innerhalb der letzten fünf Jahre vor Studieneinschluss zurückliegende, weitere Malignomerkkrankung, mit Ausnahme von adäquat behandeltem Basalzellkarzinom oder Plattenepithelkarzinom der Haut, oder jedes anderen adäquat behandelten Carcinoma in situ</li> <li>• Patienten mit aktiver, bekannter, oder vermuteter Autoimmunerkrankung. Patienten mit Vitiligo, Diabetes mellitus Typ 1, Autoimmunhypothyreose welche lediglich einer Hormonersatztherapie bedarf, Psoriasis ohne Notwendigkeit einer systemischen Therapie, oder Patienten mit einer Autoimmunerkrankung, von der nicht zu erwarten ist, dass sie ohne externen Auslöser wieder auftritt, kommen für den Studieneinschluss in Frage</li> <li>• Aktive oder chronische Hepatitis B- oder Hepatitis C-Infektion</li> <li>• Bekannte Infektion mit dem humanen Immundefizienzvirus (HIV) oder positiver HIV-Test, oder bekannte AIDS-Erkrankung (acquired immunodeficiency syndrome)</li> <li>• Jedweder Zustand, der eine systemische Therapie mit entweder Corticosteroiden (&gt; 10 mg Prednisonäquivalent täglich), oder anderer immunsuppressiver Medikation innerhalb von 14 Tagen vor Verabreichung der ersten Studienmedikation, erforderlich macht. Inhalative oder topische Steroide und Corticosteroiddosen als Nebennierenersatztherapie von &gt; 10 mg Prednisonäquivalent pro Tag sind bei Abwesenheit einer aktiven Autoimmunerkrankung erlaubt</li> <li>• Patienten mit interstitieller Lungenerkrankung, die symptomatisch ist, oder sich störend auf die Detektion oder das Management von Therapiebezogenen pulmonalen Toxizitäten auswirken könnte</li> <li>• Vorhergehende systemische Therapie mit einem anti-PD-1-, anti-PD-L1-, anti-PD-L2- oder anti-CTLA-4-Antikörper, oder jedem anderen Antikörper oder Medikament welcher/welches spezifisch auf die T-Zell-Kostimulation oder einen Immuncheckpoint-Signalweg zielt</li> <li>• Jedwede/jedeweder andere ernsthafte oder unkontrollierte medizinische Zustand, aktive Infektion, Auffälligkeit bei der körperlichen Untersuchung, Laborwertveränderung, Veränderung des Geisteszustandes oder psychiatrische Auffälligkeit, die nach Ansicht des Prüfarztes die Fähigkeit des Patienten sich an die für die Studie notwendigen Vereinbarungen zu halten beeinträchtigt, erheblich das Patientenrisiko erhöht, oder sich negativ auf die Interpretation der Studienergebnisse auswirkt</li> <li>• Bekannte Allergie oder schwere Hypersensitivitätsreaktion gegen einen Bestandteil der Studienmedikation, oder gegen jeglichen monoklonalen Antikörper</li> </ul>
Studienuntersuchungen	<p>Kohorte 1:</p> <p>Der primäre Endpunkt der Kohorte 1 ist die Ansprechrate nach Hinzunahme von Ipilimumab zur Nivolumabtherapie. Die Ansprechrate ist definiert als der Anteil von Patienten mit einer Reduktion der Tumorlast nach RECIST 1.1 (lokale Auswertung). Die Tumorkontrolluntersuchungen beginnen in der Woche 8 und werden in Therapiephase A alle 8 Wochen (+/- 1 Woche) durchgeführt, jedoch nur bis Woche 49 (C25D1), dann alle 12 Wochen. Gleichermaßen werden die Untersuchungen in Therapiephase B alle 8 Wochen durchgeführt, jedoch nur bis zur Woche 49 (C25D1), im weiteren Verlauf alle 12 Wochen (+/- 1 Woche).</p> <p>Kohorte 2:</p> <p>Der primäre Endpunkt der Kohorte 2 ist die Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab. Die Ansprechrate ist definiert als der Anteil von Patienten mit einer Reduktion der Tumorlast nach RECIST 1.1 (lokale Auswertung). Die Tumorkontrolluntersuchungen finden in der Therapiephase A in der Woche 5 (C3D1) und Woche 11 (C6D1) statt. In Therapiephase B findet die erste Tumorkontrolluntersuchung an C4D1 (+/- 1</p>

	Woche) statt und im Anschluss daran alle 8 Wochen bis Woche 47 (C24D1), im weiteren Verlauf alle 12 Wochen (+/- 1 Woche).
Studiendauer	Erster Patient erste Visite (FPFV): 04/2017 Letzter Patient erste Visite (LPFV): 04/2019 Letzter Patient letzte Visite (LPLV): 09/2020 Studienabschlussbericht: 09/2021

NSCLC, second line

**AIO-TRK-0117: Machbarkeit und Sicherheit von Nintedanib in Kombination mit Nivolumab bei vorbehandelten Patienten mit fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie - Eine AIO-Phase-Ib-Studie (NintNivo)**

<b>AIO-Studie</b>	
Studennummer:	AIO-TRK-0117 - NintNivo
Status:	Genehmigt, Rekrutierungsbeginn ab April/Mai 2018
Rekrutierungszeitraum:	2018 - 2020
Weitere Zentren:	sind aktuell für Dosisfindungsphase leider nicht möglich. Ja, für Erweiterungsphase (2019)
Letzte Aktualisierung:	16.04.2018

Prüfplan Version	V 3.0
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Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Tel: +49 30 814534431 Fax: +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Studiendesign	offene, einarmige Phase 1b Studie
Indikation	Patienten mit fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Versagen der Erstlinien-Therapie.
Anzahl Prüfzentren	Ca 10 (4 Prüfzentren für den safety run-in)
Primäre Studienziele	Die primären Studienziele sind die Bestimmung einer sicheren Dosis für die Kombinationstherapie mit Nintedanib + Nivolumab und die Erzeugung von explorativen Wirksamkeitsdaten bei vorbehandelten Patienten mit fortgeschrittenem oder metastasiertem NSCLC mit einer Adenokarzinomhistologie
Sekundäres Ziel	Untersuchung der Sicherheit und Verträglichkeit der Kombinations-therapie mit Nintedanib und Nivolumab
Exploratorische Ziele	Korrelation der PD-L1-Expression und anderer Immun-Biomarker mit Wirksamkeits-Ergebnissen.
Geplante Fallzahl	N = 56-62 Patienten <ul style="list-style-type: none"> <li>Safety run-in: N = 6-12 (3-6 Patienten je Dosislevel, nach einem 3+3 Design)</li> </ul>



	<ul style="list-style-type: none"> <li>• Phase-1b-Erweiterung: N = 50</li> </ul>
Einschlusskriterien	<ol style="list-style-type: none"> <li>14. Vorliegen einer vom Patienten unterschriebenen und datierten Einwilligungserklärung einschließlich aller lokal benötigten Genehmigungen (z.B. EU-Datenschutzrichtlinie) bevor jedwede studienspezifische Maßnahme, einschließlich Screening durchgeführt wird.</li> <li>15. Patient erklärt seine Einwilligung und ist in der Lage an Visiten, Untersuchungen und der Behandlung inklusive der Nachbeobachtung gemäß Prüfplan samt aller damit verbundenen Anforderungen teilzunehmen</li> <li>16. Alter <math>\geq 18</math> Jahre zum Zeitpunkt des Studieneinschlusses</li> <li>17. Histologisch bestätigtes Adenokarzinom der Lunge des Stadiums IIB/IV nach UICC7</li> <li>18. Vorangegangene systemische Chemotherapie einschließlich einer Erhaltungstherapie für fortgeschrittenes und metastasiertes NSCLC. Den Patienten soll eine Standard Chemotherapie, wie nach den aktuellen lokalen Leitlinien zur klinischen Praxis empfohlen, angeboten werden. Neoadjuvante und adjuvante Therapien sind erlaubt, vorausgesetzt, dass eine Krankheitsprogression / ein Rückfall mehr als 6 Monate nach Beendigung der Therapie auftrat.</li> <li>19. Allgemeinzustand nach ECOG 0-1</li> <li>20. Angenommene Lebenserwartung von mindestens 3 Monaten</li> <li>21. Patienten müssen eine nach RECIST-1.1-Kriterien messbare Erkrankung haben (mindestens eine eindimensional mittels CT oder MRT messbare Zielläsion). Wenn eine potenzielle Zielläsion zuvor bestrahlt wurde, muss ein deutlicher Nachweis der Progression am Zielort dokumentiert sein.</li> <li>22. Ein Formalin-fixierter, Paraffin-eingebetteter (FFPE) Tumorgewebeblock (archiviert oder neu) oder ca. 10-15 ungefärbte Schnitte von Tumorproben (Schnitte müssen neu sein und auf Trägern aufgebracht werden, die vom Sponsor zur Verfügung gestellt werden) müssen für PD-L1 und andere Biomarker-Tests zur Verfügung stehen. Bei der Biopsie sollte es sich um eine excisionale, inzisionale oder eine Vakuumbiopsie handeln. Eine Feinnadelpunktion ist unzureichend.</li> <li>23. Vorangegangene Therapien und Operationen sind erlaubt, wenn diese 2 Wochen (für kleinere Eingriffe) oder 4 Wochen (palliative Strahlentherapie bei Knochenschmerzen; größere Eingriffe mit kompletter Wundheilung) jeweils vor Beginn der Behandlung abgeschlossen wurden und der Patient sich von den toxischen Wirkungen erholt hat.</li> <li>24. Adäquate Blut-, Leber- und Nierenwerte (bis spätestens 14 Tage vor Beginn der Behandlung erhalten): <ul style="list-style-type: none"> <li>• Anzahl weißer Blutzellen <math>\geq 2000/\mu\text{l}</math></li> <li>• Anzahl Neutrophile <math>\geq 1500/\mu\text{l}</math></li> <li>• Anzahl Blutplättchen <math>\geq 100 \times 10^3/\mu\text{l}</math></li> <li>• Haemoglobin <math>&gt; 9,0 \text{ g/dl}</math></li> <li>• Serum-Kreatinin <math>\leq 1,5 \times \text{ULN}</math> oder Kreatinin-Clearance (CrCl) <math>\geq 40 \text{ ml/min}</math> (nach der Cockcroft-Gault Formel)</li> <li>• AST/ALT <math>\leq 1,5 \times \text{ULN}</math> (<math>&lt; 3 \times \text{ULN}</math> im Falle von Lebermetastasen)</li> <li>• Gesamt-Bilirubin <math>\leq 1,5 \times \text{ULN}</math></li> </ul> </li> <li>25. Frauen im gebärfähigen Alter müssen geeignete Methode(n) zur Empfängnisverhütung anwenden. <i>Frauen im gebärfähigen Alter sollten eine geeignete Schwangerschaftsverhütungsmethode für 5 Monate (30 Tage plus die Zeit, die Nivolumab benötigt um 5 Halbwertszeiten zu durchlaufen) nach der letzten Gabe von Nivolumab. Da der Effekt von Nintedanib auf den Metabolismus und die Wirksamkeit von Verhütungsmitteln nicht untersucht ist, sollen zur Vermeidung von Schwangerschaften Barrieremethoden als zusätzliche Form der Empfängnisverhütung angewendet werden.</i></li> <li>26. Frauen im gebärfähigen Alter müssen einen negativen Schwangerschaftstest (Serum oder Urin) innerhalb von 24 Stunden vor Studienbehandlung, monatlich während der Behandlung und bis 5 Monate nach der letzten Verabreichung der Prüfmedikation, vorweisen (minimale Sensitivität 25 IU/l oder äquivalente Einheiten des HCG)</li> </ol>

	<p>27. Männliche Patienten, die mit einer gebärfähigen Frau sexuell aktiv sind, müssen eine geeignete Empfängnisverhütungsmethode anwenden (Fehlerrate &lt; 1% pro Jahr). Sexuell aktive männliche Patienten, die Nivolumab erhalten, werden angewiesen, die Empfängnisverhütung für einen Zeitraum von 7 Monaten nach der letzten Gabe der Studienmedikation anzuwenden. Nichtgebärfähige Frauen (z.B. postmenopausal oder durch operative Sterilisation) und Männer mit Azoospermie benötigen keine Empfängnisverhütung.</p>
Ausschlusskriterien	<p>34. Mehr als eine vorhergehende Behandlungslinie für fortgeschrittenes oder metastasiertes NSCLC</p> <p>35. Patienten mit aktiven ZNS-Metastasen sind ausgeschlossen. Patienten sind einschussfähig, wenn die ZNS-Metastasen adäquat behandelt werden und die Patienten neurologisch für mindestens 4 Wochen vor Studieneinschluss zum Niveau der Basiserhebung zurückgekehrt sind (mit Ausnahme von restlichen Anzeichen oder Symptomen im Zusammenhang mit der ZNS-Behandlung). Darüber hinaus müssen die Patienten entweder ohne Kortikosteroide auskommen, oder auf einer stabilen oder abnehmenden Dosis von <math>\leq 10</math> mg täglichem Prednison (oder gleichwertig) sein.</p> <p>36. Leptomeningeale Erkrankung, karzinomatöse Meningitis, chronischer Diarrhö oder Kurzdarmsyndrom</p> <p>37. Bekannte aktivierende EGFR-Mutation oder bekannte ALK-Translokation</p> <p>38. Patienten mit symptomatischer interstitieller Lungenerkrankung</p> <p>39. Jede vorherige Behandlung mit Anti-Tumor-Impfstoffen oder immunstimulatorischen Anti-Tumor-Wirkstoffen, Nintedanib oder einem anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 Antikörper oder jeder andere Antikörper oder jedes Arzneimittel, das spezifisch gegen T-Zell-Co-Stimulation oder Immun-Checkpoint-Pathways gerichtet ist.</p> <p>40. Bestehende Toxizitäten infolge vorhergehender Anti-Tumor-Behandlung, ausgenommen Haarausfall und Fatigue, die nicht auf Grad 1 (NCI CTCAE Version 4.03) oder zum Wert der Basiserhebung vor Gabe der Studienmedikation abgeklungen ist.</p> <p>41. Größere Verletzungen innerhalb von 4 Wochen vor Beginn der Studienbehandlung mit unvollständiger Wundheilung und/oder geplante Operation während der Studienbehandlungsphase.</p> <p>42. Patienten mit aktiver, bekannter oder vermuteter Autoimmunerkrankung sind nicht einschussfähig. <b>HINWEIS:</b> Patienten mit Vitiligo, Diabetes Mellitus Typ 1, residuale Schilddrüsenüberfunktion (aufgrund einer Autoimmunerkrankung), die nur einen Hormonersatz erfordert, Psoriasis, die keine systemische Behandlung erfordert oder mit Bedingungen, die in der Abwesenheit eines externen Auslösers nicht erwartet werden, sind einschussfähig.</p> <p>43. Patienten, die aufgrund einer Erkrankung eine systemische Behandlung entweder mit Kortikosteroiden benötigen (<math>&gt; 10</math> mg pro Tag Prednisonäquivalente) oder andere immunsuppressive Medikamenten innerhalb von 14 Tagen vor der ersten Gabe der Studienmedikation. <b>HINWEIS:</b> inhalierte oder topikale Steroide oder Nebennierenersatz mit einer Dosis von <math>&gt; 10</math> mg / Tag Prednisonäquivalente, sind in Abwesenheit einer aktiven Autoimmunerkrankung erlaubt.</p> <p>44. Positiver Test auf Hepatitis-B-Virus Oberflächenantigen (HBV sAg) oder Hepatitis-C-Virus-RNA (HCV RNA), die Hinweis auf eine akute oder chronische Infektion geben, ODER positiver Test auf humanes Immundefizienz-Virus (HIV)</p> <p>45. Vorgeschichte einer schweren Überempfindlichkeitsreaktion gegen andere monoklonale Antikörper oder jegliche Inhaltsstoffe. Bekannte Überempfindlichkeit gegen Nintedanib, Erdnüsse, Soja oder jegliche Inhaltsstoffe oder Kontrastmittel.</p> <p>46. Strahlentherapie der Zielläsion innerhalb der letzten 3 Monate vor Baseline-Imaging (siehe auch Einschlusskriterium Nr. 8).</p> <p>47. Radiographischer Nachweis von kavitären oder nekrotischen Tumoren</p> <p>48. Zentral gelegene Tumore mit radiographischen Nachweis (CT oder MRT) einer lokalen Invasion der großen Blutgefäße</p> <p>49. Therapeutische Antikoagulation mit Medikamenten, die eine INR-Überwachung erfordern (außer niedrig dosiertem Heparin und / oder</p>

	<p>Heparinspülung, wie es für die Aufrechterhaltung einer intravenösen Verweilkanüle erforderlich ist) oder Anti-Thrombozyten-Therapie (mit Ausnahme der Niedrigdosis-Therapie mit Acetylsalicylsäure &lt; 325 mg pro Tag)</p> <p>50. Vorgeschichte eines klinisch signifikanten hämorrhagischen oder thromboembolischen Ereignisses in den letzten 6 Monaten</p> <p>51. Bekannte vererbte Prädisposition für Blutungen oder Thrombosen</p> <p>52. Signifikante Herzerkrankung (d.h. unkontrollierter Bluthochdruck, instabile Angina pectoris, vorhergehender Infarkt innerhalb der letzten 12 Monate vor Beginn der Studienbehandlung, kongestive Herzinsuffizienz &gt; NYHA II, schwere Herzrhythmusstörungen, perikardialer Erguss)</p> <p>53. Aktiver Alkohol- oder Drogenmissbrauch</p> <p>54. Signifikanter Gewichtsverlust (&gt; 10 % des Körpergewichts) innerhalb der letzten 6 Monate vor Studieneinschluss</p> <p>55. Vorgeschichte einer malignen Erkrankung (die sich vom NSCLC unterscheidet), die entweder fortschreitet, oder eine aktive Behandlung erfordert</p> <p>56. Patienten mit vorhergehender maligner Erkrankung (Ausnahmen sind: Nicht-Melanom-Hauttumore, und die folgenden in-situ Krebserkrankungen: der Blase, des Magens, des Dickdarms, Zervix/Dysplasie, Endometrium, Melanom oder der Brust) werden nicht eingeschlossen, es sei denn, es wurde eine vollständige Remission mindestens 2 Jahre vor dem Studieneinschluss erreicht UND es ist keine zusätzliche Therapie erforderlich oder voraussichtlich während des Studienzeitraums erforderlich.</p> <p>57. Schwangere, stillende, gebärfähige Patientinnen oder gebärfähige Patienten, die keine hocheffektive Empfängnisverhütungsmethode anwenden (Fehlerrate von weniger als 1% pro Jahr)</p> <p>58. Erhalt der letzten Gabe einer Anti-Krebs-Therapie (Chemotherapie, Immuntherapie, endokrine Therapie, gezielte Therapie, biologische Therapie, Tumor-Embolisation, monoklonale Antikörper, andere zu prüfende Wirkstoffe) ≤ 28 Tage vor der ersten Gabe der Studienmedikation</p> <p>59. Jede andere schwerwiegende oder unkontrollierte Erkrankung (z.B. aktive Geschwüre), aktive Infektion, körperliche Untersuchungsbefunde, Laborbefunde, veränderter geistiger Status oder psychiatrischer Zustand, der, im Ermessen des Prüfarztes, die Fähigkeit des Patienten beeinflussen würde, die Anforderungen der klinischen Studie zu erfüllen, das Risiko für den Patienten erheblich erhöhen oder die Interpretierbarkeit der Studienergebnisse beeinflussen würde.</p> <p>60. Vom Sponsor, Prüfzentrum oder Prüfarzt abhängige Personen</p> <p>61. Patienten, die auf gerichtliche oder behördliche Anordnung in einer Anstalt untergebracht sind (§ 40 Abs. 1 S. 3 Nr. 4 AMG).</p>						
Prüfmedikation	<ul style="list-style-type: none"> <li>• Nintedanib</li> <li>• Nivolumab</li> </ul>						
Behandlungsablauf	<p><b>Safety run-in – Dosisfindung</b></p> <p>Die safety run-in Phase wird nach einem Standard-3+3-Design zur Dosisescalation/-deescalation erfolgen, in das, je nach Auftreten von dosisbegrenzenden Toxizitäten, 3 bis 6 Patienten in jeder Kohorte nacheinander eingeschlossen werden.</p> <p>Die folgenden Dosisstufen werden untersucht:</p> <table border="1" data-bbox="499 1753 1390 1944"> <thead> <tr> <th data-bbox="499 1753 799 1816">Dosislevel A</th> <th data-bbox="799 1753 1085 1816">Dosislevel B</th> <th data-bbox="1085 1753 1390 1816">Dosislevel C</th> </tr> </thead> <tbody> <tr> <td data-bbox="499 1816 799 1944"> <ul style="list-style-type: none"> <li>• <b>Nintedanib 150 mg bid</b></li> <li>• Nivolumab 240 mg Q2W</li> </ul> </td> <td data-bbox="799 1816 1085 1944"> <ul style="list-style-type: none"> <li>• <b>Nintedanib 200 mg bid</b></li> <li>• Nivolumab 240 mg Q2W</li> </ul> </td> <td data-bbox="1085 1816 1390 1944"> <ul style="list-style-type: none"> <li>• <b>Nintedanib 100 mg bid</b></li> <li>• Nivolumab 240 mg Q2W</li> </ul> </td> </tr> </tbody> </table> <p>Die empfohlene Phase-2-Dosis (RP2D) wird die höchste Dosis sein, bei welcher die DLT-Häufigkeit unter 33% liegt, wenn keine anderen Sicherheits- oder Durchführbarkeitsüberlegungen bestehen.</p> <p><b>Erweiterungsphase</b></p> <ul style="list-style-type: none"> <li>• Nintedanib RP2D + Nivolumab 240 mg Q2W</li> <li>• Wenn die Behandlung aufgrund von Toxizitäten dauerhaft unterbrochen</li> </ul>	Dosislevel A	Dosislevel B	Dosislevel C	<ul style="list-style-type: none"> <li>• <b>Nintedanib 150 mg bid</b></li> <li>• Nivolumab 240 mg Q2W</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Nintedanib 200 mg bid</b></li> <li>• Nivolumab 240 mg Q2W</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Nintedanib 100 mg bid</b></li> <li>• Nivolumab 240 mg Q2W</li> </ul>
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	<p>wird und die Toxizitäten eindeutig eines der Studienmedikamente zugeordnet werden können, kann die Studienbehandlung als Monotherapie fortgesetzt werden.</p>
Endpunkte	<p>Primäre Endpunkte:</p> <ul style="list-style-type: none"> <li>• Sicherheit und Verträglichkeit, bestimmt durch die Häufigkeit und Schwere von unerwünschten Ereignissen</li> <li>• progressionsfreie Überlebensrate bei 6 und 9 Monaten</li> </ul> <p>Sekundäre Endpunkte:</p> <ul style="list-style-type: none"> <li>• Ziel-Ansprechrates (ORR)</li> <li>• Progressionsfreies Überleben (PFS)</li> <li>• Zeit bis zur Tumor-Progression (time to progression, TTP)</li> <li>• Gesamtüberleben (OS)</li> <li>• AEs/SAEs und therapiebedingte Nebenwirkungen nach CTC 4.03</li> <li>• Dauer des Ansprechens (duration of response, DoR) und Zeit des Ansprechens (time to response, TTR)</li> </ul> <p>Exploratorische Endpunkte:</p> <ul style="list-style-type: none"> <li>• PD-L1 Expressionsstatus</li> <li>• Korrelation der Wirksamkeit und PD-L1 Expression und andere Biomarker</li> <li>• Korrelation von Wirksamkeit und Zeit seit Beginn der Erstlinien-Therapie</li> </ul>
Rationale	<p>Zwei verschiedene Behandlungskonzepte haben zu einem verbessertem Überleben in der Zweitlinien-Behandlung des NSCLC beigetragen: im Vergleich zu Docetaxel allein hat die anti-angiogene Behandlung mit Nintedanib in Kombination mit Docetaxel eine signifikante Verlängerung des Gesamtüberlebens in der LUME Lung 1-Studie für Patienten mit Adenokarzinom gezeigt (Medianes OS: 12,6 vs 10,3 Monate; HR=0,83; 95% CI; 0,70-0,99; P=0,0359) [Reck et al. (2014), <i>Lancet Oncol.</i>]. In der Checkmate 057 Studie konnte eine Immun-Checkpoint-Inhibition mit Nivolumab im Vergleich zu Docetaxel eine OS-Verlängerung in Patienten mit Nicht-Plattenepithel-NSCLC erzielen (12,2 vs 9,4 Monate; HR=0,73; 96% CI; 0,59-0,89; P=0,002).</p> <p>Kombinationsstrategien haben das Potential das Ansprechen auf Immuntherapien zu erhöhen, indem sie die endogene Antitumor-reaktion auf verschiedenen Ebenen stimulieren.</p> <p>Es gibt zunehmendes Verständnis dafür, dass vaskuläre Endothelzellen und VEGFR-Signalisierung nicht nur für die Tumorangio-genese wichtig sind, sondern auch eine wichtige Rolle bei der Regulation von Immunantworten innerhalb der Tumor-Mikroumgebung spielen. Daher sind synergistische Effekte zwischen antiangiogenen Behandlungen und Immun-Checkpoint-Blockaden zu erwarten.</p> <p>Es wurde gezeigt, dass</p> <ul style="list-style-type: none"> <li>• VEGFR 1 und 2 eine Rolle bei der dendritischen Zellreifung spielen (VEGF hemmt die Reifung von DCs) [Dikov et al. (2005), <i>Journal of Immunol.</i>]</li> <li>• eine Inhibition der VEGFR1-Signalisierung unter Verwendung eines neutralisierenden VEGFR1-spezifischen monoklonalen Antikörpers die DC-Funktion wiederherstellt [Tartour et al. (2011), <i>Cancer Metastasis Rev.</i>; Bruno et al. (2014), <i>Front Oncol.</i>]</li> <li>• unreife DCs die Immuntoleranz fördern und regulatorische T-Zellen induzieren</li> <li>• die Inhibition von VEGFR verhindert, dass Lungenendothelzellen induziert werden, um T-Zell-Funktionen zu unterdrücken [Mulligan (2010), <i>J Immunother.</i>]</li> <li>• eine Blockade von VEGFR2 die Akkumulation von MDSCs reduziert [Finke et al. (2011), <i>Int Immunopharmacol.</i>]</li> <li>• MDSCs und regulatorische T-Zellen eine wichtige Rolle bei der Unterdrückung der Entwicklung einer Antitumor-Immunität bei Krebspatienten spielen</li> <li>• die anti-angiogene Behandlung die Verfügbarkeit von Glukose und Sauerstoff erhöht (durch die vaskuläre Normalisierung, wie für Nintedanib gezeigt [Kutluk et al. (2013), <i>Mol Cancer Ther.</i>; Mross et al. (2014), <i>BMC Cancer</i>] gezeigt) und den Verlust von ICAM-1 und VCAM-1 auf Endothelzellen verhindert, wodurch die T- Zell-Migration und Infiltration erhöht werden [Kamrava et al. (2009), <i>Molecular bioSystems</i>; Voron et al.</li> </ul>

	<p>(2014), <i>Front Oncol.</i>; Dirx et al. (2006), <i>The FASEB Journal</i>]</p> <p>Somit wird vermutet, dass eine kombinierte Behandlung mit Nintedanib und Nivolumab zu einer verbesserten Sensitivität für die PD1-Blockade führen kann, indem eine Verschiebung von einer immunsuppressiven zu einer immunsupportiven Tumor-Mikroumgebung durch Nintedanib-vermittelte Effekte induziert wird.</p> <p>In dieser Phase Ib-Studie soll die Sicherheit der Kombinationsbehandlung mit Nintedanib und Nivolumab bei Patienten mit NSCLC untersucht und erste explorative Wirksamkeitssignale generiert werden.</p>	
Sicherheitsdaten	<ul style="list-style-type: none"> <li>• Sichere Dosis und Dosis-limitierende Toxizitäten</li> <li>• AEs / SAEs / therapiebedingte Nebenwirkungen nach CTC 4.03</li> <li>• Häufigkeit abnormer Laborparameter</li> </ul>	
Rationale für die Fallzahl und Statistik	<p>Nach der Festlegung einer sicheren Dosis in N = 6-12 Patienten und einer explorativen Analyse ist geplant, 50 weitere Patienten mit vorbehandelten fortgeschrittenen Adenokarzinom der Lunge zu registrieren.</p> <p>Deskriptive statistische Instrumente werden verwendet, um die Wirksamkeit und Verträglichkeit zu beschreiben.</p> <p>Die 6-monatige PFS-Rate sowie die 9-monatige PFS-Rate werden mit den Ergebnissen der LUME 1 und der Checkmate 057-Studie verglichen und verwendet, um eine weitere Untersuchung dieser Kombination in einer randomisierten Studie zu fördern.</p> <p>Die zu rekrutierende Anzahl von Patienten beträgt N = 56-62</p>	
Zeitplan	<p>Einschluss erster Patient (FPI)</p> <p>Einschluss letzter Patient (LPI)</p> <p>Letzter Patient letzte Behandlung (LPLT)</p> <p>Studienende (Ende der Nachbeobachtungsphase nach LPLT)</p> <p>Studienreport</p> <p>Publikation</p>	<p>Q2 /2018</p> <p>nach ca. 29 Monaten</p> <p>nach ca. 35 Monaten</p> <p>nach ca. 47 Monaten</p> <p><u>Q2-Q3 2021</u></p> <p>nach ca. 57 Monaten</p> <p>nach ca. 60 Monaten</p>

### Registerstudie metastasiertes NSCLC

#### **AIO-TRK-0315: Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients (CRISP)**

##### **AIO-Studie**

Studiennummer/-Code:	AIO-TRK-0315 - CRISP
Status:	in Rekrutierung
Rekrutierungszeitraum:	2015 - 2018
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	September 2017

Study type	Open, non-interventional , prospective, multi-center clinical research platform
Contact details	<p>Sponsor: AIO-Studien-gGmbH, Berlin, info@aio-studien-ggmbh.de</p> <p>Steering Board Spokesperson: Prof. Dr. Frank Griesinger</p> <p>Pius Hospital, Oldenburg, frank.griesinger@pius-hospital.de</p> <p>Concept, Project Management and Analyses: iOMEDICO, Freiburg, annette.fleitz@iomedico.com</p>

Purpose and rationale	<p>Thorough knowledge of the treatment reality, e.g. characteristics, diagnostic, treatment and outcome of unselected patients in real-life practice, is crucial to evaluate and improve the quality of care for patients with metastatic non-small cell lung cancer (NSCLC).</p> <p>The purpose of CRISP is to set up a national clinical research platform to document uniform data on the molecular testing, treatment, course of disease in patients with advanced or metastatic NSCLC not amenable to curative treatment. A particular focus is on molecular biomarker testing of patients before the start of first-line treatment. The data shall be used to assess the current state of care and to develop recommendations concerning topics that could be improved.</p> <p>PRO assessment will provide large-scale data on quality of life and anxiety/depression for real-life patients in routine practice. In addition, two questionnaires (concerning individual quality of life and patient-caregiver communication) will be validated in German patients with metastatic NSCLC. Furthermore CRISP will set up a decentralized clinically annotated tissue repository for future collaborative, investigational scientific biomarker testing.</p>
Objectives	<p>To assess molecular biomarker testing, treatment and outcome of patients with advanced or metastatic NSCLC in Germany, in particular:</p> <ul style="list-style-type: none"> <li>• To collect data on the frequency, methodology and results of molecular biomarker testing before first-line and later-line treatment</li> <li>• To describe systemic treatments and sequential treatments applied in real-life practice</li> <li>• To assess effectiveness of systemic treatments in regards to response rate, progression free survival and overall survival</li> <li>• To describe physician-reported factors affecting treatment decision making besides biomarker profiling</li> <li>• To collect key data on specific supportive therapies</li> <li>• To investigate changes in diagnostics, treatment or outcome during the course of the project</li> <li>• To evaluate patient-reported outcomes concerning (1) general health-related and individual quality of life (QoL), (2) physical and psychological well-being, (3) anxiety and depression, (4) patient-caregiver communication</li> </ul>
Population, number of patients and sites	<p>Patients with locally advanced or metastatic NSCLC at the start of palliative first-line systemic therapy. Of all patients recruited, 3,250 patients with non-squamous cell carcinoma will be tested for molecular alterations at the start of first-line treatment (CRISP patients). 1,750 patients with squamous can be tested for molecular alterations at the start of first-line treatment (CRISP patients). The remainder will be patients with untested non-squamous carcinoma (CRISP satellite patients).</p> <p>Patients will be recruited in up to 150 study sites (certified lung cancer centers, comprehensive cancer centers, hospitals and office-based oncology practices) in Germany.</p> <p>Patients included: 1208 (September 2017)</p>
More centers?	Yes
Inclusion criteria	<p>Patients who meet all of the following criteria are eligible for the project:</p> <ul style="list-style-type: none"> <li>• Histologically confirmed non-small cell lung cancer (NSCLC)</li> <li>• Stage IV or stage IIIB (UICC7) if patient is ineligible for curative surgery and/or radiochemotherapy</li> <li>• Informed consent no later than four weeks after start of (palliative) first-line treatment</li> <li>• Age <math>\geq</math> 18 years</li> <li>• Able to understand and willing to sign written Informed Consent and to complete patient-reported-outcome assessment instruments</li> </ul> <p>It is strongly recommended that patients' tumor samples are tested for EGFR mutation in exons 18-21, ALK rearrangement and preferably ROS1</p>

	rearrangement by a certified molecular pathology laboratory before the start of first-line treatment.														
Exclusion criteria	None														
Data collection	Baseline (demographic, clinical, tumor) characteristics, details on biomarker testing, including re-testing, treatment decision making, all systemic anti-cancer therapies including details, key data on radiotherapies, surgeries and specified supportive therapies, outcome (response, progression, survival), course of disease. Data will be documented at baseline and updated at least every three months.														
Patient-reported outcomes	Patient-reported outcomes will be assessed using the questionnaires, Functional Assessment of Cancer Therapy General (FACT-G), Patient Health Questionnaire for Depression and Anxiety – ultra brief form (PHQ4), Schedule for the Evaluation of Individual Quality of Life Questionnaire (SEIQoL-Q) and Cancer Communication Assessment tool for Patients and Families – Short (CCAT-PF-Short, (disclosure scale)  PROs will be assessed at the time of recruitment (baseline), every 2 months for up to 12 months and every 3 months thereafter for a maximum of 3 years.														
Statistics	Descriptive and exploratory statistics will be performed as described in the statistical analysis plan.														
Planned timelines	<table> <tr> <td>First Patient In (FPI)</td> <td>Q4/ 2015</td> </tr> <tr> <td>Last Patient In (LPI)</td> <td>Q4/ 2018</td> </tr> <tr> <td>Individual observation time</td> <td>3 years</td> </tr> <tr> <td>Last patient out (LPO)</td> <td>Q4/ 2021</td> </tr> <tr> <td>Interim analysis</td> <td>Annually</td> </tr> <tr> <td>Final analysis</td> <td>2022</td> </tr> <tr> <td>Publication</td> <td>Various publications during and after the project</td> </tr> </table>	First Patient In (FPI)	Q4/ 2015	Last Patient In (LPI)	Q4/ 2018	Individual observation time	3 years	Last patient out (LPO)	Q4/ 2021	Interim analysis	Annually	Final analysis	2022	Publication	Various publications during and after the project
First Patient In (FPI)	Q4/ 2015														
Last Patient In (LPI)	Q4/ 2018														
Individual observation time	3 years														
Last patient out (LPO)	Q4/ 2021														
Interim analysis	Annually														
Final analysis	2022														
Publication	Various publications during and after the project														

## Arbeitsgruppe Translationale Forschung

### Colorectal Cancer - translationale Studie – Organoidmodell

#### **AIO-TF-0217: Patient derived organoids to model cancer biology and predict treatment response – First line (PROMISE-First)**

##### **AIO-Studie**

Studiennummer/-Code:	AIO-TF-0217 – PROMISE-First
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 – 2020
Weitere Zentren:	leider keine weiteren möglich
Letzte Aktualisierung	16.10.2017

Study type	prospective, explorative, single arm non-interventional trial
Background	<p>Colorectal cancer frequently presents with advanced stage and metastasis. Furthermore, resistance to standard chemotherapeutic treatments is a great challenge. Hence, 5-year survival rate of patients with metastasized CRC remains to be only about 13%.</p> <p>Precision medicine raises hope of improved cancer survival rates. However, “druggable” mutations and biomarkers for response or resistance are yet scarce. The prediction of treatment response and analysis of acquired resistance in gastrointestinal tumors are particularly challenging. Sequential tumor biopsies for molecular analysis under treatment are burdensome and not well tolerated by patients. Liquid biopsies are limited to analysis of genetic and epigenetic changes, while no functional analyses are possible with such methods.</p> <p>Functional analysis of gene-drug interactions or drug resistance by high-content screening is an important research topic to identify potential novel biomarkers for response or resistance. Yet, functional screening is largely based on cell lines and has therefore substantial limitations.<sup>1</sup> The organoid culture system recently developed by Clevers and colleagues provides an excellent tool to analyze mechanisms of drug response and resistance. High success rates around 90% for establishing organoids from biopsies have been reported.<sup>2</sup> A direct translation of organoid screening into clinical practice has, however, not been established so far.</p> <p>References:  1. Iorio, F. et al., Cell (2016). doi:10.1016/j.cell.2016.06.017  2. Van de Wetering, M. et al., Cell 161, 933–945 (2015).</p>
Purpose and rationale	Innovative study concepts are needed to study therapy response and resistance of advanced tumors. We aim to establish ex-vivo models of advanced tumors (“Avatars”) before the start of palliative treatment. By treatment of the Avatar parallel to treatment of the patient with the same drugs, we will analyze mechanisms of therapy response and emerging resistance with the help of comprehensive molecular characterization. Also, by screening different drugs in the tumor model, response predictions can be made in advance.
Objectives	With this study, we aim to model treatment of advanced gastrointestinal cancer ex-vivo and in parallel to treatment of the patient. This will be done by establishing and treating individual patient derived organoids (Avatars) with the same regimen as the study patient. Thereby we aim to assess resistance mechanisms by molecular analysis of the Avatar. We also aim to support treatment decisions by testing multiple drugs in the organoid model. In particular, we aim:



	<ul style="list-style-type: none"> <li>- To establish individual patient derived organoids of tumor and normal tissue</li> <li>- To treat the individual tumor organoid with the same substances as the patient</li> <li>- To characterize molecular alterations of the tumor organoid emerging under treatment</li> <li>- To analyze gene-drug-response associations as potential predictive biomarkers</li> <li>- To assess the efficacy of systemic chemotherapy in regards to response rate and progression-free survival</li> <li>- To compare systemic chemotherapy in the patient with treatment results of the corresponding organoid</li> </ul>
Population, number of patients	20 patients with metastatic or locally non-resectable gastrointestinal cancer before the last established line of therapy. Patients will be recruited at University Hospital Mannheim and at additional centers throughout Germany. Drug screens and sequencing will be performed at DKFZ
Inclusion criteria	<ul style="list-style-type: none"> <li>- Patients <math>\geq 18</math> years of age.</li> <li>- Performance status ECOG 0-2</li> <li>- Histologically confirmed advanced stage* gastrointestinal cancer prior last line therapy</li> <li>- Tumor accessible to biopsy and patient willing to undergo biopsy</li> <li>- Absence of HIV, HBV and HCV infection</li> <li>- At least one measurable lesion of disease according to RECIST criteria.</li> <li>- Adequate end organ function: <ul style="list-style-type: none"> <li>- renal function: serum creatinine <math>\leq 1.5 \times</math> ULN or GFR <math>\geq 30</math> mL/min.</li> <li>- hematopoietic function: white blood cell (WBC) count <math>\geq 3000/\mu\text{L}</math>, absolute neutrophil count (ANC) <math>\geq 1500/\mu\text{L}</math>, platelets <math>\geq 100000/\mu\text{L}</math>, hemoglobin level <math>&gt;9.0</math> g/dL</li> <li>- Liver function: total bilirubin <math>\leq 1.5 \times</math> ULN, AST / ALT <math>\leq 3.0 \times</math> ULN</li> </ul> </li> <li>- Signed informed consent prior to any screening procedures</li> </ul>
Study design	<p><b>PROMISE First</b></p> <p>1st line      2nd line</p> <p>organoids   drug screen   organoids   drug screen</p> <p>Planned n=20 advanced GI cancer no prior treatment ECOG 0-2</p> <p>biopsy → 1st line → Progress → 2nd line → Progress</p> <p>add. gene sequencing</p>
	<p>Fig. 1. Scheme of the PROMISE-First study.</p> <p>A biopsy of tumor/metastasis will be obtained – if possible together with normal tissue from the site of the tumor origin - prior to start of chemotherapy. With the help of this material, individual organoid cultures will be established.</p> <p>Patients will undergo standard-of care first line treatment according to established treatment guidelines. Organoids will be used to model the patient's cancer biology ex-vivo (Avatar). While the patient undergoes standard first line treatment for the cancer, the avatar will be treated with the same active drug combination, using concentrations published for ex-vivo or in-vitro assays. Thereby, emerging resistance mechanisms will be explored by molecular analysis. Furthermore, sensitivity of other drugs and drug combinations will be assessed in the avatar by drug screening. Through this approach, cancer biology and treatment can be modeled for each patient, resistance mechanisms can be revealed well in advance and based on these resistance mechanisms and drug screens in organoids, treatment strategies for each patient can be tested before</p>

	the cancer in the patient reaches the stage of non-responsiveness.
Clinical part	<p>The choice of first-line therapy will be the sole discretion of the treating physician. First-line therapy must be an established Standard-of-Care treatment recommended by current guidelines. No pharmaceutical intervention will be prescribed in the protocol. From a regulatory perspective this trial is purely observational. An appropriate ethical approval will be obtained by the coordinating investigator. The clinical part will commence as a monocenter trial.</p> <p>After informed consent patients will be followed-up for the full course of first-line therapy until disease progression, discontinuation of treatment or death. Clinical data will be acquired according to a pre-defined schedule and will include:</p> <p>Efficacy data:</p> <ul style="list-style-type: none"> <li>• tumor response evaluation according to RECIST 1.1</li> <li>• Best overall response</li> <li>• Time-to-response (TTR)</li> <li>• Duration of response (DOR)</li> <li>• Time-to-failure of treatment strategy (TTFS)</li> <li>• PFS, OS</li> </ul> <p>Safety data:</p> <ul style="list-style-type: none"> <li>• AEs / SAEs</li> <li>• dose density administered</li> <li>• dose modifications due to toxicity</li> </ul> <p>Follow-up after discontinuation of first-line therapy:</p> <p>Patients will be followed-up for subsequent cancer therapies and overall survival. The choice of second-line therapy will be the sole discretion of the treating physician. However, the results of the Avatar will be disclosed to the treating physician and may shape the decision-making process for the most suitable second-line treatment.</p>
Clinical Data assessment, study visits and re-stagings	<ol style="list-style-type: none"> <li>1. Inclusion: <ul style="list-style-type: none"> <li>- Patients with metastasized CRC before the start of palliative chemotherapy are identified by screening inpatients and endoscopy-patients</li> <li>- Patients undergo endoscopic biopsy of their CRC and organoid lines are established before start of Treatment</li> </ul> </li> <li>2. First study visit: Chemotherapy informed consent / chemotherapy initiation <ul style="list-style-type: none"> <li>- Obligatory assessments: ECOG-Status, weight, clinical examination</li> <li>- Obligatory Lab tests: Diff-BB, CEA, CA-19-9, CRP, LDH, (Na, K, Krea, Billi-Gesamt, AP, yGT, ALAT, ASAT, Quick)</li> <li>- A CT-Scan of thorax, abdomen and pelvis is obligatory before start of treatment, this must have been performed within 3 weeks before the start of chemotherapy. If the CT-scan is older, a new CT scan has to be performed before start of treatment</li> <li>- Other obligatory documentation: Primary tumor location, Metastatic sites, number and size of metastatic lesions in each organ, Chemotherapy regimen, dose-reduction, relevant co-morbidities, medication</li> </ul> </li> <li>3. Follow-up visits <ul style="list-style-type: none"> <li>- The patient receives 6 cycles (bi-weekly) of chemotherapy (12 weeks) followed by re-staging CT (thorax, abdomen, pelvis) in week 13-14. After this, another 6 cycles of chemotherapy are applied, followed by CT-scan, and so on.</li> <li>- after week 3, study nurses are informed if organoid culture was successful and if patient remains "on-study"</li> <li>- Obligatory assessment and documentation every visit (bi-weekly): <ul style="list-style-type: none"> <li>-- Therapy protocol (including regimen, dose reductions)</li> <li>-- ECOG status, weight, clinical examination (as above)</li> <li>-- Lab (as above)</li> <li>-- Chemotherapy side-effects (according to CDC)</li> </ul> </li> </ul> </li> <li>4. Re-Staging <ul style="list-style-type: none"> <li>Re-staging CT (thorax, abdomen, pelvis) is performed every 3 months (week 13-14).</li> <li>- CT-results are assessed according to RECIST-criteria</li> <li>- Both CT images and CT report have to be saved in the clinical</li> </ul> </li> </ol>

	<p>documentation system</p> <ul style="list-style-type: none"> <li>- all CT-scans should be performed “in-house” at the UMM, if external CTs are inevitable, all documents and CDs have to be obtained and saved</li> <li>- obligatory documentation after re-staging (in addition to basic documentation in every visit): <ul style="list-style-type: none"> <li>-- Response according to RECIST, size and number of metastases in affected organs, primary tumor size</li> <li>-- relevant new co-morbidities</li> </ul> </li> </ul>
Sample size	<p>The clinical part of this research project targets to enroll n=20 patient. Due to the exploratory nature of this trial no clinical hypothesis will be formulated and no formal sample size calculation will be performed.</p> <p>A sample size of n=20 shall suffice to generate informative pilot data on the feasibility and utility of the Avatar approach.</p>
Data analysis	<p>Multivariable analysis will be used to identify gene-drug associations and potential biomarkers, as well as associations between drug effects in organoids and in patients.</p> <p>Half-yearly interim analyses will be performed concerning patient characteristics, response evaluation, organoid drug response, molecular analysis, toxicity and outcome.</p>
Planned timelines	<p>First Patient In: Q2 2017  Last Patient In: Q2 2020  Last Patient Out: 2022  Individual observation time: 24 months  Interim-analysis: every 6 months  Final Analysis: 2022</p>
Contact details	<p>Prof. Dr. M. Ebert, Universitätsklinik Mannheim, Universität Heidelberg,  <a href="mailto:matthias.ebert@medma.uni-heidelberg.de">matthias.ebert@medma.uni-heidelberg.de</a></p> <p>Prof. Dr. M. Boutros, DKFZ Heidelberg, <a href="mailto:m.boutros@dkfz.de">m.boutros@dkfz.de</a></p> <p>Dr. J. Betge, <a href="mailto:johannes.betge@medma.uni-heidelberg.de">johannes.betge@medma.uni-heidelberg.de</a></p>

### AIO-TF-0317: Patient derived organoids to model cancer biology and predict treatment response – Last line study (PROMISE-Last)

#### AIO-Studie

Studiennummer/-Code:	AIO-TF-0317 - PROMISE-Last
Status:	in Vorbereitung
Rekrutierungszeitraum:	Studienstart noch offen
Weitere Zentren:	erwünscht
Letzte Aktualisierung	April 2018

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. M. Ebert, Department of Medicine II, University Hospital Mannheim, Heidelberg University, 68167 Mannheim, Phone: 0621-383 3284, matthias.ebert@umm.de
CONDITION	Patients receiving palliative chemotherapy for metastasized or locally recurrent gastrointestinal cancer before their last established palliative treatment line
OBJECTIVE(S)	With this study, we aim to establish precision oncology for patients with advanced gastrointestinal cancer by ex-vivo drug screening of individual patient derived organoids (PDOs). In particular, we aim 1) to establish individual PDOs and to perform a drug screen for identification of drugs with highest efficacy. 2) To assess the efficacy of a systemic treatment chosen by ex-vivo screening of individual PDOs in regards to response rate ( $\leq 5\%$ vs. $\geq 20\%$ , primary end-point) 3) To characterize molecular alterations of the PDOs and tumor and analyze gene-drug associations as potential predictive biomarkers
INTERVENTION(S)	Experimental intervention: 1. Biopsy to establish PDOs, 2. Treatment of the patient with best performing drug in PDO-based drug-screen Control intervention: No control intervention is performed Duration of intervention per patient: 1. Biopsy: 30-60minutes, 2. Treatment after last line therapy (until disease progression) Follow-up per patient: 24 months
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: 1. Patients $\geq 18$ years of age. 2. Performance status ECOG 0-2. 3. Histologically confirmed metastatic or locally recurrent colorectal cancer prior last line therapy. 4. Tumor accessible to biopsy and patient willing to undergo biopsy. 5. At least one measurable lesion of disease according to RECIST criteria. 5. Signed informed consent prior to any screening procedures Key exclusion criteria: 1. HIV, HBV or HCV infection. 2. Inadequate end organ function
OUTCOME(S)	Primary efficacy endpoint: Best objective response rate (ORR) per central review in last-line treated subjects ( $\leq 5\%$ vs. $\geq 20\%$ ) determined by RECIST criteria Key secondary endpoint(s): Progression-free survival, overall survival, toxicity, quality of life (QoL), predictive value of PDO screens for treatment efficiency, treatment duration and dose intensity Assessment of safety: Patients will be closely monitored for the occurrence of adverse events (AE) and serious adverse events (SAE).
STUDY TYPE	Multicentered, single armed, phase II interventional clinical trial
STATISTICAL ANALYSIS	Efficacy: Objective response rate ( $\leq 5\%$ vs. $\geq 20\%$ , primary end-point) Description of the primary efficacy analysis and population:

	<p>Descriptive analysis. The primary objective is to estimate best objective response rate (ORR) per investigator assessment in last-line treated subjects. A Fleming single-stage Phase II design will be used to test the null-hypothesis that the true ORR is 5% (P0) against a one-sided alternative that the ORR = 20% (PA). <math>H_0 : P \leq P_0</math> <math>H_A : P \geq P_A</math></p> <p>Safety: Rates of complications, adverse events and serious adverse events will be calculated with 95% confidence intervals for group comparisons.</p> <p>Secondary endpoint(s): Progression-free survival, Toxicity, QoL</p>
SAMPLE SIZE	<p>To be assessed for eligibility: (n = 70)</p> <p>To be allocated to trial: (n = 40)</p> <p>To be analyzed: (n = 30)</p>
TRIAL DURATION	<p>Time for preparation of the trial (months): 6</p> <p>Recruitment period (months): 24</p> <p>First patient in to last patient out (months): 48</p> <p>Time for data clearance and analysis (months): 3</p> <p>Duration of the entire trial (months): 57 (6 preparation, 48 study, 3 analysis)</p>
PARTICIPATING CENTERS	<p>To be involved (n): 3</p> <p>High volume centers with expertise in treatment of advanced gastrointestinal cancer</p>

### Solide Tumore mit DNA-Reparatur Defizienz, fortgeschrittene Erkrankung

#### **AIO-ST5/TF-0117/ass: Randomized Phase-2 Study of Trabectedin/Olaparib Compared to Physician's Choice in Subjects with Previously Treated Advanced or Recurrent Solid Tumors Harboring DNA Repair Deficiencies - NCT-PMO-1603**

#### **AIO-assozierte Studie**

Studiennummer/-Code: AIO-ST5/TF-0117/ass - NCT-PMO-1603

Status: in Vorbereitung

Rekrutierungszeitraum: 2018 – 2020

Weitere Zentren: sind möglich

Letzte Aktualisierung April 2018

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk National Center of Tumor diseases, Heidelberg
CONDITION	<ul style="list-style-type: none"> <li>Advanced or recurrent solid tumors harboring DNA repair deficiencies</li> <li>Relapsed and metastatic solid tumors with homologous recombination DNA repair deficiency</li> </ul>
OBJECTIVE(S)	<p><b>Primary objective</b> of the study is to gain evidence of antitumor activity of trabectedin and olaparib in adult patients with (locally) advanced or metastasized solid organ tumors refractory to conventional treatment.</p> <ul style="list-style-type: none"> <li><b>Secondary objectives</b> include tumor response rate (TRR)</li> <li>Progression-free survival (PFS)</li> <li>Overall survival (OS)</li> <li>Safety</li> <li>Quality of life (QoL)</li> </ul>

INTERVENTION(S)	combination therapy with trabectedin and olaparib vs. physician's choice
KEY EXCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Hematologic malignancies and primary brain tumors. Patients with known progressive brain metastases determined by serial imaging or declining neurologic function in the opinion of the treating physician are not eligible. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to enrollment. All patients with previously treated brain metastasis must be clinically stable for at least 1 month after completion of treatment and off steroid treatment for one month, both prior to study enrollment.</li> <li>• Concurrent treatment in another interventional clinical trial</li> <li>• Prior treatment with PARP inhibitors</li> <li>• Treated with an investigational anticancer therapy less than 6 weeks prior to study enrollment</li> <li>• Persistent toxicity (<math>\geq</math>Grade 2 according to Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) caused by preceding antineoplastic therapy</li> <li>• Dementia or significant impairment of cognitive state</li> <li>• History of HIV infection</li> <li>• Clinical signs of active infection (<math>&gt;</math>Grade 2 according to CTCAE version 4.03)</li> <li>• History of viral hepatitis (HBV or HCV)</li> <li>• Epilepsy requiring pharmacologic treatment</li> <li>• Pregnancy</li> <li>• Inability to take oral medication</li> <li>• Major surgical intervention 4 weeks prior to study enrollment</li> <li>• Known hypersensitivity to any of the study drugs</li> <li>• QTc time prolongation <math>&gt;500</math> ms or history of familial long-QT syndrome</li> <li>• Heart failure NYHA III/IV</li> <li>• Severe obstructive or restrictive ventilation disorder</li> </ul>
KEY INCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Written informed consent</li> <li>• Diagnosis of locally advanced or metastatic malignancy</li> <li>• Prior administration of standard treatment for primary and relapsed malignancy</li> <li>• Eastern Cooperative Oncology Group Performance Status <math>\leq 1</math></li> <li>• Age <math>\geq 18</math> and <math>\leq 70</math> years</li> <li>• Identification of defective DNA repair via HR, as determined by molecular analysis within NCT/DKTK MASTER. Eligibility for the study is defined based on WES and the presence of BRCAness.</li> <li>• Adequate bone marrow, renal, and hepatic function defined by laboratory tests within 7 days prior to study treatment: <ul style="list-style-type: none"> <li>○ Hemoglobin <math>\geq 10</math> g/dl</li> <li>○ Neutrophil count <math>\geq 1,500/mm^3</math></li> <li>○ Platelet count <math>\geq 100,000/\mu l</math></li> <li>○ Bilirubin <math>\leq 1.5</math> x upper limit of normal (ULN)</li> <li>○ ALT and AST <math>\leq 2.5</math> x ULN (<math>\leq 5</math> x ULN in patients with hepatic tumor involvement)</li> <li>○ Alkaline phosphatase <math>\leq 2.5</math> x ULN</li> <li>○ PT-INR/PTT <math>\leq 1.5</math> x ULN</li> <li>○ Albumin <math>\geq 25</math> g/l</li> <li>○ Creatine kinase <math>\leq 2.5</math> x ULN</li> </ul> </li> </ul>
OUTCOME(S)	Clinical efficacy, determined by disease control rate (DCR) at week 16 after five 21-days cycles of treatment
STUDY TYPE	Multicenter randomized, open-label, phase II study designed to gain evidence of safety and antitumor activity of trabectedin and olaparib in adult patients with (locally) advanced or metastatic solid tumors and homologous repair deficiency compared to treatment according to current guidelines (physician's choice)

STATISTICAL ANALYSIS	The trial compares olaparib in combination with trabectedin (experimental arm E) versus physician's choice (control arm C). Primary efficacy endpoint is the disease control rate (DCR) after 5 cycles. Efficacy evaluation involves a two-group comparison of DCR between experimental arm E (DCRE) and control arm C (DCRC). The null hypothesis is $H_0: DCRE - DCRC \leq 0$ . Assuming a DCRE of 50% for the experimental arm and a DCRC of 20% for the control arm, a total number of 102 evaluable patients (51 patients per arm) allows for rejecting the null hypothesis at a one-sided significance level of 2.5% with a power of approximately 90%. Sample size calculation is based on a score test (Pearson chi-squared test) for the difference in proportions.
SAMPLE SIZE	A total number of 102 evaluable patients (51 patients per arm) allows for rejecting the null hypothesis at a one-sided significance level of 2.5% with a power of approximately 90%.
TRIAL DURATION	Total trial duration: 46 months Duration of the clinical phase: 34 months The duration of the trial for each patient is expected to be 6 months, including 15+1 weeks of treatment and 2 months follow-up. In case of clinical benefit, it will be longer.
PARTICIPATING CENTERS	<ol style="list-style-type: none"> <li>1. NCT Heidelberg, Prof. Dr. Stefan Fröhling, Dr. Stefan Gröschel</li> <li>2. Universitätsklinikum Dresden, Dr. Gunnar Folprecht, Dr. Stephan Richter</li> <li>3. Charité Berlin, Prof. Dr. Ulrich Keilholz, Dr. Sebastian Ochsenreither</li> <li>4. Uniklinik Essen, Prof. Dr. Sebastian Bauer, Prof. Dr. Jens Siveke</li> <li>5. Universitätsmedizin Mainz, Dr. Thomas Kindler</li> <li>6. Universitätsklinikum Frankfurt, Prof. Dr. Christian Brandts</li> <li>7. Universität Tübingen, Dr. Hans-Georg Kopp</li> <li>8. Universitätsklinikum Freiburg, Prof. Dr. Nikolas von Bubnoff</li> <li>9. LMU München, Prof. Dr. Karsten Spiekermann, Dr. Klaus Metzeler</li> </ol>
current number of patients included	

### Registerstudien

#### **AIO-KRK-0413/ass: COLOPREDICT PLUS 2.0 - Register - Retro- und prospektive Erfassung der Rolle von MSI und KRAS für die Prognose beim Kolonkarzinom im Stadium I, II + III**

<b>AIO-assozierte Studie</b>	
Studiennummer/-Code:	AIO-KRK-0413/ass - COLOPREDICT PLUS 2.0
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 – 2022
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Verantwortlicher Studienleiter nach AMG	Prof. Dr. med. Andrea Tannapfel (molekulare Diagnostik/ Gewebebank) Institut für Pathologie der Ruhr-Universität Bochum Zentrale Gewebebank Bürkle-de-la-Camp-Platz 1, 44789 Bochum Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809 E-Mail: Andrea.tannapfel@rub.de
Projektkoordination	Prof. Dr. med. Anke Reinacher-Schick (Leitung klinische Registerdaten) Abteilung für Hämatologie, Onkologie und Palliativmedizin

	St. Josef-Hospital Bochum Klinikum der Ruhr-Universität Tel.: 0234-509-3591, Fax:-Nr.: 0234-509-3592 E-Mail: onkologie@klinikum-bochum.de
Kontaktadresse/ Kontaktperson:	Institut für Pathologie der Ruhr-Universität Bochum Bürkle-de-la-Camp-Platz 1, 44789 Bochum Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809 Ansprechpartner: Frau Westphal (0234-302-4924, stephanie.westphal@pathologie-bochum.de) Frau Remmel (0234-509-2368, anna.remmel@rub.de)
Das vollständige Kurzprotokoll finden Sie unter den Protokollen der AG Kolon-/Rektum-/Dünndarntumoren	

### **AIO-YMO/TF-0115: Analyse der epidemiologischen und molekularen Früherkennung zur Prognosebestimmung für Patienten mit Barrett-Ösophagus**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/TF-0115
Status:	in Rekrutierung
Rekrutierungszeitraum:	2013 - 2023
Weitere Zentren:	sind gewünscht
Letzte Aktualisierung	April 2018

Verantwortlicher Studienleiter nach AMG	PD Dr. med. Michael Quante, II. Medizinische Klinik der Technischen Universität München, Klinikum rechts der Isar
Kontaktadresse/ Kontaktperson:	PD Dr. med Michael Quante Klinikum rechts der Isar Technische Universität München II. Medizinische Klinik, Ismaninger Straße 22, 81675 München michael.quante@lrz.tu-muenchen.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologist!	



## Arbeitsgruppe Weichteilsarkome

### Advanced or metastatic soft tissue sarcoma, first and advanced treatment lines

**AIO-STS-0415: A randomized phase II study of Durvalumab (MEDI4736) and Tremelimumab compared to doxorubicin in patients with advanced or metastatic soft tissue sarcoma. MEDISARC**

#### AIO-Studie

Studiennummer/-Code:	AIO-STS-0415 - MEDISARC
Status:	in Vorbereitung
Rekrutierungszeitraum:	2017 - 2020
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Study Type	Open label, randomized, ECOG stratified phase II study
Coordinating investigator (LKP)	Prof. Dr. med. Viktor Grünwald Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation - Medizinische Hochschule Hannover Carl-Neuberg-Str. 1, D-30625 Hannover
Sponsor:	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, info@aio-studien-ggmbh.de
Objectives	<u>Primary objective:</u> To assess the efficacy of tremelimumab and durvalumab (MEDI4736) in comparison to doxorubicin in treatment-naïve STS patients <u>Secondary objectives:</u> Assessment of safety and tolerability of tremelimumab and durvalumab (MEDI4736) combination therapy <u>Exploratory objectives:</u> predictive biomarkers for ORR, PFS, OS
Endpoints	Primary endpoint: <ul style="list-style-type: none"> <li>overall survival</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>ORR according to conventional and modified RECIST 1.1 criteria</li> <li>OS mile stone rate at 24 months</li> <li>PFS</li> <li>Duration of response</li> <li>AEs / SAEs and Treatment Emergent Adverse Events according to CTCAE 4.03</li> <li>Health related Quality of Life (HR-QoL - EORTC QLQ-C30)</li> </ul>
Number of patients	<b>N=approx. 100 patients</b> Currently recruited: none
Key inclusion criteria	1. Histologically confirmed diagnosis of metastatic or advanced soft tissue sarcoma of intermediate or high grade [according to FNCLCC score; intermediate=grade 2 score of 4-5 points, high grade = grade 3

	<p>score of 6-8 points] with disease progression within 6 months prior to study inclusion:</p> <ul style="list-style-type: none"> <li>• Fibrosarcoma</li> <li>• Pleomorphic high grade sarcoma (“malignant fibrous histiocytoma”)</li> <li>• Leiomyosarcoma</li> <li>• Liposarcoma (myxoid liposarcoma, dedifferentiated liposarcoma, pleomorphic liposarcoma)</li> <li>• Malignant glomus tumor</li> <li>• Rhabdomyosarcoma, alveolar or pleomorphic (excluding embryonal)</li> <li>• Vascular sarcoma (angiosarcoma)</li> <li>• Synovial sarcoma</li> <li>• High-grade sarcoma, not otherwise specified (NOS)</li> <li>• Malignant peripheral nerve sheath tumors</li> <li>• Other types of sarcoma (not listed as ineligible), if approved by the coordinating investigator / study coordinator.</li> </ul> <p>Excluding: Uncertain differentiation (epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, malignant mesenchymoma, PEComa), chondrosarcoma, Ewing sarcomas/PNET, chordoma, malignant solitary fibrous tumors, embryonal rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumors, dermatofibrosarcoma protuberans, inflammatory myofibroblastic sarcoma (low-grade), neuroblastoma, malignant mesothelioma, and mixed mesodermal tumors of the uterus (Study inclusion is based on local histopathological diagnosis).</p> <ol style="list-style-type: none"> <li>2. Metastatic or locally advanced STS, not amendable to surgery with curative intention.</li> <li>3. No prior treatment line for advanced or metastatic disease.</li> <li>4. ECOG performance status 0-2</li> <li>5. Patients with measurable disease (at least one uni-dimensionally measurable target lesion by CT-scan or MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) are eligible.</li> <li>6. Adequate blood count, liver-enzymes, and renal function:       <ul style="list-style-type: none"> <li>• Haemoglobin <math>\geq 9.0</math> g/dL</li> <li>• Absolute neutrophil count (ANC) <math>\geq 1.5 \times 10^9/L</math> (<math>&gt; 1500</math> per <math>mm^3</math>)</li> <li>• Platelet count <math>\geq 100 \times 10^9/L</math> (<math>&gt;100,000</math> per <math>mm^3</math>)</li> <li>• Serum bilirubin <math>\leq 1.5 \times</math> ULN. This will not apply to subjects with confirmed Gilbert’s syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.           <ul style="list-style-type: none"> <li>• AST (SGOT)/ALT (SGPT) <math>\leq 2.5 \times</math> institutional upper limit of normal unless liver metastases are present, in which case it must be <math>\leq 5 \times</math> ULN</li> <li>• Serum creatinine <math>CL &gt; 40</math> mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance</li> </ul> </li> </ul> </li> <li>7. Adequate cardiac function (left ventricular ejection fraction <math>\geq 50\%</math> as assessed by ECHO)</li> </ol>
Key exclusion criteria	<ol style="list-style-type: none"> <li>1. Patients who are suitable for anthracycline-based combination therapies</li> <li>2. Cardiac events such as arrhythmias, myocardial infarction, CHF, apoplexy, lung embolism within 6 months prior to study treatment</li> <li>3. Mean QT interval corrected for heart rate (QTc) <math>\geq 470</math> ms calculated from 3 electrocardiograms (ECGs) using Fredericia’s correction</li> <li>4. Uncontrolled severe hypertension (failure of diastolic blood pressure to fall below 100 mmHg and systolic blood pressure <math>&gt; 160</math> mmHg)</li> <li>5. Previous malignancy (other than STS) which either progresses or requires active treatment.</li> </ol>

	<p>Exceptions are: basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial bladder tumor [Ta, Tis and T1].</p> <ol style="list-style-type: none"> <li>6. History or clinical evidence of CNS metastases Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria: <ol style="list-style-type: none"> <li>a) are asymptomatic and</li> <li>b) have no requirement for steroids 6 weeks prior to start of study treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases</li> </ol> </li> <li>7. Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.</li> <li>8. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)</li> <li>9. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year)</li> <li>10. Any previous treatment with a PD-1 or PD-L1 or CTLA-4 inhibitor, including durvalumab and tremelimumab</li> <li>11. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid</li> <li>12. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) <math>\leq</math> 21 days prior to the first dose of study drug or <math>\leq</math> 4 half-lives of the agent administered, whichever comes first.</li> </ol>
Scheme of therapy	<p>For all IMPs a flat dosing regimen will be implemented.</p> <p>Cycles/courses 1-3: Durvalumab 1.5g q4wks Tremelimumab 75 mg q4wks</p> <p>Cycles/courses <math>\geq</math>4: Durvalumab 1.5g q4wks Tremelimumab 75 mg q12wks</p> <p>Active comparator for randomized part: Doxorubicin 75 mg/m<sup>2</sup> q3wks for 6 courses</p> <p>Treatment will be given until progression, intolerance/toxicity, death or end of treatment, whichever occurs first.</p>

	<p style="text-align: center;"><b>MEDISARC</b> study phases and treatment schedule</p> <p><b>Screening</b> max. -4 wks</p> <p><b>Treatment phase max. 12 month</b></p> <p><b>Arm A:</b> Durvalumab 1.5g; 1h i.v.; q4w; max. 12 doses Tremelimumab 75mg; 1h i.v.; q4w for 3 cycles; then q12w; max. 6 doses</p> <p><b>Arm B – control:</b> Doxorubicin 75mg/m<sup>2</sup>; 15 min i.v.; q3w; max. 6 doses</p> <p><b>Follow-up phase</b> minimum 12 month for OS</p> <p><b>Follow-up extension</b> for OS, PFS and further treatment documentation until EoS</p>
<p>Criteria for tumor evaluation</p>	<p>RECIST 1.1</p>
<p>Rationale</p>	<p>The mainstay of therapy of soft tissue sarcoma (STS) consists of anthracyclines, which achieved an overall survival of 1 year in previous trials (Santoro et al. 1995). This benchmark remains the current standard of therapy in 1st line, despite the intensification of therapy through the combined approach of doxorubicin and ifosfamide. The 62012 study achieved an ORR of 14% for single agent doxorubicin and 26% for doxorubicin + ifosfamide (Judson et al. 2014), rendering doxorubicin a standard of care in palliative treatment.</p> <p>In later lines of therapy ifosfamide, trabectedin, or pazopanib have been licensed. However, despite the enrichment with novel therapies in the field of STS the overall survival remains poor in contemporary series. The 62012 study of the EORTC accelerated therapy by an aggressive combination of doxorubicin and ifosfamide, but failed to improve outcome (Judson et al. 2012). Overall survival was 12.8 months for single agent doxorubicin and 14.3 months for the combination regimen, indicating a ceiling effect with conventional chemotherapy regimens. It clearly shows that after decades of clinical research there is still an unmet clinical need for novel therapies with novel mechanisms of action in the field of STS.</p> <p>Programmed death -1 (PD-1) is a key immune checkpoint, which regulates T-cells. Activating ligands are secreted by the tumor or/and its microenvironment in order to escape host's immune response. PD-1 ligand (PD-L1) expression has been recently reported in sarcomas (Raj et al. ESMO 2014; Kozak et al. ESMO 2014). PD-L1 positive sarcomas achieved an overall survival of 68 months, whereas median has not been reached for PD-L1 negative sarcomas, indicating a possible prognostic role. Expression of PD-L1 was found in 58% and 65% of tumor infiltrating cells and found to be associated with poor clinical outcome (Kim et al. 2013), which renders the PD-1 checkpoint a putative therapeutic approach in STS.</p> <p>A randomized phase II study showed superior clinical efficacy for the combination of ipilimumab and nivolumab compared to single agent nivolumab, indicating that dual blockade of CTLA-4 and PD-1 may improve efficacy of immunotherapy in STS (D'Angelo et al. J Clin Oncol 35 2017 (suppl; abstr 11007)). Additionally, a phase I study showed efficacy of ipilimumab in juvenile sarcoma patients, indicating principle activity (Merchant et al. [2015]. CCR <a href="http://doi.org/10.1158/1078-0432.CCR-15-0491">http://doi.org/10.1158/1078-0432.CCR-15-0491</a>). Furthermore, durvalumab and tremelimumab have shown activity in ongoing early clinical trials. Single agent durvalumab achieved objective remissions (ORR) in 2/20 (10%), while the combination of durvalumab and</p>

	<p>tremelimumab showed ORR in 1/6 (13%) patients. Overall, data from these latter studies is not mature and given the duration to achieve ORR it is anticipated that the response rate increases over time. Furthermore, immunotherapy agents are known to deliver a higher survival benefit than the fraction of patients achieving ORR. For instance, nivolumab in renal cell carcinoma (RCC) achieved an ORR of 25%, while PFS remained unchanged between arms (Motzer et al NEJM 2015). However, for survival a HR of 0.73 (CI95% 0.57-0.93) was achieved, increasing the median OS by 5.4 months. Further investigations showed that patients derived survival benefit irrespective of their treatment response, underscoring that OS is a better outcome for clinical activity of immunotherapies.</p> <p>We hypothesize that the dual checkpoint blockade improves overall survival, in particular the 2-year OS rate, in STS when compared to doxorubicin, a standard of care.</p>
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### Gastrointestinal stromal tumor (GIST)

**AIO-ST5-0115/ass: Phase 2 trial of ponatinib in patients with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) following failure of prior therapy with imatinib (POETIG trial – PONatinib after rESistance to Imatinib in GIST)**

#### AIO-assozierte Studie

Studiennummer/-Code:	AIO-ST5-0115/ass
Status:	in Rekrutierung
Rekrutierungszeitraum:	2016 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Art der Studie Study Type	This is a non-randomized, open label, multicenter phase 2 study to evaluate the efficacy and safety of ponatinib in patients with metastatic and/or unresectable GIST after prior failure or intolerance to imatinib. Patients will be enrolled into 1 of 2 cohorts based on presence (cohort A) or absence (cohort B) of KIT exon 13 resistance mutations as measured by liquid biopsy. A third cohort will include patients who have received all approved lines of TKI treatments (imatinib, sunitinib and regorafenib).
Leiter der klinischen Prüfung	Prof. Dr. med. Sebastian Bauer Sarcoma Center, West German Cancer Center Hufelandstr. 55, 45122 Essen, Germany <a href="mailto:sebastian.bauer@uni-due.de">sebastian.bauer@uni-due.de</a> , phone: +49-201-72385011 fax: +49-201-7235547
Studienziele/ Objectives	<p><u>Primäres Studienziel:</u></p> <ul style="list-style-type: none"> <li>To assess clinical benefit in patients with KIT exon 11-mutant GIST (Cohort A) defined as clinical benefit rate (CBR), which is the composite of complete response (CR), partial response (PR) and stable disease (SD) lasting <math>\geq 16</math> weeks per modified response evaluation criteria in solid tumors (RECIST 1.1 [Demetri et al., 2012]) as a measure of disease control</li> <li>Two main strata will be used: Strata A: patients with evidence of secondary resistance mutations in exon 13 as assessed on progressing lesions or in circulating DNA; Strata B: patients with</li> </ul>

	<p>secondary resistance mutations in other exons or no resistance mutations (as measured by liquid biopsy in circulating DNA)</p> <p><u>Sekundäre Studienziele:</u></p> <ul style="list-style-type: none"> <li>• To assess progression-free survival (PFS) in each cohort and in the total patient population</li> <li>• To assess objective response rate (ORR) in each cohort and in the total patient population</li> <li>• To assess overall survival (OS) in each cohort and in the total patient population</li> <li>• To evaluate the safety and tolerability of ponatinib in the total patient population</li> <li>• To assess Quality of Life</li> <li>• To assess limited elements of pharmacokinetics (PK) in the total patient population</li> </ul> <p><u>Exploratory</u></p> <ul style="list-style-type: none"> <li>• To explore the relationship between GIST genotype and CBR with ponatinib</li> <li>• To explore the feasibility of detecting mutations in KIT and possibly other cancer-related genes using circulating nucleic acids derived from blood samples</li> </ul> <p>To explore the usefulness of “liquid biopsies” to predict treatment response and development of resistance</p>
Zielparameter/ Objectives	<p><b>Primary Endpoint</b></p> <ul style="list-style-type: none"> <li>• CBR consisting of CR+PR+SD by modified RECIST 1.1 (Demetri et al., 2012) at 16 weeks in patients with imatinib-resistant GIST (KIT-mutant) with secondary resistance mutation in exon 13 (cohort A) and other or no resistance mutations (cohort B)</li> </ul> <p><b>Secondary Endpoints</b></p> <ul style="list-style-type: none"> <li>• PFS in each cohort and in the total patient population</li> <li>• ORR (CR + PR) in each cohort and in the total patient population</li> <li>• OS in each cohort and in the total patient population</li> <li>• Safety and tolerability of ponatinib</li> <li>• QoL</li> </ul> <p><b>Exploratory Endpoints</b></p> <ul style="list-style-type: none"> <li>• Molecular genetic features of GIST at baseline and after treatment with ponatinib</li> </ul> <p>Monitoring of treatment response and resistance using “liquid biopsies”</p>
Patientenzahl Number of patients	Geplant: 60 Patienten Bereits eingeschlossen: 9
Rekrutierungszeitraum	Qu4/2016 – Qu4 2017
Weitere teilnehmende Zentren erwünscht?	4 Deutsche Zentren, 3 europäische Zentren
Haupt-Einschlusskriterien / Key inclusion criteria	<ol style="list-style-type: none"> <li>1. Male or female patients ≥18 years old</li> <li>2. GIST with failure or intolerance to imatinib defined as: <ol style="list-style-type: none"> <li>a. Histologically confirmed metastatic and/or unresectable GIST after at least 1 failure of any prior treatment with a TKI. If prior TKI treatment was neoadjuvant therapy, then relapse must have occurred during the neoadjuvant therapy in order to consider it failed therapy</li> <li>b. Patients in Cohort A must have evidence of an activating resistance mutation in KIT exon 13 (by direct sequencing of progressing lesions or by liquid biopsy). Patients in Cohort B must have evidence of resistance mutations in any other exon or no resistance mutation but evidence of progression by CT or MRI imaging</li> </ol> </li> <li>3. Measurable disease per modified RECIST 1.1 (Demetri et al., 2012). A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there is objective evidence of</li> </ol>

	<p>progression of the lesion prior to study enrollment</p> <ol style="list-style-type: none"> <li>4. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2</li> <li>5. Adequate hepatic function as defined by the following criteria: <ol style="list-style-type: none"> <li>a. Total serum bilirubin <math>\leq 1.5</math> x upper limit of normal (ULN), unless due to Gilbert's syndrome</li> <li>b. ALT <math>\leq 2.5 \times</math>ULN or <math>\leq 5.0 \times</math>ULN if liver metastases are present</li> <li>c. AST <math>\leq 2.5 \times</math>ULN or <math>\leq 5.0 \times</math>ULN if liver metastases are present</li> </ol> </li> <li>6. Adequate renal function as defined by the following criterion: <ol style="list-style-type: none"> <li>a. Serum creatinine <math>&lt; 1.5 \times</math>ULN</li> </ol> </li> <li>7. Adequate pancreatic function as defined by the following criterion: <ol style="list-style-type: none"> <li>a. Serum lipase and amylase <math>\leq 1.5 \times</math>ULN</li> </ol> </li> <li>8. For patients of childbearing potential, a negative pregnancy test must be documented prior to enrollment</li> <li>9. Female and male patients who are fertile must agree to use an effective form of contraception with their sexual partners from signing of the informed consent form for this study through 4 months after the end of treatment</li> <li>10. Provision of written informed consent</li> <li>11. Willingness and ability to comply with scheduled visits and study procedures</li> <li>12. Fully recovered (<math>\leq</math> Grade 1 or returned to baseline or deemed irreversible) from the <u>acute</u> effects of prior cancer therapy before initiation of study drug</li> </ol>
Haupt-Ausschlusskriterien / Key exclusion criteria	<ol style="list-style-type: none"> <li>1. Major surgery within 28 days prior to initiating therapy</li> <li>2. History of bleeding disorder</li> <li>3. History of acute pancreatitis within 1 year of study or history of chronic pancreatitis</li> <li>4. History of alcohol abuse</li> <li>5. Uncontrolled hypertriglyceridemia (triglycerides <math>&gt; 450</math> mg/dL)</li> <li>6. Clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: <ol style="list-style-type: none"> <li>a. Myocardial infarction within 6 months prior to enrollment</li> <li>b. Unstable angina within 6 months prior to enrollment</li> <li>c. Congestive heart failure within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards</li> <li>d. History of clinically significant (as determined by the treating physician) atrial arrhythmia</li> <li>e. Any history of ventricular arrhythmia</li> <li>f. Cerebrovascular accident or transient ischemic attack within 6 months prior to enrollment</li> <li>g. Any history of peripheral arterial occlusive disease requiring revascularization</li> <li>h. Venous thromboembolism including deep venous thrombosis or pulmonary embolism within 6 months prior to enrollment</li> </ol> </li> <li>7. Uncontrolled hypertension (diastolic blood pressure <math>&gt; 90</math> mm Hg; systolic <math>&gt; 140</math> mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control</li> <li>8. Taking medications that are known to be associated with Torsades de Pointes (Appendix A)</li> <li>9. Taking any medications or herbal supplements that are known to be strong inhibitors of CYP3A4 within at least 14 days before the first dose of ponatinib (Appendix B)</li> <li>10. Ongoing or active infection. This includes but is not limited to the requirement for intravenous antibiotics</li> <li>11. Known history of human immunodeficiency virus. Testing is not required in the absence of prior documentation or known history</li> <li>12. Pregnant or breastfeeding</li> <li>13. Malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drugs</li> <li>14. Individuals with a history of a different malignancy, other than cervical</li> </ol>

	<p>cancer in situ, basal cell or squamous cell carcinoma of the skin, are ineligible, except if they have been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy OR if the other primary malignancy is neither currently clinically significant nor requiring active intervention.</p> <p>15. Use of any approved TKIs or investigational agents within 2 weeks or 6 half-lives of the agent, whichever is longer, prior to receiving study drug</p> <p>16. Any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the drug</p> <p>17. History of apoplectic insult</p>
Therapieschema Scheme of therapy	Ponatinib 30mg qd
Tumorevaluierung Criteria for evaluation	RECIST
Rationale	<p>Ponatinib is a novel, synthetic, orally-active TKI designed to inhibit native and drug-resistant forms of Breakpoint Cluster Region-Abelson (BCR-ABL). Ponatinib also has potent activity against mutated forms of the c-kit receptor (KIT) and platelet-derived growth factor-<math>\alpha</math> (PDGFR-<math>\alpha</math>) which drive neoplastic transformation and maintenance of GIST, as well as against mutations in KIT that confer resistance to other currently approved TKIs, suggesting that ponatinib may have unique clinical benefit for patients with GIST.</p> <p>Ponatinib has been initially tested in patients with BCR-ABL-positive hematological malignancies, and has received Food and Drug Administration (FDA) approval in the United States (US) for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) that is resistant or intolerant to prior TKI therapy or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior TKI therapy. Clinical experience with ponatinib to date has come from 4 ARIAD-sponsored clinical trials of ponatinib in patients with hematological malignancies, all of which were ongoing at the time of writing: a phase 1 trial in patients with refractory hematologic malignancies; a phase 2 trial in patients with CML or Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or who have the T315I mutation; a phase 1/2 trial in Japan in previously treated CML and Ph+ ALL patients; and a randomized phase 3 trial of ponatinib compared with imatinib in newly diagnosed patients with CP-CML.</p> <p>In the phase 1 dose finding trial, patients were administered ponatinib at doses ranging from 2 mg to 60 mg. Dose-limiting toxicities (DLTs) were observed at 45 and 60 mg, and 45 mg was identified as the maximum tolerated dose and was chosen as the recommended dose for further study in adults. The most common treatment-emergent adverse events (AEs) in <math>\geq 30\%</math> of patients were the following (in descending frequency): rash, fatigue, nausea, abdominal pain, arthralgia, constipation, headache, vomiting, thrombocytopenia/platelet count decreased, edema peripheral, pyrexia, and hypertension. The most common serious adverse events (SAEs) in <math>\geq 5\%</math> of patients were the following: febrile neutropenia, pneumonia, pyrexia, neoplasm progression, pancreatitis, atrial fibrillation, abdominal pain, bacteremia, dyspnea, lung infection, neutropenic sepsis, thrombocytopenia/platelet count decreased, renal failure acute, and sepsis. Substantial activity was observed in CML chronic and advanced phases. Of 43 CP-CML patients, 72% (31) had a major cytogenetic response (MCyR) and 51% (22) had a major molecular response (MMR).</p> <p>The phase 2 pivotal trial of ponatinib enrolled 449 patients; 444 of whom were eligible and grouped into cohorts based on phase of disease. There were 270 CP-CML patients. The primary endpoint for CP-CML was MCyR. Overall, 56% of patients with CP-CML achieved MCyR (51% of those with disease resistant or intolerant to dasatinib or nilotinib [R/I], and 70% of those with the T315I mutation), the primary endpoint for CP-CML. The primary endpoint for patients with AP-CML, BP-CML, or Ph+ ALL is major</p>



hematologic response (MaHR). Overall, 57% of patients with AP-CML (58% of R/I and 50% of T315I) and 34% of patients with BP-CML or Ph+ ALL (35% R/I and 33% T315I) achieved MaHR. Consistent with the phase 1 subset analysis, patients who had less prior therapy had a trend towards higher cytogenetic response rates. In addition, younger age was found to be an important predictor of response.

Safety in the phase 2 trial was consistent with the phase 1 trial. The most commonly reported treatment-emergent AEs experienced by  $\geq 30\%$  of patients were the following: thrombocytopenia/platelet count decreased, rash, abdominal pain, headache, dry skin, and constipation. The most common SAEs in  $\geq 2\%$  of patients were the following: neoplasm progression, pancreatitis, pneumonia, abdominal pain, pyrexia, myocardial infarction (MI), cardiac failure, thrombocytopenia/platelet count decreased, anaemia, febrile neutropenia, atrial fibrillation, sepsis, hypertension, diarrhea, and lipase increased.

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in at least 27% of lclusig-treated patients from the phase 1 and phase 2 trials. Ponatinib can also cause recurrent or multi-site vascular occlusion. Overall, 20% of Ponatinib-treated patients experienced an arterial occlusion and thrombosis event of any grade. Fatal and life-threatening vascular occlusion has occurred within 2 weeks of starting Ponatinib treatment and in patients treated with average daily dose intensities as low as 15 mg per day. The median time to onset of the first vascular occlusion event was 5 months. Patients with and without cardiovascular risk factors have experienced vascular occlusion although these events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia. Long-term follow-up data indicate, that the risk of vascular occlusive events may be dose-dependent and is lower at 30mg qd.

Data from a currently ongoing phase II trial of ponatinib in GIST patients were recently presented. 35 of a planned 45 pts with pretreated (46% 2 prior lines; 46% 3 prior lines) have been enrolled. The clinical benefit rate for a dose of ponatinib 45mg (CBR at  $\geq 16$  wks) for patients with exon 11 mutations was 55% for those without a primary exon 11 mutation CBR was 22% indicating a substantial benefit even in heavily pretreated patients. Side effects were mostly mild with most common ( $\geq 30\%$ ) treatment-emergent AEs of any grade: rash (54%), fatigue (46%), myalgia (46%), dry skin (40%), headache (40%), abdominal pain (34%), constipation (34%). Treatment-emergent serious AEs (SAEs) occurring in  $\geq 2$  pts were abdominal pain (11%), nausea (6%), vomiting (6%), fatigue (6%). One pt had a myocardial ischemia. There was 1 death (pneumonia) possibly ponatinib-related.

In summary, ponatinib's potency, preclinical activity against KIT and PDGFR as well as its activity in heavily pretreated GIST paired with a favorable side effect profile support its use in patients failing imatinib.

Because of the preclinical evidence of superior potency of ponatinib against KIT exon 17 secondary mutations patients will be included in cohorts of patients stratified by the dominant secondary mutation (presence or absence of exon 17 secondary resistance mutation) as measured by liquid biopsy. A small cohort (n=10) of patients who have received  $\geq 3$  lines of prior treatments will be included in this trial with the aim to evaluate the clinical benefit rate in heavily pretreated GIST at a dose of 30mg.

This phase 2 trial will explore the potential clinical activity of ponatinib at a dose of 30mg in patients with GIST following failure of 1 prior TKI therapy. The dose of 30mg of ponatinib is expected to have an improved toxicity profile compared to other multi-TKI-inhibitors such as sunitinib or regorafenib.

Gastrointestinaler Stromatumor, adjuvante Therapie**AIO-STS-0317/ass: Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study****AIO-assozierte Studie**

Studiennummer/-Code:	AIO-STS-0317/ass
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 – 2019
Weitere Zentren:	sind derzeit leider nicht möglich
Letzte Aktualisierung	09.04.2018

APPLICANT/ COORDINATING INVESTIGATOR	The Scandinavian Sarcoma Group (SSG)/ PD Dr. Peter Reichardt
CONDITION	Patients treated with adjuvant imatinib for 3 years after complete surgical removal of high-risk GIST and who are considered to be at a high risk of GIST recurrence despite 3 years of adjuvant imatinib.
OBJECTIVE(S)	<p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>• Recurrence-free survival (RFS) after randomisation.</li> </ul> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• Overall survival.</li> <li>• GIST-specific survival.</li> <li>• Adverse events (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).</li> <li>• Quality of life</li> </ul> <p><b>Exploratory:</b></p> <ul style="list-style-type: none"> <li>• Effect of tumour site on RFS.</li> <li>• Effect of tumour mutation type on RFS.</li> <li>• Effect of imatinib dose at randomisation on RFS.</li> <li>• To evaluate tumour tissue and blood molecular markers in prediction of GIST recurrence.</li> </ul>
INTERVENTION(S)	<p><b>Arm A: Imatinib</b></p> <p>Imatinib mesylate will be administered at the dose of 400 mg/day. Dose escalation to doses greater than 400 mg/day is not allowed. Patients with KIT exon 9 mutation are an exception, and may be treated with a dose higher than 400 mg/day, but not higher than 800 mg/day.</p> <p>In case of toxicity, the dose may be reduced. In case imatinib needs to be discontinued for a time period longer than 28 days due to toxicity, imatinib treatment should be discontinued.</p> <p><b>Arm B: No imatinib</b></p> <p>No imatinib or other anti-cancer treatment will be administered in the adjuvant setting</p>
KEY EXCLUSION CRITERIA	<ol style="list-style-type: none"> <li>1. Presence of distant metastases or local recurrence of GIST.</li> <li>2. Not willing to donate tumour tissue and/or blood samples for the study molecular studies.</li> <li>3. Presence of a substitution mutation at PDGFRA codon D842 (usually D842V).</li> <li>4. Administration of adjuvant imatinib longer than for 3 years is planned regardless of the result of randomisation, or "life long" imatinib administration is planned.</li> <li>5. Prior adjuvant (+ neoadjuvant) therapy with imatinib mesylate for at least 35</li> </ol>

	<p>months has not been completed, or the total duration of prior adjuvant (+ neoadjuvant) imatinib administration exceeds the total duration of 37 months.</p> <p>6. Neoadjuvant imatinib for a duration that exceeds 9 months.</p> <p>7. Longer than 4-week break during adjuvant imatinib administration.</p> <p>8. The dose of imatinib at completion of 3 years of adjuvant imatinib was 200 mg per day or less or greater than 800 mg per day.</p> <p>9. Patient has received any investigational anti-cancer agents during adjuvant imatinib or between completion of adjuvant imatinib and the date of randomisation.</p> <p>10. Patient has been free of another malignancy for less than 5 years except if the other malignancy is not currently clinically significant nor requiring active intervention, or if the other malignancy is a basal cell skin cancer or a cervical carcinoma in situ. Recent existence of any other malignant disease is not allowed.</p> <p>11. Patient with Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., congestive heart failure, myocardial infarction within 6 months of study entry).</p> <p>12. Female patients who are pregnant or breast-feeding.</p> <p>13. Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, severe chronic renal disease, or active uncontrolled infection).</p> <p>14. Known diagnosis of human immunodeficiency virus (HIV) infection.</p> <p>15. Patient with a significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.</p> <p>16. Patients with chronic or active hepatitis B.</p> <p>17. Patients that have been committed to an institution by official or judicial order.</p> <p>18. Patients that are dependent upon the sponsor, the trial site or the investigator.</p>
KEY INCLUSION CRITERIA	<p>1. Age <math>\geq</math> 18 years.</p> <p>2. Morphological and immunohistological documentation of GIST (immunostaining for KIT [CD117] and/or DOG-1 positive, or mutation of KIT or PDGFRA present in tumour tissue).</p> <p>3. Macroscopically complete surgical resection of GIST (either R0 or R1 resection).</p> <p>4. Mutation analysis of KIT and PDGFR genes has been carried out.</p> <p>5. A high risk of GIST recurrence, either</p> <ol style="list-style-type: none"> <li>1) gastric GIST with mitotic count <math>&gt;10/50</math> HPFs, or</li> <li>2) non-gastric GIST with mitotic count <math>&gt;5/50</math> HPFs, or</li> <li>3) tumour rupture</li> </ol> <p>Tumour rupture (spillage of the tumour contents into the abdominal cavity) may have occurred either before or at surgery.</p> <p>6. ECOG performance status <math>\leq</math> 2.</p> <p>7. Adequate organ function, defined as serum total bilirubin <math>&lt;1.5 \times</math> ULN (upper limit of normal), serum AST (SGOT) and ALT (SGPT) <math>&lt;2.5 \times</math> ULN, creatinine <math>&lt;1.5 \times</math> ULN; blood ANC (neutrophil count) <math>\geq 1.0 \times 10^9/L</math>, platelet count <math>\geq 100 \times 10^9/L</math>.</p> <p>8. Female patients of childbearing potential must have a negative pregnancy test within 14 days before initiation of study drug dosing. Postmenopausal women must have amenorrhoea for at least 12 months to be considered of non-childbearing potential. Male and female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for up to 3 months following discontinuation of study drug. For females, a highly effective method for birth control must be used, which means that the method can achieve a failure rate of less than 1% per year when used consistently and correctly. All females of child-bearing potential must be informed of such methods, and must also, if sexually active, accept a monthly pregnancy test during treatment if randomized to prolonged imatinib use.</p> <p>9. Patient willing to be followed up at the study site regardless of the result of</p>

	<p>randomisation.</p> <p>10. Patient has provided a written, voluntary informed consent prior to study-specific screening procedures.</p>
OUTCOME(S)	<p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>•Recurrence-free survival (RFS) is defined by the time interval between the date of randomisation and the date of first detection of GIST recurrence or death, whichever occurs first.</li> </ul> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>•Overall survival (the time period between the date of randomisation and the date of death).</li> <li>•GIST-specific survival (the time period between the date of randomisation and the date of death considered to be caused by GIST; patients who die from other causes are censored on the date of death).</li> <li>•Safety (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).</li> <li>•Quality of Life (EQ-5D instrument).</li> </ul> <p><b>Exploratory:</b></p> <ul style="list-style-type: none"> <li>•Effect of the tumour mutation type on RFS.</li> <li>•Effect of tumour site on RFS.</li> <li>•Effect of the imatinib dose at randomisation on RFS.</li> <li>•Tumour tissue and blood molecular markers in prediction of GIST recurrence.</li> </ul>
STUDY TYPE	<p>Open-label, 2-arm, prospective, randomised, multicentre phase III trial.</p> <p>Patients diagnosed with GIST who have completed 3 years of adjuvant imatinib, who are free from GIST recurrence after 3 years of adjuvant imatinib, and who have a high risk of recurrence despite 3 years of adjuvant imatinib will be randomly allocated to one of the following 2 arms in a 1:1 ratio:</p> <p><b>A.</b> to further 24 months of adjuvant imatinib (i.e. the planned total duration of adjuvant imatinib is 5 years)</p> <p><b>B.</b> to stop imatinib (i.e. the planned total duration of adjuvant imatinib is 3 years)</p> <p>The study participants will be followed up for a minimum of 10 years post-randomisation or until death.</p>
STATISTICAL ANALYSIS	<p>This is a superiority study regarding the main endpoint (RFS). Based on the estimates from the SSG XVIII, the survival estimates from year 1 to 5 after the randomisation are assumed to be 81.2%, 64.8%, 44.2%, 36.2% and 31.1% in the 3-year imatinib treatment arm, assuming an exponential survival function fitted to the estimates extracted from SSG XVIII. In the 5-year arm, the corresponding estimates are assumed to be 91.5%, 87.7%, 71.8%, 53.0% and 39.1%. Based on simulations using log-rank tests (2-sided significance level of 0.05), 137 patients in each treatment arm are required to achieve a power of 80%. To allow for a drop-out rate of 10%, 150 patients per group will be randomised (power 0.8, 2-sided alpha 0.05, 1:1 randomisation).</p>
SAMPLE SIZE	<p>300 patients to be randomised in 1:1 ratio, 150 to imatinib for further 24 months and 150 to stop imatinib</p>
TRIAL DURATION	<p>2 years of recruitment followed by 10 years follow up after randomization</p>
current number of patients included	<p>70 pts..recruited – 6 in Germany – Stand 09.04.2018</p>
Number of sites	<p>10 German sites, 7 sites opened, 3 planned Q2/2018</p>

Chordome, Knochensarkome, fortgeschrittene Erkrankung**AIO-ST5-0217/ass: CDK4/6 inhibition in locally advanced/metastatic chordoma - NCT-PMO-1601****AIO-assozierte Studie**

Studiennummer/-Code:	AIO-ST5-0217/ass - NCT-PMO-1601
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 – 2019
Weitere Zentren:	Aktuell leider nicht möglich
Letzte Aktualisierung	31.10.2017

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk National Center of Tumor diseases, Heidelberg
CONDITION	locally advanced/metastatic chordoma
OBJECTIVE(S)	<p>Primary objective of this phase II trial is to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastasized chordoma refractory to treatment with tyrosine kinase inhibitors.</p> <p>The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of at least one confirmed complete response (CR) or confirmed partial response (PR) or stable disease (SD) according to RECIST version 1.1.</p> <p>Secondary Objectives include:</p> <ul style="list-style-type: none"> <li>• Tumor Response (TR)</li> <li>• Progression-free Survival (PFS)</li> <li>• Overall Survival (OS)</li> <li>• Safety/tolerability</li> <li>• Quality of Life</li> </ul>
INTERVENTION(S)	Palbociclib (CDK4/6-inhibition)
KEY EXCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Prior treatment with palbociclib</li> <li>• Organ insufficiency: creatinine &gt; 1.5x upper normal serum level; bilirubin, AST, or AP &gt;2.5x upper normal serum level; heart failure (New York Heart Association (NYHA) III/IV); uncontrolled hypertension; unstable angina; serious cardiac arrhythmia; severe obstructive or restrictive ventilation disorder</li> <li>• Uncontrolled infection</li> <li>• Patients with a “currently active” second malignancy other than non-melanoma skin cancer. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year.</li> <li>• Severe neurologic or psychiatric disorder interfering with ability of giving informed consent</li> <li>• Known or suspected active alcohol or drug abuse</li> <li>• Known positivity for HIV, active HAV, HBV, or HCV infection</li> <li>• Uncontrolled CNS involvement (treatment for CNS involvement prior to inclusion is allowed)</li> <li>• Cytopenia: platelets &lt;100 G/l, neutrophils &lt;1.0 G/l, hemoglobin &lt;10.0 g/dl</li> <li>• corrected QT interval (QTc) &gt;470 msec (based on the mean value of triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome, or known history of QTc prolongation or Torsade de Pointes</li> <li>• Uncontrolled electrolyte disorders that can aggravate the effects of a QTc-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia)</li> </ul>

	<ul style="list-style-type: none"> <li>• Participation in other ongoing interventional clinical trials (according to AMG).</li> </ul>
KEY INCLUSION CRITERIA	<ul style="list-style-type: none"> <li>• Patients with locally advanced or metastatic chordoma with confirmed diagnosis in a reference pathology (with immunohistology for epithelial membrane antigen, S100, Brachyury, INI-1) who have no response or have lost response to treatment with a tyrosine kinase inhibitor e.g. imatinib, lapatinib, erlotinib, sunitinib, sorafenib, etc.</li> <li>• At least one measurable tumor lesion according to RECIST 1.1 criteria</li> <li>• Loss of p16 determined immunohistochemically or CDKN2A/B genomically, presence of CDK4/6 and RB1 determined immunohistochemically or by RNA sequencing.</li> <li>• Age <math>\geq</math> 18 years, no upper age limit</li> <li>• Availability of tissue blocks preferably not older than 12 months for immunohistologic assessment (if no adequate material is available, re-biopsy should be considered before entering the study)</li> <li>• No chemotherapy two weeks before study entry</li> <li>• Non-pregnant and non-nursing. Women of child-bearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 72 hours prior to registration (WOCBP is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 months).</li> <li>• Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or begin one acceptable method of birth control (IUD, tubal ligation, or partner's vasectomy) while on therapy and for three months after the last dose of therapy. Hormonal contraception alone is an inadequate method of birth control. Female patients must agree not to donate lactation during treatment and until 3 months after end of treatment.</li> <li>• Men must agree not to father a child and must use a latex condom during any sexual contact with WOCBP while receiving therapy and for three months after therapy is stopped, even if they have undergone successful vasectomy. Sperm donation is not permitted for the same time interval.</li> <li>• Signed written informed consent</li> <li>• Performance status <math>\leq</math> 2 according to ECOG/WHO criteria</li> <li>• Ability of patient to understand the character and individual consequences of clinical trial</li> </ul>
OUTCOME(S)	disease control rate (DCR) after six cycles of palbociclib
STUDY TYPE	Non-randomized, single-arm, open-label, multicenter phase II trial
STATISTICAL ANALYSIS	<p>The study is a phase II trial with standard palbociclib dose of 125 mg once daily for 21 days in a 28-day cycle.</p> <p>The study needs 43 patients evaluable for the primary endpoint to complete. The sample size and power calculations were based on Simon's optimal two-stage design. The type I error was set at <math>\alpha = 0.05</math>, the type II error at <math>\beta = 0.2</math>. Here, the null hypothesis that the true response rate is less or equal to <math>p_0 = 0.1</math> will be tested against a one-sided alternative, where the desirable level of response is 0.25.</p> <p>In the first stage, <math>n_1 = 18</math> patients will be accrued. If there are <math>r_1 = 2</math> or fewer responses in these 18 patients, the study will be stopped and the drug rejected. Otherwise, 25 additional patients will be accrued for a total of <math>n = 43</math> patients. In the final analysis the null hypothesis will be rejected and the drug recommended for further development if 8 or more responses are observed in 43 patients.</p>
SAMPLE SIZE	<p>18 in the first stage  25 in the second stage (only if first stage was positive)  Total sample size: minimum 18 patients; maximum 43 patients</p>

TRIAL DURATION	Total trial duration: 48 months Duration of the clinical phase: 36 months
PARTICIPATING CENTERS	1. Universitätsklinikum Heidelberg, Prof. Dr. med. Stefan Fröhling 2. Universitätsklinikum Essen, Dr. med. Rainer Hamacher 3. Universitätsklinikum Ulm, Dr. Verena Gaidzik

Solide Tumore mit DNA-Reparatur Defizienz, fortgeschrittene Erkrankung

**AIO-ST5/TF-0117/ass Randomized Phase-2 Study of Trabectedin/Olaparib Compared to Physician's Choice in Subjects with Previously Treated Advanced or Recurrent Solid Tumors Harboring DNA Repair Deficiencies - NCT-PMO-1603**

<b>AIO-assozierte Studie</b>	
Studiennummer/-Code:	AIO-ST5/TF-0117/ass - NCT-PMO-1603
Status:	in Vorbereitung
Rekrutierungszeitraum:	2018 – 2020
Weitere Zentren:	sind möglich
Letzte Aktualisierung	31.10.2017

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk National Center of Tumor diseases, Heidelberg
CONDITION	<ul style="list-style-type: none"> <li>Advanced or recurrent solid tumors harboring DNA repair deficiencies</li> <li>Relapsed and metastatic solid tumors with homologous recombination DNA repair deficiency</li> </ul>
Das vollständige Kurzprotokoll finden Sie unter den Studien der Arbeitsgruppe Translationale Forschung.	

Rezidiertes Sarkom / Registerstudie**Sarcoma Relapse Registry for Relapsed Sarcoma of Bone and Soft Tissues (SAREZ = "SARKom REZidiv REGISTER")****AIO-assozierte Studie**

Studiennummer/-Code:	SAREZ-Register
Status:	in Rekrutierung
Rekrutierungszeitraum:	seit 2010
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	Oktober 2017

Indication	Relapsed sarcoma of bone and soft tissues in patients
Treatment line	Clinical registry, phase I and II trials
Principal investigator	Univ.-Professor Dr. med. Jörg Thomas Hartmann Chefarzt der Klinik Innere Medizin II, Hämatologie, Onkologie, Immunologie Katholische Hospitalvereinigung Ostwestfalen Lehrkrankenhaus der Medizinischen Hochschule Hannover Franziskus Hospital Bielefeld, Kiskerstrasse 26, 33615 Bielefeld Tel: 0521 589-1201, FAX: 0521 589-1204 E-Mail: joerg.hartmann@franziskus.de
Cooperative group	Translational Sarcoma Research Network Consortium (TranSaRNet)
Number of patients	N=131 AIO/IAWS plus 222 adult pts >50 years (Stand 10/2016); CWS n=143/COSS:93; CESS: 59 (Stand 10/2014) = total 648 pts
Start of study	01.01.2010
End of study	End of pilot phase 31.10.2011. Renewed until 31.01.2015. Minimum follow-up until 31.12.2016
Further study centers requested?	Yes Centers with registered patients: 60 Centers interested, no patients identified yet: 160
Rationale	Sarcomas comprise a rare and heterogeneous group of cancers of bone and soft tissues, which mainly affect children, adolescents, and young adults (accounting for approx. 10% of malignancies in children and adolescents, but < 5% of cancers in young adults). Because of the lack of clinical trials for adolescents and young adults, sarcoma patients of this age group have not benefited from prognosis improvements obtained at other ages. Few data exist regarding the clinical behavior and treatment of sarcoma patients after relapse. There is also little knowledge in Germany about the location of treatment (adult hospital, pediatric teaching hospital), the proposed treatment and/or enrolment in clinical trials, treatment completion, compliance and outcome in patients with sarcoma after relapse.
Primary objective/endpoint	Postrelapse 5-year event-free and overall survival
Study design	Clinical registry
Inclusion and exclusion criteria	<ul style="list-style-type: none"> <li>• Two cohorts, &lt;/&gt;50 years of age at the time of relapse</li> <li>• Histologically confirmed diagnosis (reference pathology) of bone or soft tissues at initial presentation or at relapse</li> <li>• Achievement of a disease-free status after primary treatment</li> <li>• Informed consent</li> </ul>



	<ul style="list-style-type: none"> <li>Entered into the registry by an institution participating in SAREZ and available for long-term follow-up.</li> </ul>
Statistical methods	<i>Strategy:</i> descriptive and explorative analysis of recruited patients.
Estimated number of sites	10-20

### Registry for primary and secondary angio- and radiation-induced Sarcoma of Bone and Soft Tissues (RIS) (ANGRY = "ANGio- and Radiation-induced sarcoma registry")

<b>AIO-assozierte Studie</b>	
Studiennummer/-Code:	ANGRY-Register
Status:	in Rekrutierung
Rekrutierungszeitraum:	seit 2010
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	Oktober 2017

Indication	Registry for angiosarcoma and radiation induced sarcoma (RIS)
Type of study	Clinical registry
Principal investigator	Univ.-Professor Dr. med. Jörg Thomas Hartmann Chefarzt der Klinik Innere Medizin II Hämatologie, Onkologie, Immunologie Katholische Hospitalvereinigung Ostwestfalen Lehrkrankenhaus der Medizinischen Hochschule Hannover Franziskus Hospital Bielefeld, Kiskerstrasse 26, 33615 Bielefeld Tel: 0521 589-1201, FAX: 0521 589-1204 E-Mail: joerg.hartmann@franziskus.de
Cooperative group	AIO, IAWS, TranSaRNet, SAREZ
Number of patients	137 (Stand 10/2016)
Start of study	01.01.2010
End of study	End of pilot phase 31.12.2014. Minimum follow-up until 31.12.2018
Further study centers requested?	Yes
Rationale	Sarcomas comprise a rare and heterogeneous group of cancers of bone and soft tissues. RIS has been defined as a histologically confirmed sarcoma developing adjacent to or within a previously irradiated field after a latency period of several years. Most RIS are classified histologically as angiosarcomas. Because of the lack of clinical trials for primary and secondary angiosarcomas these groups have not benefited from improvements of prognosis obtained for other histologic sarcoma subtypes. Few data exist regarding the clinical behavior and treatment of angiosarcoma patients. There is also little knowledge in Germany about the type and location of treatment, the proposed treatment and/or enrolment in clinical trials, treatment completion, compliance and outcome in patients with angiosarcoma.
Primary objective/endpoint	2-year event-free and overall survival, predictive/prognostic markers (clinical/molecular)
Study design	Clinical registry
Inclusion and exclusion criteria	<ul style="list-style-type: none"> <li>Radiation induced sarcoma at any age at the time of relapse, all histologic subtypes or</li> <li>Histologically confirmed diagnosis of primary angiosarcoma</li> </ul>

	<ul style="list-style-type: none"> <li>• Tumor material, preferentially tumor blocks</li> <li>• Informed consent</li> <li>• Availability for long-term follow-up</li> </ul>
Statistical methods	<i>Strategy:</i> descriptive and explorative analysis
Estimated number of sites	10-20

### Retrospektive Analyse

#### **AIO-STS-0116/ass: Retrospektive Analyse zur Wirksamkeit der Kombinationstherapie aus Temozolomid plus Avastin im Vergleich zu alternativen Systemtherapien bei Patienten mit Solitär Fibrösem Tumor.**

<b>AIO-assoziierte Studie</b>	
Studiennummer/-Code:	AIO-STS-0116/ass
Letzte Aktualisierung	September 2016

Art der Studie Study Type	nationale, multizentrische, retrospektive, anonymisierte Datenerhebung		
Kontaktadresse/ Kontaktperson:	<table border="0"> <tr> <td style="vertical-align: top;"> <p><b>Dr. Klaus Heißner</b> Universitätsklinikum Tübingen Zentrum für Weichteilsarkome, GIST und Knochentumoren Otfried-Müller-Straße 10 72076 Tübingen Tel. 07071 29-82127 Fax 07071 29-4399 Klaus.heissner@med.uni- tuebingen.de</p> </td> <td style="vertical-align: top;"> <p><b>Prof. Dr. Hans-Georg Kopp</b> Universitätsklinikum Tübingen Zentrum für Weichteilsarkome, GIST und Knochentumoren Otfried-Müller-Straße 10 72076 Tübingen Tel. 07071 29-82127 Fax 07071 29-4399 Hans-Georg.Kopp@med.uni- tuebingen.de</p> </td> </tr> </table>	<p><b>Dr. Klaus Heißner</b> Universitätsklinikum Tübingen Zentrum für Weichteilsarkome, GIST und Knochentumoren Otfried-Müller-Straße 10 72076 Tübingen Tel. 07071 29-82127 Fax 07071 29-4399 Klaus.heissner@med.uni- tuebingen.de</p>	<p><b>Prof. Dr. Hans-Georg Kopp</b> Universitätsklinikum Tübingen Zentrum für Weichteilsarkome, GIST und Knochentumoren Otfried-Müller-Straße 10 72076 Tübingen Tel. 07071 29-82127 Fax 07071 29-4399 Hans-Georg.Kopp@med.uni- tuebingen.de</p>
<p><b>Dr. Klaus Heißner</b> Universitätsklinikum Tübingen Zentrum für Weichteilsarkome, GIST und Knochentumoren Otfried-Müller-Straße 10 72076 Tübingen Tel. 07071 29-82127 Fax 07071 29-4399 Klaus.heissner@med.uni- tuebingen.de</p>	<p><b>Prof. Dr. Hans-Georg Kopp</b> Universitätsklinikum Tübingen Zentrum für Weichteilsarkome, GIST und Knochentumoren Otfried-Müller-Straße 10 72076 Tübingen Tel. 07071 29-82127 Fax 07071 29-4399 Hans-Georg.Kopp@med.uni- tuebingen.de</p>		
Studienziele/ Objectives	<p><u>Primäres Studienziel:</u></p> <ul style="list-style-type: none"> <li>• Progressionsfreies Überleben</li> </ul> <p><u>Sekundäre Studienziele:</u></p> <ul style="list-style-type: none"> <li>• Gesamtüberleben</li> <li>• Toxizität</li> <li>• Zeit bis zum Progress</li> <li>• Therapiedauer</li> <li>• Ansprechrate</li> <li>• Bestes Ansprechen</li> </ul>		
Rekrutierungszeitraum von/bis period of	Die Rekrutierung der Patienten bis 30.11.2016 ist retrospektiv nicht eingeschränkt. Alle Patienten, die seit der Etablierung der Tumorbanken der jeweiligen teilnehmenden Zentren eine Systemtherapie zur Behandlung eines Solitär Fibrösen Tumors erhalten haben sollen dokumentiert werden.		
Weitere teilnehmende Zentren erwünscht? More centres?	Teilnehmen dürfen alle Sarkomzentren der AIO, die Patienten mit Solitär Fibrösen Tumoren in dem o.g. Zeitraum therapiert haben.		
Haupt-Einschlusskriterien / Key inclusion criteria	Alle Patienten, die aufgrund von einem histologisch gesicherten Solitär Fibrösen Tumor eine Systemtherapie erhalten haben sollen dokumentiert werden.		

Haupt- Ausschlusskriterien /	unzureichende/ fehlende Dokumentation
Therapieschema Scheme of therapy	Es handelt sich um eine retrospektive Datenauswertung. Die Dokumentation der Patientendaten aller teilnehmenden Zentren erfolgt anonymisiert. Eine Intervention erfolgt nicht.
Tumorevaluierung Criteria for evaluation	Das Therapieansprechen wird retrospektiv anhand der schriftlichen Befunde der jeweiligen Radiologie am teilnehmenden Zentrum erfasst.
Rationale	<p>Solitär Fibröse Tumoren (SFT) repräsentieren eine sehr seltene Untergruppe von Weichteilsarkomen WTS (ca. 1% aller WTS). Wie fast alle WTS sind sie durch die vollständige Resektion heilbar. SFT metastasieren äußerst selten. Sie zeichnen sich in einer Mehrzahl der Fälle durch ein lokal verdrängendes, denn ein infiltrierendes Wachstum aus. Sie wurden aufgrund dessen in der aktuellen WHO Klassifikation als "indolent" klassifiziert.</p> <p>Systemische Therapieoptionen sind aufgrund der Seltenheit der Tumoren bislang wenig untersucht. In der Literatur sind bis heute keine prospektiven Studien publiziert worden. Die publizierten Daten basieren auf Einzelfallberichten und kleineren Fallserien. Klassische Zytostatika in Form von Mono- und Kombinationstherapien erreichen eine progressionsfreies Überleben (PFS) zwischen 4-6 Monaten. In einer Publikation von Park et al. 2011 konnte bei 14 Patienten ein PFS von 9,7 Monaten durch die Kombination aus Temozolomid und Bevacizumab erreicht werden. Die außergewöhnlich hohe Ansprechraten auf die Kombinationstherapie konnten wir jüngst auch in Tübingen beobachten. Bemerkenswert ist die Dauer des Therapieansprechens in Einzelfällen &gt;18 Monate.</p> <p>Prospektive Studien sind in der "rare disease" nicht zu erwarten. Aufgrund dessen wurden die Therapieempfehlungen auch in Zukunft auf retrospektiven Datenerhebungen beruhen müssen.</p> <p>Die hier vorgeschlagene Analyse würde über alle AIO Zentren deutschlandweit das bislang größte Patientenkollektiv in dieser Tumorentität zusammentragen. Das Ziel der Auswertung ist es die Ansprechraten auf eine Systemtherapie insgesamt zu analysieren und mit dem der Ansprechraten auf die Kombinationstherapie aus Temozolomid und Bevacizumab zu korrelieren. Anhand der Daten ließe sich eine allgemeine Therapieempfehlung in der sehr selten Tumorentität der SFT erarbeiten.</p>

## Young Medical Oncologists

### Erstlinie Cholangiokarzinom

**AIO-YMO/HEP-0315: NaI-IRI with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary-tract cancer - An open label, non-comparative, randomized, multicenter phase II trial (NIFE)**

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/ - Code	AIO-YMO/HEP-0315 - NIFE
Status:	6 Patienten rekrutiert, 5 randomisiert, Initiierungen laufen noch
Rekrutierungszeitraum:	2017 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung:	April 2018

National Coordinating Investigator	Dr. med. Thomas J. Ettrich Klinik für Innere Medizin I Universitätsklinikum Ulm Albert-Einstein-Allee 23, 89081 Ulm, Germany Phone: +49 731 500 44501, Fax.: +49 731 500 44502 E-Mail: thomas.ettrich@uniklinik-ulm.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin, Germany Phone: +49 30 814534435, Fax +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Study design	Open label, non-comparative, randomized, multicenter phase II trial
Anticipated start date	Q4/2017
Duration of study	Enrollment: 18 months total study duration 54 months (incl. follow-up)
Indication	Locally advanced or metastatic, non resectable, adenocarcinoma of the biliary tract including intrahepatic and extrahepatic bile duct
Target population	Patients with locally advanced or metastatic, non resectable, adenocarcinoma of the intrahepatic or extrahepatic biliary tract eligible for 1 <sup>st</sup> -line treatments.
Total number of sites	30
Primary objective	To determine whether a combination of 5-FU and naI-IRI prolongs progression-free survival in patients with locally advanced or metastatic adenocarcinoma of the biliary tract
Secondary objectives	<ul style="list-style-type: none"> <li>• Overall progression free survival according to RECIST 1.1</li> <li>• Overall survival</li> <li>• Disease control rate according to RECIST 1.1</li> <li>• Proportion of patients with an objective response according to RECIST 1.1</li> <li>• Toxicity/Safety according to CTC-AE-criteria (≥ Grade 3/4)</li> <li>• Health related quality of life, anxiety and depression status (EORTC QLQ-BIL21, QLQ-C30 and HADS-D questionnaires)</li> <li>• Retrospective correlation of resectability in accordance with a central surgical board compared to local surgical review</li> <li>• Retrospective central radiological review</li> </ul>
Planned	N=92 total (n=46 per treatment arm)

sample size	
Inclusion criteria	<ol style="list-style-type: none"> <li>3. Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>4. Age <math>\geq</math> 18 years at time of study entry</li> <li>5. Histologically confirmed, non-resectable, locally advanced or metastatic adenocarcinoma of the intrahepatic or extrahepatic biliary tract</li> <li>6. Non-resectability has to be stated by local interdisciplinary tumor board</li> <li>7. Measurable or assessable disease according to RECIST 1.1</li> <li>8. ECOG performance status 0-1</li> <li>9. Life expectancy of more than 3 months</li> <li>10. If applicable, adequately treated biliary tract obstruction before study entry with total bilirubin concentration <math>\leq</math> 2 x ULN</li> <li>11. Adequate blood count, liver-enzymes, and renal function: <ul style="list-style-type: none"> <li>• White blood cell count <math>\geq</math> 3.5 x 10<sup>6</sup>/mL</li> <li>• Platelet count <math>\geq</math> 100 x 10<sup>9</sup>/L (&gt;100,000 per mm<sup>3</sup>)</li> <li>• AST (SGOT)/ALT (SGPT) <math>\leq</math> 5 x institutional upper limit of normal</li> <li>• Serum Creatinine <math>\leq</math> 1.5 x institutional ULN and a calculated glomerular filtration rate <math>\geq</math> 30 mL per minute</li> </ul> </li> <li>12. Patients not receiving therapeutic anticoagulation must have an INR &lt; 1.5 ULN and PTT &lt; 1.5 ULN within 7 days prior to randomization. The use of full dose anticoagulants is allowed as long as the INR or PTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose for anticoagulants for at least three weeks at the time of randomization</li> <li>13. No prior palliative chemotherapy for biliary tract cancer</li> <li>14. No adjuvant treatment within 6 months prior to study entry</li> <li>15. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.</li> </ol>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes</li> <li>2. Premalignant hematologic disorders, e.g. myelodysplastic syndrome</li> <li>3. Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment</li> <li>4. Prior (&lt;3 years) or concurrent malignancy (other than biliary-tract cancer) which either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial urinary bladder tumor [Ta, Tis and T1].</li> <li>5. Pre-existing lung disease</li> <li>6. History or clinical evidence of CNS metastases Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria: <ol style="list-style-type: none"> <li>a) are asymptomatic and</li> <li>b) have no requirement for steroids 6 weeks prior to start of study treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases</li> </ol> </li> <li>7. History of hypersensitivity to any of the study drugs or any of the constituents of the products</li> <li>8. Known dihydropyrimidine dehydrogenase (DPD) deficiency</li> <li>9. Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy</li> <li>10. Severe non-healing wounds, ulcers or bone fractures</li> <li>11. Evidence of bleeding diathesis or coagulopathy</li> <li>12. Major surgical procedures, except open biopsy, nor significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgical procedure during the course of the study except for surgery of central intravenous line placement for chemotherapy administration.</li> <li>13. Medication that is known to interfere with any of the agents applied in the trial.</li> </ol>

	<ol style="list-style-type: none"> <li>14. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner]. Women of childbearing potential must have a negative pregnancy test (serum <math>\beta</math>-HCG) at Screening.</li> <li>15. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results</li> <li>16. Known Gilbert-Meulengracht syndrome</li> <li>17. Known chronic hypoacusis, tinnitus or vertigo</li> <li>18. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lives of previously used trial medication, whichever is of longer duration.</li> <li>19. Previous enrollment or randomization in the present study (does not include screening failure).</li> <li>20. Any other chemotherapy at study start</li> <li>21. Involvement in the planning and/or conduct of the study (applies to both Baxalta staff and/or staff of sponsor and study site)</li> <li>22. Patient who might be dependent on the sponsor, site or the investigator</li> <li>23. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</li> <li>24. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</li> </ol>
Investigational agents and active comparators	<ul style="list-style-type: none"> <li>• IRINOTECAN LIPOSOME (MM-398, nal-IRI)</li> <li>• 5-Fluorouracil (5-FU)</li> <li>• Leucovorin (calcium folinate)</li> <li>• Cisplatin</li> <li>• Gemcitabine</li> </ul>
Treatment schedule	<p><u>Experimental intervention (Arm A):</u></p> <ul style="list-style-type: none"> <li>• Nal-IRI 80 mg/m<sup>2</sup> as a 1.5 hour infusion</li> <li>• 5-FU 2400 mg/m<sup>2</sup> as 46 hour infusion</li> <li>• Leucovorin 400 mg/m<sup>2</sup> as 0.5 hour infusion</li> <li>• Cycle q2w</li> </ul> <p><u>Control intervention – standard arm (Arm B):</u></p> <ul style="list-style-type: none"> <li>• Cisplatin 25 mg/m<sup>2</sup> as 1 hour infusion on D1, D8</li> <li>• Gemcitabine 1000 mg/m<sup>2</sup> as 0.5 hour infusion on D1, D8</li> <li>• Cycle q3w</li> </ul> <p>Treatment until progressive disease or intolerable toxicity.</p> <p>Key study procedures (and routine procedures):</p> <ul style="list-style-type: none"> <li>• Tumor assessment according to standard of care q8w</li> <li>• QoL every new cycle; EORTC QLQ-BIL21, QLQ-C30 and HADS-D</li> <li>• Core biopsy</li> <li>• 2x 7.5 mL EDTA blood sample, 7.5 mL serum, 10 mL PaxGene-ccfDNA by Qiagen®</li> </ul>
Primary endpoint	Progression-free survival rate at 4 months defined as the proportion of patients with non-progressive disease 4 months after randomization by intention to treat analysis
Secondary endpoints	<ul style="list-style-type: none"> <li>• Overall Progression-free survival</li> <li>• 3-years overall survival</li> <li>• Disease control rate according to RECIST 1.1 after 2 months</li> <li>• Objective tumor response rate (ORR) according to RECIST 1.1</li> <li>• Toxicity/Safety according to CTC-AE-criteria (<math>\geq</math> Grade 3/4)</li> </ul>

	<ul style="list-style-type: none"> <li>• Patient related outcome/Quality of Life/Time to definitive deterioration (TUDD) to be assessed with the following tools: EORTC QLQ-BIL21, QLQ-C30 and HADS-D</li> <li>• Tumor resectability in accordance with a retrospective central surgical board compared to local surgical review</li> <li>• Radiological response according to RECIST 1.1 and volumetry determined by a retrospective central radiological review</li> </ul>
Exploratory objectives and endpoints	<ul style="list-style-type: none"> <li>• Exploratory biomarkers analysis (cfDNA exome sequencing, transcriptome, miRNA-arrays prior to and after start of treatment and upon progress)</li> <li>• Establishment of Predictive/Prognostic biomarker profiles for advanced cholangiocarcinoma</li> <li>• Tumor Evolution under systemic therapy</li> </ul>
Randomization procedure	<p>1:1</p> <p>Stratified permuted block randomization will be applied to ensure balanced prognostic groups.</p> <p>The stratification parameters will be:</p> <ul style="list-style-type: none"> <li>• Primary site: intrahepatic vs. extrahepatic biliary tract cancer</li> <li>• Disease stage: advanced vs. metastatic</li> <li>• Age <math>\leq 70</math> vs. <math>&gt; 70</math> years</li> <li>• Sex: male vs. female</li> <li>• WHO performance status: ECOG 0 vs. ECOG 1</li> </ul>
Rationale Hypothesis	<p>Cholangiocellular carcinoma (CCC) is a rare type of cancer, although the incidence is rising. Moreover CCC is associated with a high mortality most due to the reason of mainly advanced stages at primary diagnosis. Overall survival time does not exceed 6 months and the 5 year survival rate is less than 5% for patients with advanced or metastatic disease. Advanced CCC shows response to chemotherapy resulting in an improved disease control, improved survival and quality of life (QoL). However, OS rates of more than 10 months remain rare. There is no generally defined standard of care for advanced and metastatic CCC patients. Fluoropyrimidines, cisplatin and gemcitabine have shown activity. In the ABC-02 phase III trial, gemcitabine combined with cisplatin prolonged progression-free survival and overall survival compared with gemcitabine alone (Cis + Gem vs. Gem: OS 11.7 mo vs. 8.1 mo; PFS 8.0 mo vs. 5.0 mo) so that this could be seen as today's standard of care, but is so far not compared to other active combinational regimen. An additive effect through combination with cetuximab or sorafenib couldn't be shown (Gem + Ox vs. Gem + Ox + Cet: OS 12.4 mo vs. 11.0 mo; PFS 5.5 mo vs. 6.1 mo; Gem + Sorafenib vs. Gem OS 8.4 mo vs. 11.2 mo, PFS 3.0 mo vs. 4.9 mo. Irinotecan in combination with 5-FU showed promising results in 1st- and 2nd-line therapy of advanced biliary tract cancer and is commonly used as therapeutic option after failure of the 1st-line therapy with gemcitabine/cisplatin.</p> <p>As the tumorbiology of CCC may seem to be similar to pancreatic adenocarcinomas the already effective combination of nal-IRI plus 5-fluorouracil (NAPOLI-1 trial) can achieve similar results in advanced biliary tract cancer.</p> <p>Research hypothesis: The combinational therapy of Nal-IRI plus 5-fluorouracil is comparable in defined critical endpoints to a control group of patients treated with the recent standard of care gemcitabine plus cisplatin.</p>
Safety data	<ul style="list-style-type: none"> <li>• Treatment Emergent Adverse Events according to CTC 4.03</li> <li>• Frequency of abnormal laboratory parameters</li> </ul>

Sample size estimation	<p>Simon's optimal two-stage design: <math>H_0</math>: less than 40% of patients are progression-free by 4 months of NAL-IRI plus 5-FU/leucovorin. Alternative hypothesis: <math>\geq 60\%</math> of patients are progression-free by 4 months of nal-IRI plus 5-FU/leucovorin. If 7 or less of the first 18 patients assigned to nal-IRI plus 5-FU/leucovorin have a tumor response or stable disease at 4 months, <math>H_0</math> will be accepted and the study will be terminated. If 8 or more patients with tumor response or stable disease are observed, another 28 patients in each treatment group are to be included. At the final analysis, <math>H_0</math> will be accepted if less than 23 of the total 46 patients in the NAL-IRI plus 5-FU/leucovorin group had a tumor response or stable disease at 4 months. With this design the probability of falsely rejecting <math>H_0</math> is <math>\alpha=10\%</math> (significance level) and the probability of falsely accepting <math>H_0</math> - if in real <math>H_1</math> is true - is <math>\beta=10\%</math> (power=90%). As the study will be analyzed as ITT, all patients will be analyzed (missing data will be considered as failure). Hence, a sample size of <math>n=46</math> per treatment arm and a total <math>N=92</math> enrolled and randomized patients is required.</p> <p>It is assumed that approx. 120 patients need to be screened for eligibility.</p>												
Interim analysis	<p>A planned interim analysis will be conducted after 18 patients have been enrolled, treated and evaluated in the experimental arm. If 7 or less of the first 18 patients assigned to Nal-IRI plus 5-FU/leucovorin have a tumor response or stable disease at 4 months, <math>H_0</math> will be accepted and the study will be terminated. If 8 or more patients with tumor response or stable disease are observed, another 28 patients in each treatment group are to be included.</p>												
Study plan / time lines	<table> <tr> <td>First Patient In (FPI):</td> <td>Q4/2017</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 18 months</td> </tr> <tr> <td>Last Patient Last Visit (LPLV):</td> <td>after approx. 24-25 months</td> </tr> <tr> <td>End of follow-up period after LPLV:</td> <td>after approx. 54 months</td> </tr> <tr> <td>Study report:</td> <td>after approx. 63 months</td> </tr> <tr> <td>Publication:</td> <td>after approx. 64 months</td> </tr> </table>	First Patient In (FPI):	Q4/2017	Last Patient In (LPI):	after approx. 18 months	Last Patient Last Visit (LPLV):	after approx. 24-25 months	End of follow-up period after LPLV:	after approx. 54 months	Study report:	after approx. 63 months	Publication:	after approx. 64 months
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Publication:	after approx. 64 months												

### Cholangiokarzinom (intra- und extrahepatisch), Gallenblasenkarzinom, Zweitlinie

**AIO-YMO/HEP-0316: 5-Fluorouracil (5-FU), folinic acid and irinotecan (FOLFIRI) versus 5-FU and folinic acid as second-line chemotherapy in patients with biliary tract cancer (IRIBIL): a randomized open-label phase 2 study**

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer:	AIO-YMO/HEP-0316
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 – 2019
Weitere Zentren:	Aktuell nicht – Eröffnung weiterer Zentren ist geplant
Letzte Aktualisierung	April 2018

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Oliver Waidmann
Studienziele	<p><u>Primäres Studienziel:</u> Progressionsfreie Überleben (PFS)</p> <p><u>Sekundäre Studienziele:</u> Gesamtüberlebenszeit (OS) Zeit bis zur Tumorprogression (RECIST V1.1)</p>



	Ansprechrate (RECIST V1.1) Sicherheit Lebensqualität (EORTC QLQ-C30 Fragebogen)														
Zielparameter	Beurteilung der Wirksamkeit und Sicherheit einer Chemotherapie mit 5-FU, Folinsäure und Irinotecan (FOLFIRI) im Vergleich zur Chemotherapie mit 5-FU und Folinsäure bei Patienten mit metastasierten oder lokal fortgeschrittenen, nicht operablen Tumoren des biliären Systems (Gallengangs-, Gallenblasen- sowie Papillenkarcinome), die eine progrediente Erkrankung unter einer Erstlinienchemotherapie mit Gemcitabin- und platinhaltigen Chemotherapie zeigten.														
Patientenzahl	Geplant: 56 Patienten Bereits eingeschlossen: 2 (Stand April 2018)														
Rekrutierungszeitraum	<table> <tr> <td>Erster Patient eingeschlossen:</td> <td>Mai 2016</td> </tr> <tr> <td>Letzter Patient eingeschlossen:</td> <td>Mai 2018</td> </tr> <tr> <td>Rekrutierungsdauer:</td> <td>24 Monate</td> </tr> <tr> <td>Therapiedauer:</td> <td>12 Monate</td> </tr> <tr> <td>Follow-up-Dauer:</td> <td>alle 6 Wochen bis Tod</td> </tr> <tr> <td>Studienende:</td> <td>Mai 2019</td> </tr> <tr> <td>Gesamtdauer:</td> <td>3 Jahre</td> </tr> </table>	Erster Patient eingeschlossen:	Mai 2016	Letzter Patient eingeschlossen:	Mai 2018	Rekrutierungsdauer:	24 Monate	Therapiedauer:	12 Monate	Follow-up-Dauer:	alle 6 Wochen bis Tod	Studienende:	Mai 2019	Gesamtdauer:	3 Jahre
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Therapiedauer:	12 Monate														
Follow-up-Dauer:	alle 6 Wochen bis Tod														
Studienende:	Mai 2019														
Gesamtdauer:	3 Jahre														
Haupt-Einschlusskriterien	Einschlusskriterien <ul style="list-style-type: none"> <li>• Vorherige Einwilligung nach erfolgter Aufklärung vor Einleitung einer studienspezifischen Maßnahme</li> <li>• Patienten mit histologisch-gesichertem inoperablem oder metastasiertem Karzinom der Gallenwege und der Gallenblase.</li> <li>• Progress unter systemischer Chemotherapie mit einem Platinderivat (Oxaliplatin, Cisplatin oder Carboplatin) und Gemcitabin oder Progress <math>\leq 3</math> Monate nach Beendigung einer Chemotherapie mit einem Platinderivat und Gemcitabin</li> <li>• Alter <math>\geq 18</math> Jahre</li> <li>• ECOG Performance-Status 0-2 (Appendix 21.2)</li> <li>• Adäquate Knochenmarks, Leber- und Nierenfunktion:            Neutrophile <math>&gt; 1.500/\text{mm}^3</math>            Hämoglobin <math>&gt; 9 \text{ g/dl}</math>            Thrombozyten <math>&gt; 75 \times 10^9/\text{l}</math>            INR <math>\leq 1,5</math>            Gesamtbilirubin <math>\leq 2 \text{ mg/dl}</math>            ALT und AST <math>&lt; 5 \times \text{ULN}</math>            Kreatinin <math>&lt; 1,5 \times \text{ULN}</math></li> <li>• Child-Pugh Stadium A bei Vorliegen einer Leberzirrhose</li> <li>• Bei Frauen im gebärfähigen Alter ist ein negativer Serum-Schwangerschaftstest erforderlich, der innerhalb von 7 Tagen vor Randomisierung durchgeführt worden sein muss</li> <li>• Frauen im gebärfähigen Alter oder Männer müssen während und 90 Tage nach Ende der Studienteilnahme adäquate Verhütungsmaßnahmen einhalten (z.B. Doppel-Barriere-Methoden, orale Kontrazeption, Abstinenz).</li> </ul>														
Haupt-Ausschlusskriterien	Ausschlusskriterien: <ul style="list-style-type: none"> <li>• Resektabler Primärtumor ohne Nachweis von Fernmetastasen</li> <li>• Vorhergegangene Radiatio oder Radiochemotherapie, transarterielle Chemoembolisation (TACE), Radiofrequenzablation (RFA) oder selektive intraarterielle Radiotherapie (SIRT) innerhalb der letzten 3 Monate außer Radiatio von symptomatischen Knochenfiliae</li> <li>• Begleitende photodynamische Therapie oder intraduktale Radiofrequenzablation innerhalb der letzten 8 Wochen</li> <li>• Child Pugh Status B oder C (<math>&gt; 6</math> Punkte) bei Vorliegen einer Leberzirrhose (Appendix 21.3)</li> <li>• Massiver, nicht kontrollierbarer Aszites</li> <li>• Vorherige systemische Chemotherapie außer Gemcitabin und Platinderivat</li> </ul>														

	<p>(Cisplatin, Carboplatin oder Oxaliplatin)</p> <ul style="list-style-type: none"> <li>• Herzinsuffizienz &gt; NYHA-Klasse 2</li> <li>• Bekannte Hirnmetastasen, die nicht klinisch kontrolliert sind</li> <li>• Vorhergegangene Organ- oder Stammzelltransplantation</li> <li>• Aktive, unkontrollierte relevante Infektion &gt; CTCAE Grad 2, ausgenommen einer chronischen Hepatitis C-Virusinfektion (Appendix 21.5)</li> <li>• Größere chirurgische Eingriffe innerhalb der letzten 4 Wochen vor Beginn der Chemotherapie, Portimplantation ist erlaubt</li> <li>• Bekannte oder vermutete Allergie gegen 5-FU, Folinsäure, Irinotecan</li> <li>• Eine andere gleichzeitig oder innerhalb der letzten 3 Jahren bestehende Krebserkrankung (Ausnahmen: Zervixkarzinom in situ, behandeltes Basalzellkarzinom, oberflächliches Harnblasenkarzinom)</li> <li>• Drogenmissbrauch, medizinische, psychologische oder soziale Einschränkungen, die die Studienteilnahme behindern können</li> <li>• Teilnahme in einer anderen klinischen Studie mit einer Prüfsubstanz (unabhängig von der Intention, z.B. kurativ, prophylaktisch oder diagnostisch) innerhalb von 30 Tagen vor Studieneinschluss</li> <li>• Schwangerschaft oder stillende Frau</li> <li>• Unfähigkeit einer gültigen, schriftlichen Aufklärung über die Studie (dies trifft auch für Patienten zu, die in einem Abhängigkeitsverhältnis zum Sponsor oder Prüfarzt stehen)</li> </ul>
<p>Therapieschema</p>	<p style="text-align: center;"><b>Studiendesign - IRIBIL</b></p> <pre> graph LR     A[Histologisch gesichertes Karzinom der Gallenwege (ICC, ECC, GB-CA) nach Progress unter Gemcitabin+Platin] --&gt; B[RANDOMISATION 2:1]     B --&gt; C[FOLFIRI d1, d15, q 28d (38 Patienten)]     B --&gt; D[5-FU/Folinsäure d1, d15, q 28d (18 Patienten)]     </pre>
<p>Tumorevaluierung</p>	<p>RECIST V1.1</p>
<p>Rationale</p>	<p>In Deutschland erkranken jährlich mehr als 5000 Menschen an Karzinomen der Gallenwege oder der Gallenblase. Insbesondere im Bereich der intrahepatischen Gallenwege zeigt sich in den letzten Jahren eine deutliche Zunahme der Zahl der Neuerkrankungen am Cholangiokarzinom (CCA). Bei nicht resektablen oder metastasiertem CCA oder Gallenblasenkarzinom (GB-CA) ist eine systemische Chemotherapie mit Gemcitabin und Cisplatin der Standard. Damit lässt sich ein medianes Gesamtüberleben von 11.7 Monaten erreichen. Wenn Patienten unter der Chemotherapie mit Gemcitabin und Cisplatin einen Progress der Tumorerkrankung zeigen und in einem guten klinischen Zustand sind, wird den Patienten häufig eine Zweitlinienchemotherapie angeboten. Dabei werden zumeist 5-FU basierte Mono- oder Kombinationschemotherapien verwendet. Da die Patienten mit einer platinhaltigen Chemotherapie vorbehandelt wurden, wird häufig im Falle des Einsatzes einer Kombinationschemotherapie analog zum Kolorektalen Karzinom Irinotecan als Partner für 5-FU eingesetzt. Unter einer Kombinationschemotherapie mit 5-FU und Irinotecan fand sich in retrospektiven</p>

	Analysen vereinzelt auch ein Ansprechen von Tumoren in der Zweitlinientherapie. Weiterhin werden Kombinationschemotherapie mit 5-FU und Irinotecanformulierungen als Zweitlinienchemotherapie bei Pankreaskarzinom mit Erfolg eingesetzt. Allerdings besteht aufgrund des Mangels an prospektiven randomisierten Studien keine gute Evidenz welche Zweitlinientherapie für Patienten mit fortgeschrittenem CCA verwendet werden sollte. 5-FU-basierte Regime mit Irinotecan werden bei verschiedenen malignen Erkrankungen des Magen-Darmes-Traktes, v.a. beim Kolorektalen Karzinom und beim Magenkarzinom seit vielen Jahren eingesetzt und zeigen eine gute Wirksamkeit und auch bei längeren Therapiedauer ein gutes Sicherheitsprofil.																				
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*Metastatic adenocarcinoma of the lung (non-squamous NSCLC), second line and beyond*

**AIO-YMO/TRK-0415: Fostering efficacy of anti – PD-1 – treatment: Nivolumab plus radiotherapy in advanced NSCLC (FORCE)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/TRK-0415 - FORCE
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Study Type	Open-label, Phase-II trial		
Coordinating investigator (LKP)	<p>Dr. med. Farastuk Bozorgmehr Department of Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital Röntgenstrasse 1, 69126 Heidelberg, Germany Phone: +49 6221 396-1301, Fax: +49 6221 396-1302 E-mail: farastuk.bozorgmehr@med.uni-heidelberg.de</p> <p><b>Mentoring Investigator:</b> Univ.-Prof. Dr. Michael Thomas Thoraxklinik at Heidelberg University Hospital E-mail: michael.thomas@med.uni-heidelberg.de</p>		
Contacts:	<table> <tr> <td><b>Sponsor:</b> AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin Phone: +49 30 814534431 Fax +49 30 322932926 info@aio-studien-ggmbh.de</td> <td><b>Radiation Oncology Coordinator:</b> PD Dr. med. Stefan Rieken Department of Radiation Oncology Heidelberg University Hospital Im Neuenheimer Feld 400 69120 Heidelberg Phone: +49 6221 56-8200 Fax: +49 6221 56-5353 E-mail: stefan.rieken@med.uni-heidelberg.de</td> </tr> </table>	<b>Sponsor:</b> AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin Phone: +49 30 814534431 Fax +49 30 322932926 info@aio-studien-ggmbh.de	<b>Radiation Oncology Coordinator:</b> PD Dr. med. Stefan Rieken Department of Radiation Oncology Heidelberg University Hospital Im Neuenheimer Feld 400 69120 Heidelberg Phone: +49 6221 56-8200 Fax: +49 6221 56-5353 E-mail: stefan.rieken@med.uni-heidelberg.de
<b>Sponsor:</b> AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin Phone: +49 30 814534431 Fax +49 30 322932926 info@aio-studien-ggmbh.de	<b>Radiation Oncology Coordinator:</b> PD Dr. med. Stefan Rieken Department of Radiation Oncology Heidelberg University Hospital Im Neuenheimer Feld 400 69120 Heidelberg Phone: +49 6221 56-8200 Fax: +49 6221 56-5353 E-mail: stefan.rieken@med.uni-heidelberg.de		

Objectives	<p><u>Primary objective:</u> The primary objective is to investigate efficacy of a nivolumab-radiotherapy combination treatment in metastatic non-squamous NSCLC patients.</p> <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> <li>• To collect information on safety and tolerability of nivolumab in combination with radiotherapy by measurement of incidence and severity of AEs and specific laboratory abnormalities in all treated subjects by subject subgroups.</li> <li>• To collect further efficacy data in patients without necessity of radiotherapy.</li> <li>• To collect information on individual, patient reported and investigator-assessed quality of life.</li> <li>• To explore immune related RECIST criteria as an evaluation method for clinical benefit of nivolumab and nivolumab/radiotherapy.</li> </ul> <p><u>Exploratory objectives:</u></p> <ul style="list-style-type: none"> <li>• Tissue collection and blood sampling whilst course of disease to explore potential predictors of response to nivolumab The following exploratory objectives with regard to biomarkers will be investigated: <ul style="list-style-type: none"> <li>○ PD-L1 assessment</li> <li>○ phenotypical analysis of lymphocytes</li> <li>○ functional analysis of T-cells</li> <li>○ analysis of T-cell receptor specificities</li> <li>○ biomarker assessment of tumor IHC beyond PD-L1</li> <li>○ soluble pro- and anti-inflammatory markers</li> </ul> </li> <li>• To address the role of radiotherapy in the context of immune modulation, several aspects of radiation planning and treatment are planned to be explored. This includes both the location and composition of radiation targets and the anatomical profile of abscopally responding lesions. Therefore, treatment-related aspects characterizing the irradiated targets and abscopally responding target lesions will be documented by the treating radiation oncologist and radiologist.</li> </ul>
Endpoints	<p><u>Primary endpoint:</u></p> <ul style="list-style-type: none"> <li>• ORR according to RECIST 1.1 criteria</li> </ul> <p><u>Secondary endpoints:</u></p> <ul style="list-style-type: none"> <li>• PFS according to RECIST 1.1 criteria</li> <li>• PFS and ORR using assessment according to irRECIST</li> <li>• OS</li> <li>• 1 year OS rate</li> <li>• Descriptive sub-group analyses of efficacy in relation to PD-L1 expression levels (e.g. cut-off 1%, 5%, 10%)</li> <li>• Treatment Emergent Adverse Events according to CTC 4.03</li> <li>• Frequency of abnormal laboratory parameters</li> <li>• QoL [FACT-L]</li> </ul>
Number of patients	<p><b>N=130 total</b> Currently recruited: 48</p>
Accrual period	Q4/2016 – Q2/2019 (30 months)
More centres?	No (Target number: 15)
Key inclusion criteria	<p>14. Age &gt; 18 years at time of study entry. 15. ECOG performance status 0-1. 16. Patients with metastatic non-squamous non-small cell lung cancer after failure of platinum-based doublet chemotherapy and a) no necessity of radiotherapy (group B) or</p>

	<p>b) the necessity of radiotherapy of a metastatic bone lesion or soft tissue lesion (group A)                      For details see protocol section 3.2.</p> <p>17. Patients must have measurable disease by CT or MRI per RECIST 1.1 criteria. For details see protocol section 3.2.</p> <p>18. For each patient a formalin fixed, paraffin-embedded tumor tissue block (archival or recent) or a minimum of 15 unstained slides of tumor sample (slices must be recent and collected on slides provided by the sponsor) must be available for biomarker (PD-L1) evaluation. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.</p>
<p>Key exclusion criteria</p>	<ol style="list-style-type: none"> <li>1. Patients who require ongoing treatment with more than 10-mg of prednisone (or steroid equivalent, excluding inhaled or topical steroids) daily.</li> <li>2. Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).</li> <li>3. Patients with an active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger. (Subjects with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders, (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.)</li> <li>4. Any serious or uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy (see section 3.3 for details).</li> <li>5. Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required or anticipated to be required during the study period.</li> <li>6. Brain metastases mandating active treatment in terms of WBI (whole brain irradiation).</li> <li>7. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for 12 weeks after treatment is complete and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (&gt; 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.</li> <li>8. Known activating EGFR mutation or a known ALK translocation.</li> </ol>
<p>Scheme of therapy</p>	<p><b>Group A:</b>                      Nivolumab 240 mg fixed dose (q2w). First dose followed by radiotherapy. Radiotherapy has to start at the latest 72 hours after nivolumab administration.                      Radiotherapy: A metastatic site will be treated with a radiation dose of 4 Gy for a total of 5 courses during a two week time interval (total dose 20 Gy)</p> <p><b>Group B:</b>                      Nivolumab 240 mg fixed dose (q2w).</p> <ul style="list-style-type: none"> <li>• Radiologic tumor assessments every 6 weeks (± 5 days) starting after 9 weeks of treatment for the first year on treatment, then every 12 weeks after the first year on treatment until documented disease progression.</li> </ul>

	<p style="text-align: center;"><b>FORCE – Patient allocation and efficacy analysis strategy</b></p>
<p>Criteria for tumor evaluation</p>	<p>RECIST 1.1</p>
<p>Rationale</p>	<p>The rationale for the FORCE trial can be synthesized into three interconnected goals:</p> <ul style="list-style-type: none"> <li>• to determine the safety and feasibility of the radio-immunological treatment approach with particular focus on potential differences between a concurrent and sequential immunological intervention with nivolumab;</li> <li>• to increase PD-L1 check-point inhibitor efficacy in PD-L1 low expressing metastatic adenocarcinoma of the lung by inducing an immune-sensitizing effect (abscopal-like effect) with radiotherapy;</li> <li>• to explore the fundamental immunological principles governing check-point inhibitor efficacy and the immune-stimulating effect of radiotherapy in order to elucidate tumor-host biology and to find potential novel biomarkers.</li> </ul> <p>The trial will enroll patients with metastatic non-squamous non-small cell lung cancer with and without the necessity of radiotherapy of a metastatic site (e.g. bone) in second-line treatment and beyond. Patients will be stratified according to the necessity of radio-therapy (Arms A+B vs. Arm C) and patients with a requirement for radiotherapy will additionally be randomized between concomitant or sequential combination of radiotherapy and check-point inhibitor treatment (nivolumab; Arm A vs. Arm B). Treatment will by default continue until progressive disease and can optionally be extended beyond progression. The efficacy analysis will include a retrospective PD-L1 IHC assessment. Due to the fact that for patients with non-squamous NSCLC treated with nivolumab a PD-L1 expression cut-off of at <math>\geq 1\%</math> seemed to segregate patients who substantially benefit from checkpoint inhibition, the same cut-off will be used in this trial as a stratification variable for the efficacy analysis. The treatment is flanked by a biomaterial acquisition and subsequent exploratory assessment.</p> <p><b>Hypothesis:</b> The formal treatment-centered hypothesis of this trial is as follows: It is hypothesized that radiotherapy combined with nivolumab is safe and feasible and will improve efficacy of nivolumab through the „abscopal effect”.</p>
<p>Statistical considerations</p>	<p>Based on the results of the Checkmate-057 study the following assumptions and hypothesis are formulated.</p> <p>Patients treated with nivolumab (all-comer population) have an ORR of 19% during nivolumab treatment (historic control) and those with high PD-L1 expression (<math>\geq 10\%</math>) an ORR of 37% (historic control).</p> <p>It is assumed that patients who are treated with a combination of radiotherapy and nivolumab will achieve an ORR of 35% regardless of their PD-L1 status.</p> <p>The study requires N=50 subjects (in Group A) to detect whether the</p>

	<p>proportion responding (ORR) is higher than 19%, by applying a binomial test at a one-sided significance level of 0.05 with a probability of <math>1-\beta=0.8</math>, assuming an actual response rate of 35%. N=65 patients per arm will then be enrolled to take potential dropouts and patients with a lacking PD-L1 assessment into account.</p> <p>Based on historical data from n=535 patients (CheckMate studies 017, 057 and 063), drug-related Grade 3-4 AEs are expected to occur for 11% of patients receiving nivolumab only. For the planned sample size of N=65 patients per arm and under the assumption of a comparable safety profile for the radiotherapy/nivolumab combination arm (assuming a Grade 3-4 AE rate of 10.77%, i.e. N=7 patients with an event being observed), the two-sided exact 90%-confidence interval for the drug-related Grade 3-4 AE rate in the combination arm would range from 5.2% to 19.3%, thus illustrating the potential evidence for the safety profile of the combination therapy that can be provided with the planned sample size.</p> <p>The readouts of the control arm will be used to verify historic data and for descriptive comparative analyses of safety and efficacy.</p> <p>After 25 patients have been treated in Group A (nivolumab plus radiotherapy), a descriptive safety report will be done.</p> <p>N=130 (N=65 per Arm)</p>
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### Metastatic non-small cell lung cancer (NSCLC)

#### **AIO-YMO/TRK-0416: DURvalumab (MEDI4736) in frail and elderly patients with metastatic NSCLC [DURATION]**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/TRK-0416 - DURATION
Status:	In Rekrutierung
Rekrutierungszeitraum:	Q4 2017 – Q1 2020
Weitere Zentren:	vollständig
Letzte Aktualisierung	April 2018

Study design	Open label, treatment stratified and randomized phase II study
National Coordinating Investigator	Dr. med. Jonas Kuon Internistische Onkologie der Thoraxtumoren Thoraxklinik – Universität Heidelberg Röntgenstrasse 1, 69126 Heidelberg jonas.kuon@med.uni-heidelberg.de
Sponsor	AIO-Studien-gGmbH, Dr. Aysun Karatas Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, Fax +49 30 322932926 info@aio-studien-ggmbh.de
Anticipated start date	Q4/2017
Duration of study	Enrollment: 24 month Treatment and follow-up: 24 month
Indication	metastatic non-small cell lung cancer (NSCLC)
Target population	Frail or elderly patients with metastatic NSCLC with no targetable molecular

	alterations (EGFRwt; ALKtransl-) and not amenable to cisplatin-based standard-combination chemotherapy but eligible for at-least mono-chemotherapy with gemcitabine or vinorelbine.
Total number of sites	30
Primary objective	To assess the safety and tolerability of sequential therapy consisting of standard of care mono- or combination chemotherapy followed by durvalumab in comparison to standard of care mono- or combination chemotherapy in frail/elderly patients. For this purpose treatment related adverse events including those with a potential inflammatory or immune-mediated mechanism will be assessed. These include colitis, pneumonitis, ALT/AST increases, hepatitis, hepatotoxicity, neuropathy, neuromuscular toxicity (e.g. encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and myasthenia gravis), endocrinopathy (e.g. hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism), dermatitis, nephritis and pancreatitis.
Secondary objectives	To explore additional efficacy, safety and Quality of Life parameters and to investigate the utility of geriatric assessments for treatment guidance.
Exploratory objectives	predictive biomarkers for efficacy variables
Planned sample size	<b>N=200 randomized patients in total</b> Anticipated uninformative drop-outs: 15%  Currently randomized: 19
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations</li> <li>2. Age <math>\geq</math> 70 years at time of study entry and/or Charlson-Comorbidity-Index (CCI) <math>&gt;1</math> and/or Performance status ECOG <math>&gt;1</math></li> <li>3. Histologically confirmed diagnosis of metastatic NSCLC and no targetable molecular alterations (EGFRwt; ALKtransl-) and not amenable to cisplatin-based standard-combination chemotherapy.</li> <li>4. Patients with measurable disease (at least one uni-dimensionally measurable target lesion not previously irradiated, by CT-scan or MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) are eligible.</li> <li>5. A formalin fixed, paraffin-embedded (FFPE) tumor tissue block (fresh or archival less than 3 years old or recent) or a minimum of 10 unstained slides of tumor sample (slices must be 2-3 <math>\mu</math>m in thickness and less than 90 days old and collected on SuperFrost slides provided by the sponsor) must be available for biomarker (PD-L1) evaluation. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is inappropriate.</li> <li>6. No prior chemotherapy or any other systemic therapy for metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for locally advanced disease are eligible, provided that progression has occurred <math>&gt;6</math> months from last therapy.</li> <li>7. Prior radiotherapy and surgery are allowed if completed 4 weeks (for minor surgery and palliative radiotherapy for bone pain: 2 weeks) prior to start of treatment and patient recovered from toxic effects or associated adverse events.</li> <li>8. Adequate blood count, liver-enzymes, and renal function: <ul style="list-style-type: none"> <li>• Haemoglobin <math>\geq</math> 9.0 g/dL</li> <li>• Absolute neutrophil count (ANC) <math>\geq</math> 1.5 x 10<sup>9</sup>/L (<math>&gt;</math> 1500 per mm<sup>3</sup>)</li> <li>• Platelet count <math>\geq</math> 100 x 10<sup>9</sup>/L (<math>&gt;</math>100,000 per mm<sup>3</sup>)</li> <li>• Serum bilirubin <math>\leq</math> 1.5 x ULN. This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the</li> </ul> </li> </ol>



	<p>absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.</p> <ul style="list-style-type: none"> <li>• AST (SGOT)/ALT (SGPT) <math>\leq 2.5</math> x institutional upper limit of normal unless liver metastases are present, in which case it must be <math>\leq 5</math>x ULN</li> <li>• Serum creatinine <math>CL &gt; 40</math> mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance</li> </ul> <p>9. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits, examinations including follow up and appropriate contraception.</p>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Mixed small-cell lung cancer and NSCLC histology</li> <li>2. Mean QT interval corrected for heart rate (QTc) <math>\geq 470</math> ms calculated from 3 electrocardiograms (ECGs) using Fredericia's correction</li> <li>3. History of another primary malignancy except local prostate cancer without need for systemic treatment (e.g. active surveillance, operation without need for adjuvant treatment) and malignancies treated with curative intent and with no known active disease <math>&gt; 2</math> years before the first dose of study drug and of low potential risk for recurrence, e.g. adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, adequately treated carcinoma in situ without evidence of disease (e.g. cervical cancer in situ)</li> <li>4. Pre-existing peripheral neuropathy of Grade <math>\geq 2</math></li> <li>5. Brain metastasis or spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment.</li> <li>6. Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.</li> <li>7. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)</li> <li>8. History of primary immunodeficiency</li> <li>9. History of allogeneic organ transplant</li> <li>10. History of hypersensitivity to durvalumab or any excipient</li> <li>11. History of hypersensitivity to any of the comparator agents</li> <li>12. Medication that is known to interfere with any of the agents applied in the trial.</li> <li>13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent</li> <li>14. Clinical diagnosis of active tuberculosis</li> <li>15. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab</li> <li>16. Male patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year)</li> <li>17. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results</li> <li>18. Participation in another clinical study with an investigational product during the last 30 days before inclusion</li> <li>19. Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab</li> <li>20. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid</li> <li>21. Receipt of the last dose of anti-cancer therapy (chemotherapy,</li> </ol>

	<p>immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) <math>\leq 21</math> days prior to the first dose of study drug or <math>\leq 4</math> half-lives of the agent administered, which ever comes first.</p> <p>22. Previous enrollment or randomization in the present study.</p> <p>23. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff of sponsor and study site)</p> <p>24. Patient who might be dependent on the sponsor, site or the investigator</p> <p>25. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>26. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].</p> <p>27.</p>
Investigational agent	<ul style="list-style-type: none"> <li>• durvalumab (MEDI4736)</li> </ul> <p>Comparators and standard chemotherapies:</p> <ul style="list-style-type: none"> <li>• <i>nab</i>-Paclitaxel</li> <li>• gemcitabine</li> <li>• vinorelbine</li> <li>• carboplatin</li> </ul>
Treatment schedule	<p>Dosage/Timepoints</p> <p>Experimental arms:</p> <ul style="list-style-type: none"> <li>• Induction: 2 cycles of mono-chemotherapy or combination chemotherapy followed by two cycles durvalumab 1125 mg Q3W</li> <li>• Maintenance: durvalumab 1500 mg Q4W</li> </ul> <p>Treatment will be given until progression, intolerance/toxicity, or withdrawal of consent, whichever occurs first.</p> <p>Control arms -active comparators (SOC CTx):</p> <p>Mono-chemotherapies:</p> <ul style="list-style-type: none"> <li>• Vinorelbin 30 mg/m<sup>2</sup> D1 + D8 Q3W</li> <li>• Gemcitabine 1000 mg/m<sup>2</sup> D1 + D8 Q3W</li> </ul> <p>Combination chemotherapy:</p> <ul style="list-style-type: none"> <li>• <i>nab</i>-Paclitaxel: 100mg/m<sup>2</sup> D1,D8 + Carboplatin AUC 5.0 D1; Q3W</li> </ul> <p>Treatment will be given for a maximum of 4 cycles (chemotherapy) or until intolerance/toxicity, progressive disease or withdrawal of consent.</p> <p><b>Key study procedures (and routine procedures):</b></p> <ul style="list-style-type: none"> <li>• CARG-score for treatment (stratification) allocation</li> <li>• geriatric assessments (G8-questionnaire, Timed up&amp;go, 6MWT)</li> <li>• HR-QOL (FACT-L)</li> <li>• tumor response evaluation</li> <li>• tumor tissue and blood biomarker assessments</li> </ul>
Primary endpoint	Rate of treatment related Grade III/IV adverse events (CTCAE V4.03)
Secondary endpoints	<ul style="list-style-type: none"> <li>• ORR according to RECIST 1.1 criteria</li> <li>• Progression free survival (PFS)</li> <li>• Overall survival (OS)</li> <li>• AEs / SAEs according to CTCAE 4.03</li> <li>• Health related Quality of Life (HR-QoL)</li> </ul>
Stratification	<p>According to the predictive model for treatment-related toxicity in older adults (Hurria et al., JCO 2011), stratification will be performed with the following cut-offs:</p> <ul style="list-style-type: none"> <li>• Total risk score <math>\leq 3</math> → combination chemotherapy</li> <li>• Total risk score <math>&gt; 3</math> → mono-chemotherapy</li> </ul>
Randomization procedure	1:1 after CARG-score stratification
Rationale	Metastatic non-small cell lung cancer (NSCLC) bears a dismal prognosis with a median survival not exceeding 10-12 month. The impact of combination

chemotherapy is limited with median progression-free survival times ranging from 3-4 month. In subgroups of about 20% of adenocarcinoma patients, defined by molecular alterations (activating EGFR-mutation; ALK-translocation), treatment with tyrosine-kinase inhibitors impacts on prolonging median progression-free survival up to 9-11 months and median survival up in a range of 3 years. In the non-molecularly altered population chemotherapy-only is still the standard of care [1]. In patients aged over 70 years and those with a restricted performance score (ECOG-2) or "frail" physical condition mono-chemotherapy (e.g. Vinorelbine; e.g. Gemcitabine) [2, 3] or a dose adopted combination of carboplatin (AUC6) / Paclitaxel (90 mg/m<sup>2</sup>; d1+8+15) [4] is considered to improve prognosis. So, in a randomized trial, enrolling patients aged > 70 (> 80 years, 25%; PS-ECOG 2, 27%; Charlson-Comorbidity -Index > 2, 24%), superiority of the afore mentioned regimen compared to mono-chemotherapy (Gemcitabine; Vinorelbine) could be shown [4]: RR, 27% vs. 10%; PFS, 6.0 vs. 2.8 months (median), 13% vs. 2% (1-year-rate), 5% vs. 0.4% (2-year-rate); OS, 10.3 vs. 6.2 months (median), 44% vs. 25% (1-year-rate), 22% vs. 12% (2-year-rate). Moreover, a randomized phase II trial (Carboplatin, AUC5 / Vinorelbine, 25 mg/m<sup>2</sup>; d1+8 vs. Erlotinib, 150 mg daily) provided evidence on the feasibility of Carboplatin / Vinorelbine in patients aged > 70 [5], with efficacy-rates comparing to Carboplatin / Paclitaxel: RR, 28% PFS, 4.3 months (median), 15% (1-year-rate); OS, 17.7 months (median), 40% (1-year-rate), 25% (2-year-rate). In the recent past, with the impact-assessment of nab-paclitaxel, by head-to-head comparison of carboplatin/paclitaxel vs. carboplatin/nab-paclitaxel (n = 744), a superior response rate (25% vs. 33%, p < 0.001) paralleled by significantly lesser grade 3/4 neutropenia (47% vs. 58%, p < 0.001) and grade 3/4 neuropathy (18% vs. 9%, p < 0.001) in favor of nab-paclitaxel could be shown [6]. Moreover, in patients > 70 years (n = 105), overall survival favored carboplatin / nab-paclitaxel (HR = 0.58) [6]. However, due to the considerable toxicities choosing the appropriate chemotherapy regimen is still a notable clinical challenge.

With the advent of immunooncology in the treatment of lung cancer, new options arise at the horizon. So checkpoint inhibition, targeting PD-1 and PD-L1, is advancing up to 1st line treatment in comparison to combination chemotherapy. Anti- PD- 1/PD- L1 antibodies have demonstrated impressive efficacy results in NSCLC and first marketing approvals have been granted (nivolumab/Opdivo® and pembrolizumab/Keytruda®) [7-11]. The rate of treatment emergent adverse events is lower than with conventional chemotherapies and side effects of immune-checkpoint inhibitors are generally manageable.

There is however, currently a lack of clinical evidence to assess the tolerability and safety of check-point inhibition as a treatment option in frail and elderly patients.

Thus an appropriately defined patient population (EGFRwt; ALKtransl-), characterized by:

age ≥ 70 and / or

Charlson-Comorbidity-Index (CCI) > 1 (frailty) and / or

performance status ECOG > 1,

not amenable to cisplatin-based standard-combination chemotherapy, should be tested for treatment with PD-L1 – antibody - after an induction chemotherapy of 2 cycles (mono or combination chemotherapy) in comparison to either mono-chemotherapy or combination therapy (Carboplatin/nab-Paclitaxel).

It is expected, that two cycles of induction chemotherapy lead to a prompt disease stabilizing effect, which can be efficaciously extended by a consecutive durvalumab monotherapy with even less toxicity in comparison with standard of care chemotherapy. In frail and elder patients with NSCLC two cycles of chemotherapy is well feasible, side effects are manageable, and no or minor alteration in QoL should be expected.

To assort patient to treatments (combination vs. mono) by stratification, an adopting scoring system will be employed (Hurria 2011). In both strata PD-L1 – antibody treatment given after 2 cycles of chemotherapy (mono or

	<p>combination) will serve as a comparator.</p> <p>This will give the opportunity to assess the “extent of frailty/comorbidity” and the potential impact of PD-L1 – antibody treatment 1st line in those patients.</p> <p><b>Hypothesis:</b> We hypothesize that PD-L1 checkpoint blockade (durvalumab) given after induction of 2 cycles of chemotherapy will lead to a reduced rate of CTC grade III/IV toxicity and improves the overall survival when compared to standard of care mono- or combination chemotherapy.</p>
Safety data	<ul style="list-style-type: none"> <li>• AEs, SAEs and Treatment Emergent Adverse Events according to CTC 4.03</li> <li>• Frequency of abnormal laboratory parameters</li> <li>• Immune related (ir)AEs of special interest will require additional reporting (colitis, hepatitis, hypophysitis, uveitis or pneumonitis, pancreatitis)</li> </ul>
Sample size and statistical analysis considerations	<p>Sample size calculation: The primary safety endpoint for the study is the occurrence of a CTC grade III/IV toxicities assessed from first dose up to 90 days after last dose of IMP. This is also the primary study endpoint on which the sample size calculation is based. According to the results of Rizvi presented at ASCO 2015 it is assumed that the probability for a CTC grade III/IV toxicity for patients from the pooled experimental arms B+C receiving durvalumab amounts to <math>PB+C=0.18</math>. It is furthermore assumed from reported data of selected treatment related adverse events (combination chemotherapy nab-paclitaxel / carboplatin: Socinski, JCO 2012, mono-chemotherapy gemcitabine / vinorelbine: Quoix, Lancet 2011) that the rate of patients with a CTC grade III/IV toxicity in the pooled control arms A+D receiving chemotherapy only amounts to <math>PA+D=0.35</math>. With the planned number of patients of <math>N=200</math>, the assumed difference between these two groups can be detected using a Chi-square test at a two-sided significance level of <math>\alpha=10\%</math> with a probability of <math>1-\beta=0.80</math>, also taking a dropout rate of 15% into account. Sample size calculation was performed using ADDPLAN v6.1.</p> <p>It should be noted that the study is not powered to detect significant differences with regard to the efficacy endpoints, since its primary aim is to assess safety and tolerability. Hence, no confirmatory evidence can be drawn from the efficacy evaluation. Accordingly, all p-values for efficacy outcomes are only to be interpreted descriptively and no adjustment for multiple testing will be done.</p> <p>Statistical analysis considerations for the primary endpoint: The null hypothesis for the primary (safety) endpoint of the trial is defined as <math>H_0: PB+C = PA+D</math> (i.e., the rate of patients with a CTC grade III/IV toxicity is equal in the pooled experimental arms B+C and the pooled control arms A+D), which is tested against its alternative <math>H_1: PB+C \neq PA+D</math> (i.e., there is a difference between the pooled experimental arms B+C and the pooled control arms A+D with regard to the rate of patients with a CTC grade III/IV toxicity). These hypotheses will be assessed at a two-sided significance level of <math>\alpha=0.1</math> using a Mantel-Haenszel Chi-square test adjusting for the stratum “adopted combination/not prone to combination”. Furthermore, the odds ratio and risk ratio will be calculated together with the corresponding 90% confidence interval. 90% confidence intervals will also be determined for the estimated grade III/IV toxicity in the pooled arms A+B and C+D and for the estimated grade III/IV toxicity in the four separate treatment arms. The analysis of the primary endpoint will be based on the Safety Population.</p>
Biomarker measurements	<ul style="list-style-type: none"> <li>• PD-L1 expression and optionally other biomarkers in tumor tissue samples</li> </ul> <p>Optional:</p> <ul style="list-style-type: none"> <li>• phenotypical analysis of lymphocytes by FACS</li> <li>• analysis of T-cell receptor specificities (T-cell receptor sequencing)</li> </ul>

	<ul style="list-style-type: none"> <li>• mRNA profiling of T-cells</li> <li>• soluble pro- and anti-inflammatory markers and Glycodelin</li> <li>• Analysis of mutational load based on cfDNA</li> </ul>												
QoL measurements	FACT-L												
Study plan / time lines	<table> <tr> <td>First Patient In (FPI):</td> <td>Q4/2017</td> </tr> <tr> <td>Last Patient In (LPI):</td> <td>after approx. 24 month</td> </tr> <tr> <td>Last Patient Last Visit (LPLV):</td> <td>after approx. 48 month</td> </tr> <tr> <td>End of follow-up period after LPLV:</td> <td>after approx. 48 month</td> </tr> <tr> <td>Study report:</td> <td>after approx. 60 month</td> </tr> <tr> <td>Publication:</td> <td>after approx. 63 month</td> </tr> </table>	First Patient In (FPI):	Q4/2017	Last Patient In (LPI):	after approx. 24 month	Last Patient Last Visit (LPLV):	after approx. 48 month	End of follow-up period after LPLV:	after approx. 48 month	Study report:	after approx. 60 month	Publication:	after approx. 63 month
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### AEG-Karzinome, 1st line palliativ

#### **AIO-YMO-0111/STO: Randomized controlled trial of S-1 maintenance therapy in metastatic esophagogastric cancer (MATEO)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO-0111 - MATEO
Status:	in Rekrutierung
Rekrutierungszeitraum	2015 - 2019
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	April 2018

Study design	Randomized, controlled, parallel-group, open-label, multicenter study
Principal Investigators	Dr. Georg Martin Haag NCT- Med. Onkologie, Im Neuenheimer Feld 460, 69120 Heidelberg GeorgMartin.Haag@med.uni-heidelberg.de
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Tel.: 030-322932934, FAX:030-322932926 E-Mail: info@aio-studien-ggmbh.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Ösophagus-/ Magenkarzinom!	

Registerstudie - Patienten mit Barrett-Metaplasie im Ösophagus**AIO-YMO/TF-0115: Analyse der epidemiologischen und molekularen Früherkennung zur Prognosebestimmung für Patienten mit Barrett-Ösophagus**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/TF-0115
Status:	in Rekrutierung
Rekrutierungszeitraum:	2013 - 2023
Weitere Zentren:	sind gewünscht
Letzte Aktualisierung	April 2018

Studiendesign	Multizentrische, prospektive Studie
Verantwortlicher Studienleiter nach AMG	PD Dr. med. Michael Quante, II. Medizinische Klinik der Technischen Universität München, Klinikum rechts der Isar
Kontaktadresse/ Kontaktperson:	PD Dr. med Michael Quante Klinikum rechts der Isar - Technische Universität München II. Medizinische Klinik, Ismaninger Straße 22, 81675 München michael.quante@tum.de
Studienziele/ Objectives	<ol style="list-style-type: none"> <li>1. Analyse von potentiellen Biomarkern (Expression, Sequencing, Methylierung) als diagnostisches und prognoserelevantes Kriterium zur Bestimmung des Risikos im Barrett-Ösophagus (Metaplasie) eine Neoplasie zu entwickeln.</li> <li>2. Bestimmung der Inzidenz der Entwicklung von LG-IEN, HG-IEN und AEG ausgehend von einem BE</li> <li>3. Bestätigung, dass die Ursprungszelle des BE, wie in der Maus, in der Cardia lokalisiert ist, in den Ösophagus wandert und dort zur metaplastischen und dysplastischen Zelle differenziert.</li> <li>4. Korrelation von epidemiologischen und anamnestischen Faktoren mit der BE-Progression und möglichen Serumparametern.</li> </ol>
Zielparameter/ Objectives	In den letzten Jahrzehnten hat sich gezeigt, dass das Adenokarzinom des gastro-ösophagealen Übergangs (AEG) die Tumorentität mit der am schnellsten wachsenden Inzidenz in der industrialisierten Welt ist. Da die Prognose des AEG trotz verbesserter Therapiemodalitäten sehr schlecht ist, ist es wichtig die maligne Entartung frühzeitig zu diagnostizieren und zu behandeln. Barrett-Ösophagus (BE) ist der wichtigste Risikofaktor für die Entwicklung eines AEG, weshalb Patienten mit BE regelmäßig endoskopiert werden, um mögliche intraepitheliale Neoplasien frühzeitig zu diagnostizieren. Biomarker, die mit wenig Surveillance Biopsien eine individuelle Prognose für die maligne Entartung der Metaplasie (BE) und damit eine Risikoevaluation ermöglichen, fehlen leider bisher. Um in Zukunft eine deutlichere Prognose zu ermöglichen und somit die Abstände der Surveillance-Endoskopien verlängern und die Belastung für den Patienten, als auch die Kosten minimieren zu können, wir nun in ein deutschlandweites Register (AIO BarrettNET) überführen.
Patientenzahl Number of patients	Geplant 2.000 Bereits eingeschlossen: Anzahl Studienpatienten: 542 (Stand 10.04.2018) Anzahl Studienproben: 697 (Stand 10.04.2018)
Rekrutierungszeitraum	01/2013 – 12/2023
Weitere teilnehmende Zentren erwünscht?	Ja Rekrutierung weiterer Studienzentren ist in Prozess Stand zum 10.04.2018 : initiiert: 20, davon geschlossen: 2, geplante

	Initiierungen: 3
Haupt-Einschlusskriterien Key inclusion criteria	Alter zwischen 18 und 80 Jahren Überwachungsendoskopie bei Patienten mit bereits diagnostiziertem Barrett-Ösophagus ohne bisher bekannter LG-EIN, HG-IEN oder AEG (Barrett-Ösophagus sollte anhand der Prag-Klassifikation ausgemessen sein und mindestens C0M1 sein) unterschiedene Einwilligungserklärung
Haupt-Ausschlusskriterien Key exclusion criteria	andersartige Tumorerkrankung (unabhängig der Therapie) fehlende Zustimmungsfähigkeit zur Studie Kontraindikation zur Biopsie-Entnahme (Thrombozytopenie < 50.000/ $\mu$ l, Quick < 60%, pTT > 50 sec) Patienten in reduziertem Allgemeinzustand
Therapieschema Scheme of therapy	<b>Studienablauf:</b> Patienten, die alle Ein- und Ausschlusskriterien erfüllen, erhalten ein Aufklärungsgespräch mit dem verantwortlichen Arzt bevor die erste Untersuchung durchgeführt wird. Die endoskopischen Kontrollen sollen nach Empfehlung der behandelnden Gastroenterologen in Abhängigkeit der histopathologischen Befunde nach internationalem Standard im halb- bis dreijährigen Abstand erfolgen, wobei auch die Studienbiopsien entnommen werden. Sich im Verlauf entwickelnde und diagnostizierte Neoplasien werden innerhalb der Studienbiopsien analysiert und als Endpunkt definiert. Im Falle eines biopsisch gesicherten mukosomalen Karzinoms wird unabhängig von der Studie die weitere Diagnostik und Therapie eingeleitet und vom Studienprotokoll nicht beeinflusst. Die Patienten werden mit Beginn der Therapie nicht weiter beobachtet werden.
Tumorevaluierung Criteria for evaluation	Die histologische Begutachtung erfolgt nach histopathologischem Goldstandard mit leichter zeitlicher Verzögerung im Institut für Pathologie am Klinikum rechts der Isar, sowie durch einen Referenzpathologen (PD Dr. med M Vieth, Klinikum Bayreuth). Ein vom pathologischen Befund der Routine-Biopsie abweichender Befund wird in einem Nachtrag zum originalen Befund dem behandelnden Arzt (Gastroenterologen) mitgeteilt. Weiterhin werden zu Studienzwecken RNA, DNA und Protein von den Proben zur weiteren Analyse isoliert.
Rationale	In den letzten Jahrzehnten hat sich gezeigt, dass das Adenokarzinom des gastroösophagealen Übergangs (AEG) die Tumorentität mit der am schnellsten wachsenden Inzidenz in der industrialisierten Welt ist. Die Prognose des AEG ist hinsichtlich des Langzeitüberlebens sehr limitiert, da der Tumor bei Diagnosestellung häufig kurativ nur noch durch eine radikale Operation behandelt werden kann. Auch nach der kurativ intendierten Operation ist die 5-Jahresüberlebensrate mit ca. 20% niedrig. Der Barrett-Ösophagus (BE) ist der wichtigste Risikofaktor für die Entwicklung eines AEG. Man geht davon aus, dass das Plattenepithel des Ösophagus im distalen Bereich durch chronischen Reflux von Mageninhalt alteriert und durch präkanzeröses, spezialisiertes, intestinal-metaplastisches Zylinderepithel ersetzt wird. Ein BE wird, älteren Daten nach, bei ca. 10% aller Refluxpatienten diagnostiziert und zeigt in weiteren 10% eine Entartungstendenz so dass eine Inzidenz der Entstehung von AEG aus BE mit ca. 0,5-1%pr Jahr (abhängig von der Definition angenommen wird. Diese verläuft von der histopathologisch fassbaren „niedriggradigen intraepithelialen Neoplasien“ (LG-IEN) über die „hochgradige intraepitheliale Neoplasien“ (HG-IEN) hin zum AEG. Dieser Umstand hatte zur Folge, dass regelmäßige endoskopisch-biopsische Kontrollen (sogenannte Surveillance-Endoskopien) empfohlen wurden, um die Entartungssequenz möglichst in einem Frühstadium zu detektieren. Derzeit ist die Surveillance-Endoskopie die einzig etablierte Methode der Überwachung der Barrett-Patienten. Obwohl hierdurch für Erkrankte die Prognose hinsichtlich des Gesamtüberlebens verbessert werden konnte, gerät die Surveillance-Strategie aufgrund des enormen Aufwands und der hohen Kosten sowie des pro Patienten kalkulierten, niedrigen Gesamtrisikos

	ein AEG zu entwickeln zunehmend in die Kritik. Somit besteht der dringende Bedarf nach eindeutigen Markern oder Prognosekriterien, um die Wahrscheinlichkeit - aber auch die Ursache - der Entwicklung einer LG-IEN oder HG-IEN aus dem BE zu beurteilen. Identifizierung von neuen Biomarkern, die eine deutlichere Prognose ermöglichen und somit die Abstände der Surveillance-Endoskopien verlängern können, würde sowohl die Belastung für den Patienten, als auch die Kosten minimieren.
Statistik (optional)	Primäres Studienziel ist die Identifizierung (Sequencing), Analyse und Bestätigung (Maus-Model) von Biomarkern die zur Prognosebestimmung der Entwicklung einer Neoplasie in metaplastischem Gewebe genutzt werden können. Die ermittelten Biomarker sollten zur Prognose zwischen Barrett-Patienten mit bzw. ohne maligner Transformation mit wenigstens 80% Sensitivität und 80% Spezifität unterscheiden können. Bei einer Wahrscheinlichkeit von 1% für das Vorliegen oder Entstehen einer malignen Transformation während des Beobachtungszeitraumes ergibt sich daraus ein negativer prädiktiver Wert von mindestens 99,75%. Die Wahrscheinlichkeit, dass ein Patient mit "negativem Testergebnis" bei Verwendung eines solchen Biomarkers tatsächlich keine maligne Transformation hat, ist also sehr hoch, nur 0,25% (einer aus 400) der Patienten wären falsch-negativ getestet, sodass ein solcher Biomarker als Ausschluss-Test gesehen werden kann.

### Metastasiertes Pankreaskarzinom, Retrospektive Analyse

#### **AIO-YMO/PAK-0515: Histopathologische, molekulargenetische und klinische Charakterisierung von Patienten mit isolierten Lungenmetastasen eines Pankreaskarzinoms.**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/PAK-0515
Status:	retrospektiv
Rekrutierungszeitraum:	2016 - 2019
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	April 2018

Art der Studie Study Type	Retrospektive Analyse
Kontaktadresse/ Kontaktperson:	Dr. Kruger / Prof. Böck (Verantwortlicher Studienleiter nach AMG) Comprehensive Cancer Center Medizinische Klinik und Poliklinik III Hämatologie und Onkologie Klinikum der Universität München, Campus Großhadern Marchioninistraße 15, 81377 München
Studienziele/ Objectives	<u>Primäres Studienziel:</u> Gesamtüberleben von Patienten mit isolierten Lungenmetastasen
Zielparameter/ Objectives	<ul style="list-style-type: none"> <li>• Gesamtüberleben sowie progressionsfreies Überleben von Patienten mit isolierten Lungenmetastasen.</li> <li>• Rezidivfreie Überleben bis zur pulmonalen Metastasierung</li> <li>• Prognostische Faktoren einer pulmonalen Metastasierung.</li> <li>• Stellenwert verschiedener therapeutischer Verfahren bei Patienten mit isolierten Lungenmetastasen.</li> </ul>



	<ul style="list-style-type: none"> <li>• Translationale Analysen</li> </ul>
Patientenzahl Number of patients	Geplant: ca. 130 Patienten Bereits eingeschlossen: 120
period of	Retrospektiv
More centres?	Ja
Key inclusion criteria	<ul style="list-style-type: none"> <li>• Patienten mit der histologisch gesicherten Diagnose eines Pankreaskarzinoms,</li> <li>• Histologischer oder radiologischer Nachweis von pulmonalen Metastasen</li> <li>• klinisch messbare Tumorläsion, beurteilbar nach den RECIST-Kriterien für die Evaluation des Tumoransprechens auf eine Therapie durch bildgeben-de/radiologische Verfahren</li> </ul>
Key exclusion criteria	Gleichzeitiges Vorhandensein einer Peritonealkarzinose oder von Fernmetastasen außerhalb der Lunge (zum Zeitpunkt der Erstdiagnose pulmonaler Metastasen)
Tumorevaluierung Criteria for evaluation	CT/MRT-Bildgebung
Rationale	<p>Um mehr über die Tumorbilogie des Pankreaskarzinoms und die Rolle einzelner Mutationen zu lernen, eignen sich insbesondere Patienten mit besonders günstigem oder ungünstigem klinischen Verlauf. Eine interessante Subpopulation bilden dabei Patienten mit isolierten Lungenmetastasen eines Pankreaskarzinoms. Während bei mehr als 80% Prozent der Patienten mit einem metastasierten Pankreaskarzinom Lebermetastasen vorliegen, ist eine isolierte pulmonale Metastasierung selten. Erste Ergebnisse einer retrospektiven Auswertung an der LMU München zeigen, dass eine isolierte pulmonale Metastasierung prognostisch günstig ist und in vielen Fällen ein ungewöhnlich langes Gesamtüberleben anzeigt.</p> <p>Wir planen daher im Rahmen eines YMO-Projektes eine retrospektive, multizentrische Analyse zu diesem Thema. Dadurch wird voraussichtlich eines der bislang größten klinisch charakterisierte Kollektiv von Patienten mit isolierten Lungenmetastasen eines Pankreaskarzinoms entstehen</p>

Registerstudie – Duktales Adenokarzinom des Pankreas**AIO-YMO/PAK-0215 Eine multizentrische Registerstudie zur Erfassung klinischer, epidemiologischer und biologischer Parameter beim duktalem Adenokarzinom des Pankreas (PDAC, PaCaReg)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/PAK-0215 - PDAC, PaCaReg
Status:	Einschluss des 1. Patienten steht unmittelbar bevor
Rekrutierungszeitraum:	Geplanter Start Q2/2018
Weitere Zentren:	bitte wenden Sie sich ggfs. an die Studienleitung
Letzte Aktualisierung	April 2018
<b>Studienleitung</b>	Dr. med. Thomas Ettrich Universitätsklinikum Ulm, Klinik für Innere Med. I 89081 Ulm, Tel. 0731-500 44774, thomas.ettrich@uniklinik-ulm.de Mentoring Investigator: Univ.-Prof. Dr. Thomas Seufferlein Universitätsklinikum Ulm, Klinik für Innere Medizin I
<b>Studienkollektiv</b>	Patienten ab dem 18. Lebensjahr mit histologisch oder zytologisch gesichertem PDAC, resektabel (incl. <i>borderline</i> resektabel), lokal fortgeschritten oder metastasiert.
<b>Primäre Zielgröße</b>	<ul style="list-style-type: none"> <li>Erfassung der eingesetzten Therapiemodalitäten (Operation, Chemotherapie, Strahlentherapie, Behandlungsschemata, Gründe für Therapieentscheidungen, Therapiedauer, Leitlinienkonformität) und Erfassung der Lebensqualität von Patienten mit Erstdiagnose eines PDAC (anhand des EORTC QIQ30 Bogens)</li> </ul>
<b>Sekundäre Zielgrößen</b>	<ul style="list-style-type: none"> <li>Registrierung aller Patienten mit neu diagnostiziertem PDAC an den beteiligten Zentren</li> <li>Erfassung der definitiven Tumorstadien (TNM-Klassifikation, CRM, UICC-Stadium)</li> <li>Erfassung klinischer Parameter bei Erstdiagnose und im Verlauf (Tumoransprechen, krankheitsfreies Überleben, progressionsfreies Überleben, Gesamtüberleben, Überleben in Abhängigkeit vom Tumorstadium)</li> <li>Erfassung epidemiologischer, Patienten-bezogener Basisdaten</li> <li>Korrelation von Lebensqualität und Therapiekonzept</li> <li>Asservierung von Biomaterial der Patienten für die Evaluation prognostischer und prädiktiver Biomarker (Tumorgewebe, Blut/ Plasma) in der Biobank der Klinik für Innere Medizin I des Universitätsklinikums Ulm sowie dem Institut für Pathologie der Universität Ulm/Biobank des Comprehensive Cancer Centers Ulm (CCCU)</li> </ul>
<b>Einschlusskriterien</b>	<ul style="list-style-type: none"> <li>Zytologisch oder histologisch gesichertes duktales Adenokarzinom des Pankreas</li> <li>Alter <math>\geq</math> 18 Jahre</li> <li>Schriftliches Einverständnis zur Teilnahme an der Studie</li> </ul>
<b>Ausschlusskriterien</b>	<ul style="list-style-type: none"> <li>Papillenkarcinome</li> <li>Neuroendokrine Neoplasien des Pankreas</li> <li>PDAC-spezifische Vortherapie, außer Tumorsektion</li> <li>Schwere neurologische oder psychiatrische Störungen die eine</li> </ul>

	<p>Einwilligungsfähigkeit beeinträchtigen</p> <ul style="list-style-type: none"><li>• Kein Einverständnis für die Registrierung, Lagerung und Handhabung der personenbezogenen Krankheitsdaten</li></ul>
<b>Studiendesign</b>	Registerstudie zur Erfassung epidemiologischer und klinischer Eckdaten und Lebensqualität, sowie Etablierung biologischer Marker bei Patienten mit Erstdiagnose eines duktalem Adenokarzinoms des Pankreas
<b>Datenschutz</b>	Das Vorhaben ist an das empfohlene Datenschutzkonzept der Telematikplattform für Medizinische Forschungsnetze (TMF e.V.) für Biobanken und klinische Forschungsregister angelehnt. Klinische Daten und Biomaterial werden ausschließlich in pseudonymisierter Form gespeichert und bearbeitet. Für klinische Daten wird eine PaCaReg Identifizierungsnummer vergeben. Zur Asservierung des Biomaterials wird durch die Referenzlabore ein weiterer pseudonymisierter PaCaReg-Bio Identifier vergeben. Identifizierende und personenbezogene Daten der Patienten werden von einem unabhängigen Datentreuhänder (Institut für Epidemiologie und Biometrie der Universität Ulm) verwaltet.
<b>Zentren</b>	Kliniken und Praxen in Deutschland, die Patienten mit duktalem Adenokarzinom des Pankreas behandeln

Registerstudie – Seltene Maligne Tumore der Schilddrüse**AIO-YMO/ENC-0216: Multicenter registry for patients with rare malignant tumors of the thyroid (ThyCa)**

<b>AIO-Studie</b>	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/ENC-0216 - ThyCa
Rekrutierungszeitraum:	retrospektiv 2000 – 2013, prospektiv ab 2014
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	Oktober 2016

Art der Studie Study Type	Retrospective and prospective registry study
Kontaktadresse/ Kontaktperson:	<p>PD Dr. Dr. Matthias Kroiß          Universitätsklinikum Würzburg          Medizinische Klinik und Poliklinik I          Schwerpunkt Endokrinologie/Diabetologie          Oberdürrbacher Str. 6          97080 Würzburg</p> <p>Julia Wendler          Tel.: 0931/201-39717          Email:          Wendler_J@ukw.de</p>
Studienziele/ Objectives	<p><u>Primary objectives:</u>          Prospective collection of histopathologic, clinical, clinical chemical and imaging data and biomaterial of newly diagnosed patients with rare malignant tumors of the thyroid (anaplastic thyroid carcinoma, ATC; medullary thyroid carcinoma, MTC; radioiodine refractory thyroid carcinoma, RDTc; poorly differentiated thyroid carcinoma, PDTC) and parathyroid glands (PaTC). The aim is to improve diagnosis and treatment of patients by definition of</p> <ul style="list-style-type: none"> <li>- Parameters and biomarkers for diagnosis.</li> <li>- Parameters and biomarkers of treatment response and side effects</li> <li>- Parameters for risk stratification.</li> <li>- Parameters and biomarkers for follow-up</li> </ul> <p><u>Secondary objectives:</u>          Establishment of</p> <ul style="list-style-type: none"> <li>- cooperative structures for rare malignant tumors of the thyroid.</li> <li>- a clinical cancer registry for rare malignant tumors of the thyroid at the national European centers.</li> <li>- Structures to facilitate translational research.</li> <li>- Structures to enable future prospective clinical trials.</li> </ul> <p>Collaborative evaluation of data collected retrospectively in individual centers</p>
Zielparameter/ Objectives	overall survival, disease free survival, time to progression, time to recurrence
Patientenzahl Number of patients	not restricted; current recruitment: 127 ATC, 543 MTC, 56 PDTC (incl. Hürthle-cell), 74 RDTc, 25 PaTC
Rekrutierungszeitraum von/bis period of	retrospective: 2000 – 2013 prospektive: 2014 – <i>not defined</i>
Weitere teilnehmende	current centers (10/2017):

<p>Zentren erwünscht? More centres?</p>	<ul style="list-style-type: none"> <li>- Universitätsklinikum Würzburg</li> <li>- Klinikum Augsburg</li> <li>- Universitätsklinikum Düsseldorf</li> <li>- Universitätsklinikum Gießen und Marburg – Standort Marburg</li> <li>- Universitätsklinikum Greifswald</li> <li>- Endokrinologische-Nuklearmedizinische Gemeinschaftspraxis Heidelberg</li> <li>- Universitätsklinikum Leipzig</li> <li>- Klinikum der Universität München - Campus Großhadern</li> <li>- Helios Kliniken Schwerin</li> <li>- Diakonie Klinikum Stuttgart</li> </ul> <p style="text-align: center;">additional centers are invited to participate</p>
<p>Haupt-Einschlusskriterien Key inclusion criteria</p>	<p>Histologically confirmed medullary, poorly differentiated and anaplastic thyroid carcinoma; histologically confirmed differentiated thyroid carcinoma documented to be refractory to radioiodine</p>
<p>Haupt-Ausschlusskriterien / Key exclusion criteria</p>	<p>inability to provide informed consent</p>
<p>Therapieschema Scheme of therapy</p>	<p>standard of care; investigational therapies</p>
<p>Tumorevaluierung Criteria for evaluation</p>	<p>standard of care; per protocol for investigational therapies</p>
<p>Rationale</p>	<p>Malignant tumors of the thyroid gland are the most frequent endocrine malignancies in humans. The annual incidence is 1/20.000. More than 90% of thyroid cancers are differentiated thyroid carcinomas (DTC). Medullary thyroid carcinoma (MTC) has its origin from calcitonin producing C-cells of the thyroid. DTC are often detected routinely upon ultrasound examination of the thyroid gland and appear as cold nodules at scintigraphy. In most cases these tumors can be cured by radical surgery and post-operative radioiodine treatment. However, some tumors lose differentiation and become refractory to radioiodine (radioiodine refractory; RDTC), others are poorly (PDTC) differentiated at diagnosis. Anaplastic thyroid cancer (ATC) mostly appears as a rapidly growing neck mass or through symptoms of tumor invasion into neck structures. Prognosis is very poor even with multimodal treatment. The low incidence of MTC, PDTC, ATC and RDTC has hampered establishment of evidence-based treatment concepts. With the advent of multi-tyrosine kinase inhibitors and other targeted therapies, the therapeutic landscape has changed importantly both in MTC and in RDTC. At variance, effective treatment of ATC is still not established.</p>
<p>Statistik statistics (optional)</p>	<p>descriptive statistical methods as appropriate for variable under study; time to event using Kaplan-Meier estimates; comparison between groups using log-rank test; multivariable adjustment using Cox proportional hazard model.</p>

## Arbeitsgruppe ZNS-Tumoren/Meningeosis

### Registerstudie

#### Prospektive Beobachtungsstudie zur Behandlungspraxis des ZNS-Befalls aggressiver Lymphome in der klinischen Routine (Deutschland 2011-2016) (SZNSL Register D-2011-2016)

#### AIO-assozierte Studie

Studiennummer/-Code:

Status: in Rekrutierung

Rekrutierungszeitraum: 2011 – 2016

Weitere Zentren: sind sehr erwünscht

Letzte Aktualisierung: Oktober 2016

Art der Studie	Registerstudie
Projektleiter, wiss. Leiter:	PD Dr. med. Agnieszka Korfel Dr. med. Lars Fischer Studienleitung der Deutschen Studiengruppe Primäre ZNS Lymphome (G-PCNSL-SG) - Im Kompetenznetz Maligne Lymphome (KML) Medizinische Klinik III, Campus Benjamin Franklin, Universitätsmedizin Berlin Hindenburgdamm 30, 12200 Berlin Tel: 030 8445 4096, FAX: 030 8445 2896 E-Mail: agnieszka.korfel@charite.de, E-Mail: lars.fischer@charite.de
Datenmanagement:	Frau Brigitta Rieger Medizinische Klinik III, Campus Benjamin Franklin Universitätsmedizin Berlin, Hindenburgdamm 30, 12200 Berlin Tel: 030 8445 4096, FAX: 030 8445 2896 E-Mail: brigitta.rieger@charite.de
Rationale	Lymphombefall im ZNS ist insgesamt selten, die Inzidenz beträgt entsprechend diverser retrospektiver Studien etwa 5%, kann jedoch abhängig von Histologie und Risikokollektiv bis zu 26% betragen (Alvarnas <i>et al</i> , 2000; Colocci <i>et al</i> , 2004; Feugier <i>et al</i> , 2004; Kasamon <i>et al</i> , 2005; van Besien <i>et al</i> , 1998; Williams <i>et al</i> , 1994a; Hollender <i>et al</i> , 2002; Keldsen <i>et al</i> , 1996; Bishop <i>et al</i> , 1999; Liang <i>et al</i> , 1990; Montserrat <i>et al</i> , 1996). ZNS-Rezidive aggressiver Lymphome treten überwiegend im ersten Jahr nach Diagnosestellung auf und manifestieren sich zumeist in einem meningealen oder parenchymalen Befall (Kasamon <i>et al</i> , 2005; van Besien <i>et al</i> , 1998), während ein kombinierter Befall beider Kompartimente eher seltener ist (Haïoun <i>et al</i> , 2000; Hollender <i>et al</i> , 2002; Tilly <i>et al</i> , 2003; van Besien <i>et al</i> , 1998). Die Angaben zur Häufigkeit eines gleichzeitigen systemischen Rezidives bzw. Progresses variieren, allerdings tritt ein systemischer Progress in der Mehrzahl der Fälle im weiteren Verlauf ein und wird als häufige Todesursache angesehen (Alvarnas <i>et al</i> , 2000; Bokstein <i>et al</i> , 2002; Bollen <i>et al</i> , 1997; Colocci <i>et al</i> , 2004; van Besien <i>et al</i> , 1998; Feugier <i>et al</i> , 2004; Johnson <i>et al</i> , 1984). Die Prognose gilt als sehr ungünstig mit medianen Überlebenszeiten von unter 6 Monaten
Therapie	Die optimale Therapie ist bisher nicht etabliert. Zur Verfügung stehen: <ul style="list-style-type: none"> <li>• Bestrahlung</li> <li>• intrathekale Therapie</li> <li>• systemische Chemotherapie.</li> </ul> Abgesehen von 3 prospektiven Studien (Phase II Methotrexat/ Procarbacin/ Cytarabin, Vergleich von MTX und Thiotepa intrathekal sowie von Cytarabin und liposomalem Cytarabin intrathekal) (Bokstein <i>et al</i> , 2002; Glantz <i>et al</i> ,

	<p>1999;Grossman <i>et al</i>, 1993), liegen nur retrospektive Studien oder Fallberichte zur Therapie der SZNSL vor. Meist bestand hier die Behandlung aus intrathekaler Chemotherapie und/oder Radiatio. Zwar konnte in den meisten Studien bei z.T. erheblichem Anteil der Patienten eine Besserung der Symptome und „Sanierung“ des Liquorraumes (definiert als kompletter Rückgang der Tumorzellen im Liquor) erreicht werden, das Ansprechen war allerdings nur kurz, was sich in den medianen Überlebenszeiten von maximal 6 Monaten widerspiegelte (Bashir <i>et al</i>, 1991;Bokstein <i>et al</i>, 2002;Bollen <i>et al</i>, 1997;Hoerni-Simon <i>et al</i>, 1987;Recht <i>et al</i>, 1988;van Besien <i>et al</i>, 1998;Zinzani <i>et al</i>, 1999;Colocci <i>et al</i>, 2004). In der eigenen retrospektiven Analyse konnte ein Langzeitüberleben nur bei intensiv systemisch behandelten Patienten beobachtet werden (Jahnke <i>et al</i>, 2005).</p> <p>Prospektive Studien zur Therapie der SZNSL, die über den palliativen Ansatz hinausgehen, fehlen weitgehend. Erst kürzlich wurde eine deutsche Phase II Studie der G-PCNSL-SG beendet, deren endgültige Auswertung noch aussteht (siehe unten).</p>
	<p><b>Lokale Strahlentherapie</b> radiologisch sichtbarer Lymphom-Manifestationen wird insbesondere bei Patienten mit fokalen neurologischen Defiziten angewendet mit dem Erfolg einer passageren symptomatischen Besserung bei bis zu 1/3 der Fälle. Eine Bestrahlung der gesamten Neuroachse wurde in den letzten Jahren seltener verwendet, nicht zuletzt wg. der ausgeprägten Hämatoxizität. Eine Ganzhirnbestrahlung zusammen mit einer Hochdosischemotherapie führte zu einem medianen Gesamtüberleben von 10 Mo und einem 2J EFS von 40%, allerdings mit einer schweren Neurotoxizität bei 1/3 der Patienten (Williams 1994). Aufgrund dieser Erfahrung wird heutzutage die Ganzhirnbestrahlung bei SZNSL eher als Zweitlinienbehandlung nach Versagen systemischer Chemotherapie angesehen (Magrath 1996).</p>
	<p>Eine <b>intrathekale Therapie</b> wird im Allgemeinen als Bestandteil der Therapie der SZNSL angesehen, insbesondere beim Vorliegen eines meningealen Befalls. Es ist nicht geklärt, ob bei systemischer Anwendung Zytostatika, die das ZNS penetrieren, auf die intrathekale Therapie nicht verzichtet werden kann. Eine alleinige intrathekale Chemotherapie ist für eine längerfristige Krankheitskontrolle sicher nicht ausreichend. Als Standard gilt die intrathekale Applikation von MTX und Cytarabin (mit oder ohne ein Kortikosteroid), verabreicht aufgrund der kurzen Halbwertszeit alle 3 Tage. Eine Diffusion in den gesamten Liquorraum ist bei lumbaler Punktion wegen kurzer Halbwertszeit und möglicher Liquorzirkulationsstörungen trotzdem oft nicht gewährleistet (Fleischhack <i>et al</i>, 2005). Die Applikation des liposomalen Cytarabins Depocyte ist aufgrund seiner langen Halbwertszeit nur alle 2 Wochen notwendig. Dabei ist Depocyte in der Behandlung meningealer NHL-Rezidive in Bezug auf Ansprechen freiem Cytarabin bei vergleichbarer Nebenwirkungsrate überlegen (Glantz <i>et al</i>, 1999).</p> <p>In einer kleinen Phase I Studie wurde die Effektivität und Toxizität von Rituximab intrathekal geprüft. Dosen bis 25 mg wurden ohne nennenswerte Nebenwirkungen toleriert, während 50 mg zu Übelkeit, Erbrechen, arterieller Hypertension, Doppelbildern und Tachypnoe führte. Objektivierbares Ansprechen wurde bei der Hälfte der Patienten erreicht, allerdings war es zumeist nur von kurzer Dauer (Rubenstein 2007).</p>
	<p><b>Hochdosischemotherapie mit autologer Stammzelltransplantation</b></p> <p>Bei rezidiviertem aggressivem Lymphom ist für das Erreichen einer langanhaltenden Remission eine Hochdosischemotherapie mit Stammzelltransplantation nötig (Philip <i>et al</i>, 1995). Die Gültigkeit dieses Prinzips ist für ZNS-Rezidive zu postulieren. Bei der Wahl der Konditionierungstherapie bei SZNSL ist wahrscheinlich die ZNS-Gängigkeit der Zytostatika von Bedeutung. Beim primären ZNS-Lymphom wurde über eine nur geringe Effektivität des BEAM-Protokolls im Vergleich zu BCNU, Thiotepa oder Busulfan enthaltenden Protokollen berichtet (Abrey 2003, Illerhaus 2006, Soussain 2008). Dieser Unterschied könnte damit erklärt werden, dass die Bestandteile des BEAM-Protokolls im Vergleich zu BCNU,</p>

	<p>Thiotepa oder Busulfan nur eine geringe CNS Gängigkeit besitzen (Busulfan und Thiotepa 80% des Serumspiegels, Carmustin 50–80%, Etoposid 5%, AraC 6–22%, Melphalan 10%; Wiebe 1992).</p> <p>In retrospektiven Studien wurde die Wirksamkeit der Hochdosistherapie mit nachfolgender autologer oder allogener Stammzelltransplantation bei SZNSL untersucht. Dabei zeigte sich neben der Verlängerung von progressionsfreiem und Gesamtüberleben für einen Teil der Patienten eine langfristige Remission (Alvarnas <i>et al</i>, 2000; Kasamon <i>et al</i>, 2005; Williams <i>et al</i>, 1994b). In der retrospektiven Auswertung der EBMT fand sich ein entscheidender Einfluss des Remissionsstatus vor der Hochdosischemotherapie für das <i>outcome</i> der Patienten mit 5J PFS von 42% für Patienten mit Remission und nur 9% für Patienten mit aktiver ZNS-Erkrankung (Williams 1994). In einer aktuellen retrospektiven Analyse war eine Hochdosistherapie gefolgt von autologer Stammzelltransplantation signifikant mit längerem Überleben assoziiert (Bromberg <i>et al</i>, 2013).</p> <p>In der kürzlich abgeschlossenen Phase II Studie der G-PCNSL-SG wurden Patienten <math>\leq 65</math>J. mit ZNS-Rezidiven aggressiver Lymphome mit folgendem Schema behandelt</p>
	<p>1-2 Zyklen        HDMTX 4g/m<sup>2</sup> (Tag 1)        Ifosfamid 2g/m<sup>2</sup> (Tag 3-5)        Depocyte 50mg ith. (Tag 6)        Dexamethason 2x4 mg (Tag 6-10)</p> <p>1-2 Zyklen        HD AraC 3g/m<sup>2</sup> (Tag 1-2)        Thiotepa 40mg/m<sup>2</sup> (Tag 2)        Depocyte 50mg ith. (Tag 3)        Dexamethason 2x4mg (Tag 3-7)</p> <p>gefolgt von einer Hochdosischemotherapie mit:        BCNU 400mg/m<sup>2</sup> (Tag -5)        Thiotepa 2x5mg/kg (Tag -4 bis -3)        Etoposid 150mg/m<sup>2</sup> (Tag -5 bis -3)</p> <p>und autologer Stammzelltransplantation.</p> <p>Ein Ansprechen wurde mit der gesamten Therapie bei 71% der Patienten erreicht. Die Therapieversagensrate nach 2J betrug 49% für alle 30 Patienten und 58% für die 24, die tatsächlich transplantiert wurden (Korfel <i>et al</i>, Hematologica 2013). Ein kuratives Potential des verwendeten Protokolls wird vermutet.</p>
	<p>Diese Therapiebeobachtung ist eine prospektive Studie (prospektives Register). Aus diesem Grund werden weder diagnostische noch therapeutische Maßnahmen vorgeschrieben.</p> <p>Zur besonderen Beachtung: Entsprechend Amendment 1 wird die Frist für die Meldung schwerer unerwünschter Ereignisse komplett aufgehoben.</p>
Beobachtungsziel	<p>Ziel der Beobachtung ist die Erfassung und Dokumentation von Daten zu Behandlungsstrategien bei SZNSL in der klinischen Routine, unabhängig davon, ob diese im Rahmen von klinischen Studien oder außerhalb von Studien gewonnen werden. Insbesondere werden folgende Fragestellungen spezifiziert:</p> <ul style="list-style-type: none"> <li>• Welche Therapieansätze werden verfolgt?</li> <li>• Wie ist das klinische Ergebnis der verschiedenen Behandlungsoptionen?</li> <li>• Wie ist die Frequenz schwerer unerwünschter Ereignisse bei den jeweiligen Therapieansätzen?</li> </ul> <p>Zu diesem Zweck soll in der vorliegenden Untersuchung die routinemäßige Therapie und Diagnostik von SZNSL in Deutschland dokumentiert werden. Mit der Durchführung der Beobachtungsstudie/Registerstudie ist keine Intervention hinsichtlich Auswahl und Durchführung des konkreten Therapieschemas, Diagnostik und Untersuchungsfrequenz während und nach der Behandlung verbunden. Die Patienten werden um Ihre Zustimmung zu evtl. später folgenden wissenschaftlichen Untersuchungen am Gewebe (Blut,</p>



	Tumorgewebe und ggf. daraus entnommenem genetischen Material), sofern für die Diagnosedstellung nicht mehr benötigt, gebeten.
Auswahl der Prüfarzte	Die Beobachtungsstudie soll in Kliniken, Ambulanzen und bei niedergelassenen onkologisch tätigen Ärzten durchgeführt werden. Die Prüfarzte werden durch die deutsche G-PCNSL-SG-Studiengruppe bzw. das KML zur Teilnahme aufgefordert. Mit Meldung eines Patienten werden die personenbezogenen Daten des den Patienten einschließenden Arztes erfasst und in Form einer Listendokumentation zusammengestellt.
Patienten	Alle Patienten mit einem systemischen Lymphom und ZNS-Befall (einschließlich transformierter indolenter Lymphome und Mantelzelllymphome, jedoch kein Burkitt- oder lymphoblastisches Lymphom) können und sollen in die Untersuchung aufgenommen werden unabhängig davon, welche Therapieoptionen genutzt werden und unabhängig davon ob es sich um eine Erstlinienbehandlung, die Behandlung eines Rezidives oder um eine Erhaltungstherapie bei SZNSL handelt. Mit der Durchführung der Beobachtungsstudie ist keine Intervention hinsichtlich Auswahl und Durchführung des konkreten Therapieschemas, der Diagnostik und Untersuchungsfrequenz während und nach der Behandlung verbunden.
Patientenzahl	Es wird geschätzt, dass ca. 100 Patienten prospektiv dokumentiert werden. Aktuell sind 205 Pat. eingeschlossen. (Stand Okt. 2017)
Beobachtungsdauer	Entsprechend Amendment 1 wird die auf insgesamt 6 Jahre verlängert werden und auf das europäische Ausland erweitert. Die Nachbeobachtung von 3 Jahren verbleibt.
Rekrutierungszeitraum	Juli 2011- ca. Ende 2016
Weitere teilnehmende Zentren erwünscht?	Es handelt sich um eine Registerstudie, damit kann jedes Zentrum Patienten einbringen!

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