# STUDIENKURZPROTOKOLLE

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## Impressum

Arbeitsgemeinschaft
Internistische Onkologie (AIO)
in der Deutschen
Krebsgesellschaft e.V.
Kuno-Fischer-Straße 8
14057 Berlin
Tel. 030-322 932 933
Fax 030-322 932 943
aio@krebsgesellschaft.de

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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 Cylcles of Platinum Doublet Chemotherapy, MX39795 (CUPISCO)**

**AIO-assoziierte Studie**

| | |
|---|---|
| Studiennummer: | AIO-CUP-0117/ass - CUPISCO |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2018 – 2020 |
| Weitere Zentren: | Ggfs. auf Anfrage direkt bei Prof. Krämer |
| Letzte Aktualisierung | Oktober 2018 |

| | |
|---|---|
| Art der Studie: | randomisierte Phase-II-Studie |
| | Prof. Dr. Alwin Krämer |
| Verantwortlicher Studienleiter nach AMG / Kontakt | Prof. Dr. Alwin Krämer<br>Klinische Kooperationseinheit Molekulare Hämatologie/Onkologie<br>Deutsches Krebsforschungszentrum und<br>Medizinische Klinik V, Universität Heidelberg<br>Im Neuenheimer Feld 581,<br>69120 Heidelberg<br>Tel: +49-6221-42-1440<br>Fax +49-6221-42-1444. |
| Studienziele | Primary Endpoint: PFS - Progression Free Survival (from randomization to first occurrence of disease progression)<br>Secondary Endpoints: Overall survival (OS), Overall Response Rate (ORR), Duration of Clinical Benefit (DCB) |
| Patientenzahl | 790 patients. – Aktuell eingeschlossen: 10 (Okt. 2018) |
| Rekrutierung | Rekrutierungsbeginn international Mai 2018, Deutschland November 2018 |
| Zentren | 101 Zentren in 23 Ländern, bisher 15 Länder aktiviert, 13 Zentren in Deutschland |
| Einschlusskriterien | • Histologic or cytologic proven, non-resectable carcinoma of unknown primary (adenocarcinoma or poorly differentiated carcinoma or squamous cell carcinoma)<br>• Measurable tumor lesion(s) according to RECIST criteria<br>• WHO PS 0 to 1<br>• Signed written informed consent<br>• ≥18 years of age<br>• Sufficient tumor tissue sample (for NGS-testing)<br>• No prior lines of chemotherapy<br>• Life expectancy >= 12 weeks<br>• Effective contraception for both male and female subjects if the risk of conception exists<br>• Adequate hematologic and organ function |

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| Ausschlusskriterien | • CNS-metastases or leptomeningal disease<br>• Spinal cord compression not definitely treated<br>• Non epithelial cancer<br>• Patients belonging to subsets of CUP with good prognosis:<br>  ○ Women with axillary node metastasis as predominant tumor site<br>  ○ Women with papillary adenocarcinoma of the peritoneal cavity<br>  ○ Men with poorly diff. ca. with midline distribution<br>  ○ Squamous cell carcinoma in cervical lymph nodes<br>  ○ Poorly diff. neuroendocrine tumors<br>  ○ Men with blastic bone metastases and elevated PSA<br>  ○ Isolated inguinal adenopathy<br>  ○ Single, potentially resectable tumor site<br>• Investigational agents or participation in clinical trials within 28 days before treatment start in this study<br>• Clinically relevant coronary disease, renal disease, (dialysis), HIV, active tuberculosis, major surgery within 4 weeks before study entry, severe allergic reaction to study drugs |
| Therapieschema | • 3 cycles platinum doublet (carboplatin/paclitaxel or cisplatin/gemcitabine) (During this time: molecular genomic profiling)<br>• If CR, PR, SD: randomize 3:1: molecular guided therapy or inv. choice vs. platinum doublet continuation<br>• If PD: molecular guided therapy or inv. choice |
| Tumorevaluierung | According to RECIST-criteria 1.0 |

# Arbeitsgruppe Endokrine Tumoren

## *Nebennierenrindenkarzinom – adjuvante Therapie*

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

**AIO-assoziierte Studie**

| | |
|---|---|
| Studiennummer/-Code: | ADIUVO |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2011 - 2020 |
| Weitere Zentren: | leider nicht möglich |
| Letzte Aktualisierung | Oktober 2018 |

| | |
|---|---|
| Studiendesign | Randomisierte, prospektive, kontrollierte, nicht-geblindete Multicenterstudie |
| Studienleiter: | Prof. Massimo Terzolo<br>University Hospital of Turin, Italien<br>terzolo@usa.net |
| Internat. Studienkoordinator | Prof. Dr. Martin Fassnacht (Leiter d. klin. Studie Deutschland)<br>Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie<br>Universitätsklinikum Würzburg<br>Oberdürrbacherstr. 6, 97080 Würzburg<br>Tel 0931-201-39021, Fassnacht_m@ukw.de |
| Statistiker | Prof. Gianni Ciccone, University of Turin, Italy<br>Prof. Dr. Hans-Helge Müller, LMU München, Germany |
| Protokoll-Kommittee: | 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 mittleren Rezidivrisiko. |
| Teilnehmerzahl | 200 Patienten (100 in jeder Gruppe)<br>Eingeschlossene Patienten: 89 (Stand Oktober 2018) |
| 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<br>Aktueller Stand der Studienzentren: Berlin, Dresden, Düsseldorf, Hamburg, München, Würzburg |
| Einschlusskriterien | • Histologisch gesichertes Nebennierenrinden Karzinom (NN-Ca)<br>• Z.n. kompletter Resektion des Tumors ohne Hinweis auf Fernmetastasen<br>• Niedriges/mittleres Rezidivrisiko definiert als: histologisch belegte komplette Resektion (R0) und Ki67 ≤ 10%<br>• Akzeptabler körperlicher Zustand (ECOG performance status 0-2) |

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| | • Alter > 18 Jahre<br>• Adäquate Knochenmarksreserve<br>• Effektive Kontrazeption bei Männern und bei prämenopausalen Frauen<br>• Vorliegen der unterschriebenen Patienteneinverständnis |
| Ausschlusskriterien | • Zeitraum zwischen Operation und Randomisierung > 3 Monate<br>• Operation wegen Rezidiv des NN-Ca<br>• Nachweis einer autonomen adrenocorticalen Hormonproduktion (auch ohne Nachweis der Erkrankung in der Bildgebung)<br>• Eigenenanamnese anderer Neoplasien mit Ausnahme definitiv kurierter Malignome mit einer mehr als 3 Jahre dauernden erkrankungsfreien Zeit<br>• Frühere Therapie mit Mitotane oder andere Tumortherapien für das NN-Ca (incl. Bestrahlung)<br>• Gravierende Niereninsuffizienz oder Lebererkrankung<br>• Schwangerschaft oder Stillen<br>• Andere schwerwiegende klinische Situationen, die nach Einschätzung des lokalen Untersuchers den Patienten einem erhöhten Risiko aussetzen |
| Endpunkte | Primärer Endpunkt: Rezidivfreies- und erkrankungsfreie Überleben<br>Sekundäre Endpunkte:<br>• Quality of life (Lebensqualität)<br>• Gesamtüberleben<br>• Toxizität (nach NCI-CTC-Kriterien) |
| Behandlungsplan | Patienten erhalten randomisiert:<br>I) Orale adjuvante Mitotanegabe (Dosistitrierung nach Blutspiegel (Ziel 14-20 mg/l) und Verträglichkeit für 2 Jahre<br>II) Keine adjuvante Therapie<br>Evalution 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. |
| Statistische Analyse | 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 konfirmatorsiche 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. |
| Studiendauer | 9 Jahre |
| Deutsche Studienzentren | Berlin: Klinische Endokrinologie, Charite, Campus Mitte<br>Dresden: Medizinische Klinik III, Universitätsklinikum<br>Hamburg: ENDOC Praxis<br>München: Medizinische Klinik IV, Klinikum der Universität München<br>Würzburg: Medizinische Klinik I, Universitätsklinikum |
| Unterstützung der Studie | • European Network for the Study of Adrenal Tumors (ENSAT)<br>• Arbeitsgemeinschaft Internistische Onkologie (AIO) – AG Endokrine Tumoren<br>• Förderung durch die Europäische Union im Rahmen des FP-7 Programms |

*Unresectable Adrenocortical Carcinoma*

**AIO-ENC-0118/ass - A Single center, Open-label, Phase II Study to Evaluate the Efficacy and Safety of Cabozantinib in Advanced (Unresectable or Metastatic) Adrenocortical Carcinoma (CaboACC)**

| **AIO-assoziierte Studie** | |
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| Studiennummer/-Code: | AIO-ENC-0118/ass - CaboACC |
| Status: | In Vorbereitung |
| Rekrutierungszeitraum: | 2019 – 2021 |
| Weitere Zentren: | Nicht geplant |
| Letzte Aktualisierung | 10/2018 |

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| Art der Studie<br>Study Type | Prospective multicenter open label phase-II |
| Kontaktadresse/<br>Kontaktperson: | Verantwortlicher Studienleiter nach AMG:<br>PD Dr. Dr. Matthias Kroiß<br>Tel.: 0931/201-39740<br>Email: Kroiss_M@ukw.de<br><br>Universitätsklinikum Würzburg<br>Medizinische Klinik und Poliklinik I<br>Schwerpunkt Endokrinologie/Diabetologie<br>Oberdürrbacher Str. 6<br>97080 Würzburg |
| Studienziele/<br>Objectives | To determine the efficacy and safety of cabozantinib as a treatment for unresectable/advanced adrenocortical carcinoma.<br><br>To explore the relationship between cabozantinib pharmacokinetics and treatment response and tolerability<br><br>To study steroid hormone biomarkers and targeted metabolomics as markers of disease response.<br><br>To study the effect of cabozantinib on immune markers by obtaining blood samples collection at baseline, during therapy and at time of progression.<br><br>To explore the relation between pharmacogenetic variants and cabozantinib pharmacokinetics.<br><br>To explore the relation of c-MET copy number (FISH), mutations (incl. ΔExon14), c-MET mRNA expression (RNAscope) and VEGFR2 expression (IHC) and response in archival formalin-fixed paraffin-embedded tissue specimens<br><br>To characterise pre-defined populations of immune cells, immune cell differentiation status and functionality in available fresh/fresh frozen tumor specimens |
| Zielparameter/<br>Objectives | Primary end point:<br>- progression free survival at 4 months<br><br>Secondary end points:<br>- overall survival<br>- Best Objective Response Rate (ORR)<br>- duration of response (DR)<br>- progression-free survival<br>- best percentage change in size of target lesions<br>- incidence and severity of adverse events possibly related to cabozantinib graded according to CTC-AE 4.03<br>- quality of life by EORTC QLQ-C30 |

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| | Exploratory<br>- steady-state trough plasma concentration of cabozantinib by quantile<br>- biochemical response: defined as reduction of one or more marker steroids in urine or plasma by >50% at any time (excluding patients treated with inhibitors of steroidogenesis concomitantly).<br>- control of cortisol excess: defined as normalization of elevated urinary free cortisol at baseline at any time (excluding patients treated with inhibitors of steroidogenesis concomitantly)<br>- change from baseline of pre-specified immune cell markers at during treatment<br>- correlation of steady state trough cabozantinib plasma concentration with pre-specified variants of enzymes of drug metabolism and disposition<br>- descriptive analysis of expression of tissue markers and response |
| Patientenzahl<br>Number of patients | Planned: 37<br>Already included: 0 |
| period of | 2019 - 2021 |
| Weitere teilnehmende Zentren erwünscht?<br>More centres? | single center trial |
| Haupt-Einschlusskriterien<br>/<br>Key inclusion criteria | 1. ≥ 18 years old on the day of consent<br>2. histological confirmation of ACC<br>3. Locally advanced or metastatic disease not amenable to surgery with curative intent with measurable disease per RECIST 1.1 within 28 days before the first dose of cabozantinib<br>4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2<br>5. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy<br>6. Life expectancy of at least 3 months<br>7. Organ and bone marrow function and laboratory values within pre-<br>8. Capable of understanding and complying with the protocol requirements.<br>9. Sexually active patients of reproductive potential (men and women) must agree to use medically accepted barrier methods of contraception (e.g. male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used.<br>10. Able to give written informed consent |
| Haupt-Ausschlusskriterien<br>Key exlusion criteria | 1. cytotoxic chemotherapy, radiation therapy, or targeted therapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies), or other investigational agent within 28 days of study enrollment.<br>2. Treatment with mitotane <28 days prior study inclusion OR mitotane serum/plasma con-centration documented of ≥2 mg/L.<br>3. Prior treatment with cabozantinib or other cMET inhibitors<br>4. Known brain metastases or cranial epidural disease unless adequately treated with radio-therapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment.<br>5. Prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 28 days before the first dose of study treat-ment.<br>6. Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct throm-bin and Factor Xa inhibitors), platelet inhibitors (e.g., clopidogrel) or therapeutic doses of low molecular weight heparins (LMWH). Low dose aspirin for cardioprotection (per local applicable guidelines) and low dose LMWH are permitted. Anticoagulation with therapeutic doses of LMWH is |

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| | allowed in subjects who are on a stable dose of LMWH for at least 6 weeks before the first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.<br>7. The use of strong CYP3A4 inhibitors (with the exception of ketoconazole).<br>8. The subject has experienced any of the clinical conditions defined in the full protocol<br>9. evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rec-tum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib, or the subject with radiographic evidence of cavitating pulmonary lesion(s); or subjects with tumor invading or encasing any major blood vessels.<br>10. Uncontrolled, significant concurrent or recent illness or disorders as specified in the protocol.<br>11. Any of the following within 6 months before the first dose of study treatment:<br>• abdominal fistula<br>• gastrointestinal perforation<br>• bowel obstruction or gastric outlet obstruction<br>• intra-abdominal abscess<br>12. Unable to swallow tablets<br>13. QTcF>500 milliseconds within 28 days before first dose of study<br>17. Pregnancy or breastfeeding.<br>18. A previously identified allergy or hypersensitivity to components of the study treatment formulation.<br>19. Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.<br>20. Evidence within 2 years of the start of study treatment of another malignancy which re-quired systemic treatment except for breast ductal carcinoma-in situ, cured non-melanoma skin cancer, or cured in situ cervical carcinoma<br>21. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality which, in the judgment of the investigator, would have made the patient inappropriate for entry into this study. |
| Therapieschema<br>Scheme of therapy | Cabozantinib tablets 60 mg qd. |
| Tumorevaluierung<br>Criteria for evaluation | RECIST1.1 |
| Rationale | Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with poor prognosis and limited response to therapy. Recurrence after surgical resection is very common in patients presenting with localized disease and systemic therapy is the primary treatment for patients with recurrent or advanced disease. The combination of cisplatin/etoposide/doxorubicin/mitotane is the current standard of care for metastatic ACC (Fassnacht et al., NEJM 2012). This combination has a suboptimal response rate of 23% with median time to progression of about 5 months while second line therapy (streptozocin with mitotane) has response rate of 9% with median time to progression of about 2 months.<br>In vitro evidence demonstrated increased HGF/cMET expression in human ACC samples (Phan et al, Cancer Res 2015) and in vitro data point to cMET up-regulation as a mechanism of drug resistance. A case series of seven ACC patients refractory to standard treatment with cabozantinib showed partial remission in two, SD in two and progressive disease in two patients. The median progression-free survival was 20 weeks and overall survival 58 weeks. Treatment was overall well tolerated with no treatment emergent serious adverse events. The results of this retrospective study are remarkable in that all patients had progressed to prior mitotane and 1-8 additional systemic therapies and compares favorably with the poor prognosis of most patients with advanced ACC. |

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| Statistik (optional) | The primary analysis is the analysis of the binary primary endpoint progression-free survival at 4 months (PFS4) in the two-stage Simon design. Point estimation for the underlying rate of PFS4 by the uniformly minimum variance unbiased estimator (UMVUE), p-value for testing in Simon's two-stage design and two-sided 90% confidence interval according to Koyama & Chen (2008).<br>Sample size calculation according to the algorithm of Simon for two-stage phase II trials:<br>Based on these results of Kroiss et al. (2012) and Fassnacht et al. (2015) and on clinical experience we consider p0 = 0.05 (5%) as the largest proportion for PFS at 4 months which, if true, implies that Cabozantinib is not warrant further investigation. Furthermore we consider p1 = 0.20 (20%) as the smallest proportion which, if true, implies that Cabozantinib is promising and warrants further investigation.<br>Requirements for testing the null hypothesis H0 that the underlying proportion of patients with PFS at 4 months is ≤ p0 = 0.05: The sample size has to be sufficiently large to ensure that the probability for rejecting H0 if in fact H0 is true (that means p ≤ 0.05) is 0.05 as well as the probability for rejecting H0 if in fact p ≥ p1 = 0.20 holds, is 0.80.<br>Then the optimal Simon two-stage design requires a maximum of 29 ACC patients with progressing disease after standard therapy. After evaluation of the primary endpoint for 10 patients in the first stage the trial will be terminated because of futility (insufficient efficacy) if none patient has survived progression-free at 4 months. Otherwise the trial goes on the second stage and a total of 29 patients will be studied. If the total number of patients with PFS at 4 months is less than or equal to 3 the null hypothesis of insufficient efficacy (that means ≤ p0 = 0.05), is not rejected. Assuming a drop-out rate of 20% within 4 months 37 patients have to be included in the study. Sample size calculation was done with the software PASS14 (NCSS).<br>For the time-to-event endpoints progression-free survival (PFS), overall survival (OS) as well as duration of complete response (CR) and partial response (PR) the 'survival' functions will be estimated by the Kaplan-Meier product-limit estimator. From this unbiased descriptive statistics, e.g. median 'survival' time, will be estimated. |

*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 2018 |

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| Studienleiter | Prof. Dr. Martin Fassnacht (Head of the ACC working group of ENSAT)<br>Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie<br>Universitätsklinikum Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg<br>Tel 0931-201-39021, Fassnacht_m@ukw.de |
| Kontaktadresse/ Kontaktperson: | Frau Michaela Haaf (Study Nurse)<br>Schwerpunkt Endokrinologie und Diabetologie, Medizinische Klinik I,<br>Universitätsklinik Würzburg, Oberdürrbacher Str. 6, 97080 Würzburg<br>Tel.: 0931 – 201 39717, Fax: 0931 – 201 639716<br>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.<br>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.<br>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.<br>Anfangs werden die Patienten retrospektiv analysiert. Mit dem Zeitpunkt der Erstaufnahme in das Register erfolgt eine prospektive Beobachtung.<br>Parallel zu den klinischen Daten werden Bioproben (Tumor, Blut und Urin) von den Patienten gesammelt und ausgewertet. |
| Weitere teilnehmende Zentren erwünscht? | Ja |
| Erfasste Patienten | Oktober 2018: 3166 (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 Operationonsverfahren (Brix Eur Urol 2010; Reibetanz Ann Surg 2012) oder zur Therapie beim Rezidiv |

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| | (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).<br>Weitere Informationen und bisherige Publikationen unter: www.nebennierenkarzinom.de; www.ensat.org |
| Förderung | Initial über die Deutsche Krebshilfe<br>Seit 2011 Förderung durch die Europäische Union im Rahmen des FP-7 Programms |

## Malignes Phäochromozytom / Paragangliom – palliative Therapie

### First International Randomised STudy in MAlignant Progressive Phaeochromocytoma and Paraganglioma (FIRST-MAPPP) – Sunitinib vs. Placebo

**AIO-assoziierte Studie**

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

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| Art der Studie | Randomisierte, prospektive, kontrollierte, placebo-kontrollierte, doppel-geblindete Multicenterstudie |
| Sponsor | Institut Gustav Roussy, Villeneuf, Frankreich |
| Studienleiter: | Prof. Eric Baudin<br>Institut Gustav Roussy, Villeneuf, Frankreich |
| Kontaktadresse/ Kontaktperson: | Prof. Dr. med. Martin Fassnacht (Leiter der klinischen Prüfung)<br>Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie<br>Universitätsklinikum Würzburg<br>Oberdürrbacherstr. 6, 97080 Würzburg<br>Tel 0931-201-39021, Fassnacht_m@ukw.de |
| Studienziele | **Primäres Studienziel:**<br>• Progressionsfreies Überleben<br>**Sekundäre Studienziele: (Auswahl)**<br>• Overall Surival<br>• Quality of life (Lebensqualität)<br>• Gesamtansprechrate, Dauer des Ansprechens |
| Patientenzahl | Mehrstufiges Studiendesign mit 34 bis 144 Patienten<br>Aktuell (Okt 2018: 74) |
| 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 |

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| Studienstart: | Dezember 2011 (Frankreich), Juni 2013 (Deutschland) |
| Studienende: | Studie läuft mind. bis 2019 |
| Einschlusskriterien | • Unequivocal diagnosis of malignant PPGL<br>• Metastatic disease not amenable to radical surgical resection<br>• Evaluable disease according to RECIST 1.1 criteria<br>• Progressing disease within 18 months prior to randomisation according to RECIST 1.1<br>• Age ≥ 18 years |
| Ausschlusskriterien | • History of prior malignancy<br>• Severe renal or hepatic insufficiency, or bone marrow impairment<br>• Major cardiovascular events within the last 12 months<br>• Uncontrolled hypertension despite therapy<br>• Prior systemic treatment with any tyrosine kinase inhibitors or anti VEGF angiogenic inhibitors. However, patients who have received other systemic therapies such as 131-I-MIBG or cytotoxic therapies are accepted. |
| Therapieschema | Patienten erhalten randomisiert:<br>• Sunitinbib 37.5 mg oral einmal täglich<br>• Placebo |
| Tumorevaluierung | Die Evaluation des Ansprechens erfolgt alle 12 Wochen. |
| Statistik | 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.<br>**Efficacy:** 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.<br>**Description of the primary efficacy:**<br>**Phase IIa:** The optimal two-stage design [Simon, Controlled Clinical Trials 1989] has been adopted (alpha=10%, 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 (n=17) 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)<br>**Phase IIb:** 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 ≤ 58 months and hazard ratio (HR) for PFS ≥ 1.33=1/0.75 (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 1.667=1/0.60 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 < 10% 144 - 150 patients have to be randomised. |

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| | **Safety:** 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). **Secondary endpoints:** Analysis of Quality of Life, objective tumour response rate, and overall survival will be descriptive. |
| Deutsche Studienzentren | Berlin: Klinische Endokrinologie, Charite, Campus Mitte<br>Dresden: Medizinische Klinik III, Universitätsklinikum<br>Lübeck: Universitätsklinikum, Medizinische Klinik<br>München: Medizinische Klinik IV, Klinikum der Universität München<br>Würzburg: Medizinische Klinik I, Universitätsklinikum |
| Unterstützung der Studie | • Bundesministerium für Bildung und Forschung (BMBF)<br>• Förderung durch die Europäische Union im Rahmen des FP-7 Programms (European Network for the Study of Adrenal Tumors (ENSAT-CANCER)<br>• Sunitinib und Placebo werden von der Firma Pfizer zur Verfügung gestellt<br>• Arbeitsgemeinschaft Internistische Onkologie (AIO) – AG Endokrine Tumoren |

## *Registerstudie - Medulläres und dedifferenziertes (anaplastisches und radiojodrefraktäres) Schilddrüsenkarzinom*

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

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| **AIO-Studie** | 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 2018 |

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

# Arbeitsgruppe Hepatobiliäre Tumoren

*Frühes HCC, kurativ / First Line*

**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**

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| Studiennummer/-Code: | AIO-HEP-0417/ass |
| Status: | Studie bei EK und PEI beantragt; Antrag noch in Bearbeitung |
| Rekrutierungszeitraum: | Studienstart noch offen (geplant: Q4/2018, 12 Monate Rekrutierung) |
| Weitere Zentren: | sind leider nicht mehr möglich |
| Letzte Aktualisierung | 22.10.2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. med. Arndt Vogel<br>Hannover Medical School<br>Department of Gastroenterology, Hepatology and Endocrinology<br>Carl-Neuberg-Str. 1<br>30625 Hannover |
| CONDITION | Early stage hepatocellular carcinoma (HCC) |
| OBJECTIVE(S) | Primary:<br>Overall response rate (ORR) before local ablation<br>Secondary:<br>Time to recurrence (TTR), recurrence free survival, and overall survival (OS)<br>Safety and tolerability<br>Identification of predictive molecular biomarkers |
| INTERVENTION(S) | pembrolizumab 200mg IV Q3W on D1C1 and D1C2<br>RFA / MWA will be performed on D1C3<br>pembrolizumab 200mg IV administration on D3C3<br>pembrolizumab 200mg IV Q3W for up to one year total treatment duration |
| KEY EXCLUSION CRITERIA | • Extrahepatic disease<br>• Fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC<br>• Tumor thrombus involving main trunk of portal vein<br>• Patient is awaiting liver transplantation (LTx)<br>• Prior history of Grade ≥ 2 hepatic encephalopathy<br>• Pericardial effusion, uncontrollable pleural effusion, or clinically significant ascites<br>• Autoimmune disease requiring systemic treatment |
| KEY INCLUSION CRITERIA | • Histologically confirmed diagnosis of HCC<br>• Child-Pugh Classification score ≤ 6<br>• Candidate for local ablation (via either RFA or MWA)<br>• High risk patient<br>(Presence of ≤ 5 tumor nodules with diameters ≤ 5cm [longest axis] each and not a candidate for resection)<br>• No prior systemic therapy for HCC<br>(TACE >8 weeks before study allocation permitted)<br>• Measurable disease based on RECIST<br>• Archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion |

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| | • ECOG performance status 0 to 1 |
| OUTCOME(S) | Efficacy :<br>• 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).<br>• We hypothesize that peri-interventional treatment with pembrolizumab will increase TTR, recurrence free survival and overall survival after RFA / MWA.<br>Safety:<br>• We hypothesize that combination of RFA / MWA with peri-interventional administration of pembrolizumab is safe and well tolerated. |
| STUDY TYPE | Interventional, single-arm, open-label, multicenter |
| STATISTICAL ANALYSIS | 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.<br>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). |
| SAMPLE SIZE | n=30 |
| TRIAL DURATION | max. 42 months from FPI to LPO<br>(consisting of 12 months recruitment, 12 months treatment after LPI, and 18 months FU for OS after LPLT) |
| PARTICIPATING CENTERS | 10 sites planned |

## *Hepatocellular Carcinoma, First Line*

**AIO-HEP-0318/ass: A phase I/II multicenter, open-label Study of DKN-01 to investigate the anti-tumor activity and safety of DKN-01 in Patients with Hepatocellular Carcinoma and WNT signaling Alterations**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | AIO-HEP-0318/ass |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum: | Studienstart noch offen, antizipiert 2018 – 2021 |
| Weitere Zentren: | ggfs. im Verlauf möglich |
| Letzte Aktualisierung | 09.08.2018 |

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| PRINCIPAL INVESTIGATOR | Jun. Prof. Dr. J. U. Marquardt<br>Prof. Dr. Markus Möhler |

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| TRIAL OFFICE | I. Medizinische Klinik und Poliklinik<br>Universitätsmedizin Mainz<br>Langenbeckstr. 1, 55131 Mainz |
| SPONSOR | Universitätsmedizin Mainz |
| CONDITION | Advanced Hepatocellular Carcinoma (HCC) |
| DESIGN | Phase I/II multicenter, open-label, single arm Study |
| INDICATION | HCC with WNT signalling alterations |
| OBJECTIVE(S) | Safety and efficacy of DKN01 |
| INTERVENTION(S) | DKN01 in combination with sorafenib |
| OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH | Mechanisms of DKN01 response |
| BACKROUND/RATIONALE | Alterations in the WNT/β-catenin signaling pathway are among the most common changes observed in liver cancer and can be considered true drivers of disease initiation and progression. Furthermore, activation of the pathway is associated with adverse clinical features (Monga, 2015). Therefore, treatment strategies targeting activity of the pathway or selected members are highly desirable. In this context, elevated expression of DKK1, a prominent member of the pathway, are observed in up to 70% of patients with HCC and associated with WNT activation and a poor clinical outcome (Andersen et al., 2010; Shen et al., 2012; Yu et al., 2009). For these reasons, the here proposed DKK1 inhibition with DKN-01 harbors great potential to improve the limited outcome of affected HCC patients with activation of the pathway. Furthermore, several lines of evidence indicate that inhibition of WNT might synergistically modulate the therapeutic potential of sorafenib in HCC. To explore the therapeutic effects of DKN-01 with and without the combination with sorafenib, therefore, seems highly promising to improve the outcome of patients with HCC. |
| KEY EXCLUSION CRITERIA | - Patients with the following histology of hepatocellular cancer are not eligible for enrollment: fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma.<br>- New York Heart Association Class III or IV cardiac disease, myocardial infarction within the past 6 months, or unstable arrhythmia.<br>- Specific cardiac preconditions : Fridericia-corrected QT interval (QTcF) >470 msec (female) or >450 msec (male), or history of congenital long QT syndrome. Any ECG abnormality that in the opinion of the Investigator would preclude safe participation in the study; patients with pacemakers where QTc is not a reliable measure will require an evaluation by a cardiologist to exclude co-existing cardiac conditions which would prohibit safe participation in the study.<br>- Active, uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry requiring systemic therapy.<br>- Known to be human immunodeficiency virus (HIV) positive,<br>- History of major organ transplant (i.e., heart, lungs, liver, or kidney).<br>- History of autologous/allogenic bone marrow transplant.<br>- Serious non-malignant disease that could compromise protocol objectives in the opinion of the Investigator and/or Sponsor.<br>- Pregnancy or nursing.<br>- Major surgical procedures, open biopsy or significant traumatic injury within 4 weeks prior to treatment start (minor procedures within 1 week)<br>- History of osteonecrosis of the hip or evidence of structural bone abnormalities in the proximal femur on magnetic resonance imaging (MRI) |

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| | scan that are symptomatic and clinically significant. Degenerative changes of the hip joint are not exclusionary. Screening of asymptomatic patients is not required.<br>- Symptomatic central nervous system (CNS) malignancy or metastasis. Patients with treated CNS metastases are eligible provided their disease is radiographically stable, asymptomatic, and they are not currently receiving corticosteroids and/or anticonvulsants. Screening of asymptomatic patients without a history of CNS metastases is not required.<br>- Known osteoblastic bone metastasis. Screening of asymptomatic patients without a history of metastatic bone lesions is not required.<br>- Medical or psychological conditions that would jeopardise an adequate and orderly completion of the trial.<br>- Thrombotic or embolic events (except HCC tumor thrombus <pVT4) within the past 6 months (including cerebrovascular accidents)<br>- Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 6 months<br>- Patients with portal thrombosis >pVT4<br>Medication Related<br>- Prior locoregional therapy or radiation therapy within 28 days prior to study entry.<br>- prior systemic therapy for HCC<br>- Currently receiving any other investigational agent or received an investigational agent within last 30 days of study entry.<br>- Previously treated with an anti-DKK1 therapy.<br>- Treatment with strong inducers of CYP3A4 within 7 days prior to study entry (including Cyclosporin, Erythromycin, Ketoconazole, Itraconazole, Quinidine, Phenobarbital salt with Quinidine, Ritonavir, Valspodar, Verapamil, St John's wort, rifampicin).<br>- Significant allergy to a pharmaceutical therapy that, in the opinion of the Investigator, poses an increased risk to the patient.<br>- History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product.<br>Lifestyle-Related<br>- Active substance abuse.<br>- Involuntary incarcerated patients |
| KEY INCLUSION CRITERIA | - Ambulatory male or female patients ≥ 18 years<br>- Patients must have histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of advanced stage or recurrent diagnosis of HCC based on histopathologic findings.<br>- Tumor tissue is mandatory for pre-treatment evaluation (baseline) (fresh biopsy during 4- weeks screening time preferred. Archived specimen (≤6 months) is only acceptable, if ≤ 6 months old). Baseline tumor biopsy samples must be available prior to the first dose of DKN-01.<br>- Tumor tissue (FFPE) must be received by central histopathology laboratory for correlative studies (fine needle aspiration and bone metastasis samples are not acceptable).<br>- Patients with activated WNT/β-catenin signaling identified by glutamine synthetase staining (high positive staining in tumor tissue) by an approved lab. Positive staining must be confirmed prior to first dose of DKN-01.<br>- Child-Pugh score <7 (Child-Pugh Class A).<br>- Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease not amenable to resection, locoregional therapy or refractory to locoregional therapy.<br>- At least one tumor lesion measurable on radiographic imaging as defined by mRECIST for HCC that has not been previously treated by locoregional therapies. |

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| | - Locoregional therapies or radiation therapy must be completed at least 4 weeks prior to baseline scan. All toxic effects > grade 1 (NCI CTCAE v4.03) related to any prior HCC treatment must be resolved. Palliative radiotherapy for symptomic control is acceptable and no additional radiotherapy for the same lesion is planned. (like bone metastases should not be targets for RECIST).<br>- ECOG performance status (PS) of 0 or 1.<br>- Estimated life expectancy of at least 3 months, in the judgment of the Investigator.<br>- Disease-free of active second/secondary or prior malignancies for ≥2 years with the exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or breast.<br>- Patients are eligible to enroll if they have non-viral-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows:<br>o HBV-HCC: Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) or chronic HBV infection (as evidenced by detectable HBV surface antigen or HBV DNA). PatientPatients with chronic HBV infection must have HBV DNA < 2000 IU/mL and must be on antiviral therapy.<br>o HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody<br>- Acceptable liver function:<br>o Total bilirubin ≤2.0 × upper limit of normal (ULN).<br>o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN.<br>- Acceptable renal function:<br>o Creatinine normalized for age: if serum creatinine is abnormal for age the patient must have a calculated creatinine clearance ≥50 mL/min using the Cockcroft and Gault Method (Cockroft and Gault 1976).<br>- Acceptable hematologic status:<br>o Neutrophil Granulocyte ≥1500 cells/µl.<br>o Hemoglobin ≥ 8,5 g/dL (transfusion permitted within 30 days of study entry).<br>o Platelet count ≥75,000 cells/µl.<br>- Acceptable coagulation status:<br>o INR ≤ 1.7 and no active bleeding, (i.e., no clinically significant bleeding within 14 days prior to first dose of study therapy<br>- Women post-menopausal for more than two years can participate in the trial. Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 7 days prior to first dose of DKN-01. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. Women of childbearing potential and sexually active males must be willing to practice a highly effective and medically accepted contraception method during trial and for 18 months after last dose of study drug. Reliable contraception comprises systematic contraceptives (oral, implant, injection) or diaphragm / condoms / intrauterine devices (IUP) with spermicide.<br>- Provided written informed consent prior to any study-specific procedures.<br>- Ability of patient to understand nature, importance and individual consequences of clinical trial. |
| OUTCOME(S) | Part A:<br>Evaluation of safety and tolerability using frequency and severity of adverse events to establish the recommended phase II dose (RP2D) of DKN-01 when administered as monotherapy for 8 weeks and in combination with sorafenib for 4 weeks in adult patients with HCC.<br>Part B:<br>To assess the time to progression (TTP1, TTP2) in treatment naïve patients with advanced HCC after treatment with DKN-01 monotherapy until PD1 and |

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| | in combination with sorafenib until PD2. TTP1 and TTP2 will be determined according to mRECIST. |
| STATISTICAL ANALYSIS | Definition:<br>PD1: Progressive Disease according to mRECIST with DKN-01 monotherapy.<br>PD2: Progressive Disease according to mRECIST with combination therapy of DKN-01 and sorafenib. Disease progression will be judged versus the status before start of sorafenib therapy.<br>Primary analysis variable:<br>TTP2 is defined as the time from first DKN-01 intake until PD2. Patients will be censored at study end or discontinuation of the study. The TTP2 will be analyzed by a one-sided logrank test. For the primary analysis no covariates will be considered. Moreover, TTP2 will be displayed by the median survival time and the corresponding 95% confidence interval. Kaplan Meier plots will be presented. A similar analysis for the TTP1 (time from first DKN-01 intake until PD1) will also be performed.<br>Secondary analysis variables:<br>- Overall survival is defined as the time from first DKN-01 intake until death from any cause. Progression free survival (PFS1, PFS2) is defined as the time from first DKN-01 intake until death or PD1 or PD2 respectively whichever comes first. Survival parameters (OS, PFS1, PFS2) will be analyzed by survival analysis methods i.e. Kaplan-Meier plots and median event time including the corresponding 95% confidence interval. ORR (CR or PR) and DCR (CR, PR or SD) after 2, 4 and 6 months will be analyzed by absolute and relative frequencies.<br>- For duration of response (time from first to the last disease control (CR, PR, or SD)) will be displayed by descriptive statistics.<br>- Adverse events will be coded by MedDRA terminology and analyzed by absolute and relative frequencies, DLTs will be graded according to the NCI CTCAE v4.03<br>Interim analysis:<br>There will be no formal interim analysis. After each cohort (10 patients each) in Part A a safety assessment will be performed and the next dose strength will be determined. After Part A (20 patients) the safety profile will be assessed. This is an exploratory study, therefore type 1 error inflation and statistical power will not be considered after Part A. |
| SAMPLE SIZE | Part A 20 patients; Part B 50 patients |
| TRIAL DURATION | 3 years |
| PARTICIPATING CENTERS | Mainz, Hannover, Hamburg, Frankfurt, Cologne, Mannheim |
| FURTHER CENTERS DESIRED? | Potentially |
| NUMBER of PATIENTS | 70 |
| CURRENT NUMBER of PATIENTS | 0 |

*HCC, periinterventionelle Studie, First Line*

**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)**

**AIO-Studie**

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| Studiennummer: | AIO-HEP-0217 - IMMUTACE |
| Status: | Rekrutierung (6 Patienten eingeschlossen) |
| Rekrutierungszeitraum: | 2018 - 2019 |
| Weitere Zentren: | Geplante Anzahl Zentren erreicht. Interessierte Zentren können sich auf die Warteliste setzen lassen |
| Letzte Aktualisierung: | Oktober 2018 |

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| National Coordinating Investigator (LKP) | Prof. Dr. med. Arndt Vogel<br>Klinik für Gastroenterologie, Hepatologie und Endokrinologie<br>Medizinische Hochschule Hannover<br>Carl-Neuberg-Str. 1, 30625 Hannover<br>Tel: +49 511-532-9590<br>FAX.: +49-511-532-8392<br>E-Mail: vogel.arndt@mh-hannover.de |
| Sponsor | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431<br>Fax +49 30 322932926<br>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<br>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 ≥ 18 years. Limited metastatic disease may be considered (see inclusion/ exclusion criteria). |
| Total number of sites | 10 (9 sites initiated) |
| Primary objective | The aim of the study is the assessement 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<br>1.) efficacy by PFS, TTP, TTFS, DoR and OS and<br>2.) safety and tolerability of nivolumab in combination with TACE in patients with intermediate stage HCC.<br>3) Quality of Life |
| Planned sample size | N=49 enrolled to receive TACE followed by nivolumab mono-therapy |
| 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<br>2. Age ≥ 18 years at time of study entry |

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| | 3. Multinodular or large, solitary HCC, not eligible for resection or local ablation, Tumor burden below 50% of liver volume.<br>4. Histologically confirmed diagnosis of HCC.<br>5. At least one measurable site of disease as defined by modified RECIST (mRECIST) criteria with spiral CT scan or MRI.<br>6. Child-Pugh A, performance status (PS) ≤ 2 (ECOG scale).<br>7. Subjects with chronic HBV infection must have HBV DNA viral load < 100 IU/mL at screening. In addition, they must be on antiviral therapy per regional standard of care guidelines prior to initiation of study therapy.<br>8. Life expectancy of at least 12 weeks.<br>9. Adequate blood count, liver-enzymes, and renal function:<br>• Haemoglobin ≥ 8.5 g/dL, absolute neutrophil count ≥ 1,500 /L, platelets ≥70 x$10^3$/L;<br>• Total bilirubin ≤ 3x upper normal limit;<br>• AST (SGOT), ALT (SGPT) ≤ 5 x upper normal limit;<br>• International normalized ratio (INR) ≤1.25;<br>• Albumin ≥ 31 g/dL;<br>• Serum Creatinine ≤ 1.5 x institutional ULN or creatinine clearance (CrCl) ≥ 30 mL/min (if using the Cockcroft-Gault formula below):<br>Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$<br>Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$<br>10. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial.<br>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).<br>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:**<br>1. Diffuse HCC or presence of vascular invasion or extrahepatic spread with the following exceptions:<br>a) Invasion of a segmental portal vein or hepatic veins<br>b) Limited extrahepatic metastases with one organ system manifestations, e.g. lymphnodal, pulmonary, ossary metastases. For lymphonodal 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.<br>2. Patients on a liver transplantation list or with advanced liver disease as defined below:<br>a) Encephalopathy;<br>b) Untreatable ascites.<br>3. Any contraindications for hepatic embolization procedures:<br>a) Known hepatofugal blood flow;<br>b) Known porto-systemic shunt;<br>c) Impaired clotting test (platelet count <70 x$10^3$/L, INR >1.25); |

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| | d) Renal failure/ insufficiency requiring hemo-or peritoneal dialysis;<br>e) Known severe atheromatosis;<br>f) Total thrombosis or total invasion of the main branch of the portal vein.<br>4. History of cardiac disease:<br>a) Congestive heart failure >New York Heart Association (NYHA) class 2;<br>b) Active coronary artery disease (CAD) (myocardial infarction ≥6 months prior to study entry is allowed);<br>c) Cardiac arrhythmias (>Grade 2 NCI-CTCAE Version 3.0) which are poorly controlled with anti-arrhythmic therapy or requiring pace maker;<br>d) Uncontrolled hypertension;<br>e) Clinically significant gastrointestinal bleeding within 4 weeks prior to start of study treatment (TACE + nivolumab)<br>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.<br>6. Prior systemic anti-cancer therapy OR endocrine- OR immunotherapy<br>7. Prior treatment with TACE<br>8. RFA and resection administered less then 4 weeks prior to study treatment start.<br>9. Radiotherapy administered less then 4 weeks prior to study treatment start.<br>10. Major surgery within 4 weeks of starting the study treatment OR subjects who have not recovered from effects of major surgery.<br>11. Patients with second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix.<br>12. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).<br>13. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lifes of previously used trial medication, whichever is longer.<br>14. Previous treatment in the present study (does not include screening failure).<br>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:<br>a) history of interstitial lung disease<br>b) HBV and HCV coinfection (i.e double infection)<br>c) known acute or chronic pancreatitis<br>d) active tuberculosis<br>e) any other active infection (viral, fungal or bacterial) requiring systemic therapy<br>f) history of allogeneic tissue/solid organ transplant<br>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.<br>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, |

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| | 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.<br>i) Live vaccine within 30 days prior to the first dose of nivolumab-monotherapy treatment or during study treatment.<br>j) History or clinical evidence of CNS metastases<br>Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:<br>a. are asymptomatic and<br>b. have no requirement for steroids 6 weeks prior to start of nivolumab-monotherapy treament. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases<br>**Drug related criteria:**<br>16. Medication that is known to interfere with any of the agents applied in the trial.<br>17. Has known hypersensitivity to nivolumab or any of the constituents of the products.<br>18. Any other efficacious cancer treatment except protocol specified treatment at study start.<br>19. Patient has received any other investigational product within 28 days of study entry.<br>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)<br><br>**Safety criteria:**<br>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 β-HCG) at screening.<br><br>**Regulatory and ethical criteria:**<br>22. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.<br>23. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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 |

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| 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:<br>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.<br>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 administred. In cases of extensive hypervascularity microspheres can be considered.<br>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<br><br>The actual TACE technique will be investigators choice.<br><br>Treatment will be divided into 4-week cycles from the starting date of TACE. The second TACE will be repeated on day 1 (± 4 days) of cycle 3 (after 8 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.<br><br>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.<br>Patients are allowed to continue with the study, if a progressive or new lesion can successfully be treated with <u>one</u> additional local therapy (TACE, radiofrequency ablation [RFA]/ microwave ablation [MWA] or resection).<br><br>Study assesssments:<br>• *Safety Lead-in:* These patients will be observed for the first 4 week cycle with weekly safety visits.<br>• *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. |
| Primary endpoint | ORR according to modified RECIST for HCC |
| Secondary endpoints | Additional secondary endpoints:<br>• tumor response according to RECIST 1.1<br>• PFS<br>• TTP<br>• Time-to-Failure-of-Strategy (TTFS):<br>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.<br>• Duration of response<br>• Duration of treatment<br>• OS<br>• QoL (EORTC QLQC30 and HCC-18)<br>• AEs/SAEs |
| Translational research: | **Biomarker assessment:** |

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| Exploratory objectives and endpoints | • Tumour blocks or slides of all patients confirming diagnosis of HCC according to the inclusion criterion prior to treatment will be collected.<br>• Standardized histopathological examination will be performed.<br>• DNA, RNA, miRNA will be extracted from tumours and subjected to molecular analysis using immunohistochemistry, RT-PCR analysis, RNA seq and Panel seq.<br>• 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.<br><br>**Central Review of radiological response:**<br>• 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.<br><br>**QoL-adjusted cost-effectivness analysis:**<br>• 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. |
| Rationale and Hypothesis | 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 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).<br><br>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 surival 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.<br><br>3.) Monoclonal antibodies (mAbs) that target the immune checkpoints cytotoxic T- lymphocyte-asscociated 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 metastastic melanoma and non-small-cell lung cancer (NSCLC) [12].<br>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-L1$^{low}$/ human leukocyte antigen class I (HLA |

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| | 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].<br><br>4.) Doxorubicin has been shown to trigger imunogenic 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].<br><br>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.<br>**Research hypothesis:**<br>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<br>• Frequency of clinically significant abnormal laboratory parameters |
| Sample size estimation and<br><br>Statistical analysis considerations | 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 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 ≤ 35 % ($P_0$) against a one-sided alternative that the ORR ≥ 55 % ($P_A$).<br>$H_0 : P \leq P_0 \quad H_A : P \geq P_A$<br>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 P ≤ 0.35 is rejected with a one-sided target error rate of alpha=0.05 (actual alpha 0.05). If the number of responses is 19 or less, the alternative hypothesis that P ≥ 0.55 is rejected with a target error rate of beta=0.2 (Power = 80%; actual beta 0.17). 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). |
| Study plan / time lines | First Patient In (FPI): Q1/2018<br>Last Patient In (LPI): after approx. 12 months<br>Last Patient Last treatment (LPLT): after approx. 20 - 36 months<br>End of follow-up period after LPI: after approx. 26 - 46 months<br>Study report: after approx. 35 - 51 months<br>Publication: after approx. 35 - 51 months |

*Fortgeschrittenes HCC, First line*

**AIO-HEP-0218/ass IMMUNIB - An open-label, single-arm phase II study of immunotherapy with nivolumab in combination with lenvatinib for advanced stage hepatocellular carcinoma (HCC)**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | AIO-HEP-0218/ass - IMMUNIB |
| Status: | in Einreichung<br>Verträge mit Förderern unterschrieben, Protokoll final |
| Rekrutierungszeitraum: | Studienstart steht bevor, FPI Q4/2018 geplant |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | 22.10.2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. med. Arndt Vogel<br>Hannover Medical School<br>Department of Gastroenterology, Hepatology and Endocrinology<br>Carl-Neuberg-Str |
| CONDITION | Multinodular, advanced stage hepatocellular carcinoma (HCC) in first line therapy |
| OBJECTIVE(S) | Primary efficacy endpoint:<br>Objective response rate (ORR) according to RECIST 1.1<br><br>Primary safety endpoint:<br>Safety (according to NCI-CTCAE v 4.03) and tolerability<br><br>Secondary endpoints:<br>• ORR according to iRECIST<br>• Time-to-progression (TTP)<br>• Progression free survival (PFS)<br>• Overall survival (OS)<br>• Translational research program |
| INTERVENTION(S) | • Lenvatinib peroral qd (8 mg for patients with body weight <60kg and 12 mg for patients with body weight ≥ 60kg)<br>• Nivolumab i.v. q2w (240mg fixed dose IV) |
| KEY EXCLUSION CRITERIA | ➢ Previous systemic therapy in the first-line setting.<br>Patients on a liver transplantation list or with advanced liver disease as defined below:<br>○ Encephalopathy<br>○ Untreatable Ascites.<br>➢ Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.<br>➢ Prior organ allograft or allogeneic bone marrow transplantation.<br>Local therapies ongoing or completed <4 weeks prior to the baseline scan. |
| KEY INCLUSION CRITERIA | Unresectable, multinodular tumour, not eligible for resection or local ablation<br>➢ Histologically confirmed diagnosis of hepatocellular carcinoma<br>Has a Child-Pugh Classification score ≤ 6 for assessed liver function within 7 days before allocation (Appendix 4: Child-Pugh Score) – patients with BCLC stage B can be included if they are no longer eligible for local ablation (i.e. after progress under local concept)<br>➢ At least one measurable site of disease as defined by RECIST 1.1 criteria with spiral CT scan or MRI. |

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| | ➢ Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.<br>➢ Life expectancy of at least 12 weeks. |
| OUTCOME(S) | The primary efficacy endpoint is:<br>• Objective response rate (ORR) according to RECIST 1.1 based on the ITT population<br><br>The primary safety endpoint is:<br>• Safety (according to NCI-CTCAE V 4.03) and tolerability |
| STUDY TYPE | Open-label, single-arm, multicenter phase II trial |
| STATISTICAL ANALYSIS | The present trial is designed as an explorative, single-arm phase II study which aims to estimate the therapeutic efficacy of an experimental combination regimen. ORR analysed according to the ITT principle is the primary efficacy endpoint. The efficacy assumptions are derived from historical data.<br>Descriptive analysis will be performed according to the study specific SAP. |
| SAMPLE SIZE | n=50 |
| TRIAL DURATION | ➢ Duration of recruitment: 13 months<br>➢ Maximum treatment duration will be 18 months (estimated 5 months median treatment duration)<br>➢ The individual follow-up period will end when all study patients have been followed for at least 6 months from their date of enrolment |
| PARTICIPATING CENTERS | 15 sites planned |

*Cholangiokarzinom, First Line*

**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**

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| Studiennummer/-Code: | AIO-HEP-0117 - IMMUCHEC |
| Status: | Rekrutierung (23 registriert / 23 randomisiert) |
| Rekrutierungszeitraum: | 2018 - 2019 |
| Weitere Zentren: | Aktuell nicht möglich |
| Letzte Aktualisierung | Oktober 2018 |

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| EudraCT No. | 2017-001538-25 |
| National Coordinating Investigator | Prof. Dr. med. Arndt Vogel<br>Klinik für Gastroenterologie, Hepatologie und Endokrinologie<br>Medizinische Hochschule Hannover<br>Carl-Neuberg-Str. 1, 30625 Hannover, Germany<br>Tel: +49 511-532-9590 , FAX.: +49-511-532-8392<br>E-Mail: vogel.arndt@mh-hannover.de |
| Sponsor | AIO-Studien-gGmbH<br>Dr. Aysun Karatas<br>Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431, Fax +49 30 322932926<br>info@aio-studien-ggmbh.de |
| Study design | phase II, open-label, three-arm, 1:1:1 randomized, non-comparative, |

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| | calibrated, multi-centre clinical trial |
| Anticipated start date | Q1/2018 |
| Duration of study | Enrollment: 18 month + 6 month treatment + 6 month FU<br>Total study duration: ~30 months |
| Indication | Advanced or metastatic CCA |
| Total number of sites | 15 (13 sites initiated) |
| 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 | **N=63 total** |
| Inclusion criteria | 1. Fully-informed written consent and locally required authorization (European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.<br>2. Age ≥ 18 years.<br>3. Histologically documented diagnosis of cholangiocarcinoma or gall bladder carcinoma and available tumor tissue (block or at least 10 slides) for translational research.<br>4. Performance status (PS) ≤ 1 (ECOG scale).<br>5. At least one measurable site of disease as defined by RECISTv1.1 criteria.<br>6. Adequate bone marrow and renal function including the following: Hemoglobin ≥ 9.0 g/dL; absolute neutrophil count ≥ 1.5 x $10^3$/L; platelets ≥100x $10^9$ /L; Creatinine ≤ 1.5 x upper normal limit.<br>7. Calculated creatinine clearance ≥40 mL/min as determined by the Cockcroft-Gault equation<br>8. Adequate hepatic function (with stenting for any obstruction, if required) including the following: Total bilirubin ≤ 2x upper normal limit; AST (SGOT), ALT (SGPT) ≤ 5 x upper normal limit; prothrombin time ≥ 60%; albumin ≥ 30 g/L.<br>9. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial.<br>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:<br>– Women <50 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).<br>– Women ≥50 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- |

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| | induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).<br>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. |
| Exclusion criteria | 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<br>2. Participation in another clinical study with an investigational product within 21 days prior to the first dose of the study treatment.<br>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.<br>4. Prior chemotherapy with gemcitabine and cisplatin (exception: gemcitabin in the adjuvant setting, last infusion has to be ≥ 6 months prior randomization).<br>5. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria<br>○ Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.<br>○ 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.<br>6. Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for 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).<br>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.<br>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.<br>9. History of allogenic organ transplantation.<br>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:<br>○ Patients with vitiligo or alopecia<br>○ Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement<br>○ Any chronic skin condition that does not require systemic therapy<br>○ Patients without active disease in the last 5 years may be included but only after consultation with the study physician<br>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<br>12. History of another primary malignancy except for: |

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| | ○ Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence<br>○ Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease<br>○ Adequately treated carcinoma in situ without evidence of disease<br>13. History of leptomeningeal carcinomatosis<br>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.<br>15. History of active primary immunodeficiency<br>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.<br>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:<br>○ Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)<br>○ Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent<br>○ Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)<br>18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IMP. **Note:** Patients, if enrolled, should not receive live vaccine whilst receiving IMP and up to 30 days after the last dose of IMP.<br>19. Body weight ≤30 kg.<br>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.<br>21. Known allergy or hypersensitivity to any of the IMPs or any of the constituents of the product.<br>22. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.<br>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.<br>24. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |
| Investigational medical products | • Durvalumab (MEDI4736)<br>• Tremelimumab<br><br>Standard chemotherapy:<br>• Cisplatin<br>• Gemcitabine |
| Treatment schedule | **Experimental arm 1 (arm A)** |

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| | • Gemcitabine will be administered at a dose of 1000 mg/m² 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.<br>• 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.<br>• 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).<br><br>**Experimental arm 2 (arm B)**<br>• Cisplatin will be administered over 1 hour at a dose of 25 mg/m² as an IV on day 1 and 8 of each 3-week cycle.<br>• Gemcitabine will be administered at a dose of 1000 mg/m² as an IV infusion over 30 minutes, on day 1 and 8 of each 3-week cycle.<br>• Both, gemcitabine and cisplatin, will be administered for up to a total of 24 weeks (8 cycles) according to the ABC-02 study.<br>• 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.<br>• 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 be administered, otherwise alone. After completion of chemotherapy durvalumab will be maintained at a dose of 1500 mg to be repeated every 3 weeks.<br><br>**Standard Arm (Arm C)**<br>• Cisplatin will be administered over 1 hour at a dose of 25 mg/m² as an IV on day 1 and 8 of each 3-week cycle.<br>• Gemcitabine will be administered at a dose of 1000 mg/m² as an IV infusion over 30 minutes, on day 1 and 8 of each 3-week cycle.<br>• Number of cycles will be left to the investigator`s discretion.<br><br>Treatment until progressive disease, unacceptable toxicity, withdrawal of consent or death. |
| Primary endpoint | Objective response rate (ORR) according to RECIST 1.1 |
| Secondary endpoints | • PFS<br>• OS<br>• Duration of Response<br>• AEs / SAEs and Treatment Emergent Adverse Events according to CTC 4.03<br>• Health related Quality of Life (HR-QoL) – EORTC-QLQ-C30 |
| Randomization procedure | 1:1:1 |
| Rationale | 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.<br><br>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 |

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| | 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 biliray 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 (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).<br>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.<br>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).<br>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 |

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| | 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.<br>**Hypothesis:**<br>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. |
| Safety data | • AEs / SAEs /Treatment Emergent Adverse Events according to CTCAE 4.03<br>• Frequency of abnormal laboratory parameters<br>• Immune related (ir)AEs of special interest will require additional reporting (e.g. colitis, hepatitis, hypophysitis, uveitis or pneumonitis, pancreatitis) |
| Sample size estimation | 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:<br>a) the objective response rate of the standard cisplatinum+gemcitabine treatment is 20% (historical control)<br>b) the objective response rates of each of the experimental treatments is 50%.<br><br>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 $\leq$ 20 % ($P_0$) against a one-sided alternative that the ORR ≥ 50 % ($P_A$). The test will be performed for each experimental treatment arm.<br>$H_0 : P \leq P_0 \quad H_A : P \geq P_A$<br>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 P ≤ 0.2 is rejected with a one-sided target error rate of alpha=0.05 (actual alpha 0.04). If the number of responses is 6 or less, the alternative hypothesis that P ≥ 0.5 is rejected with a target error rate of beta=0.2 (Power = 80%; actual beta 0.17).<br><br>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 **N=63**. |
| QoL measurements | EORTC-QLQ-C30 |

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| Study plan / time lines | First Patient In (FPI):<br>Last Patient In (LPI):<br>Last Patient Last Visit (LPLV):<br>End of follow-up period after LPLV:<br>Study report:<br>Publication: | Q1/2018<br>after approx. 18 month<br>after approx. 24 month<br>after approx. 30 month<br>after approx. 39 month<br>after approx..40 month |

**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)**

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| **AIO**-Studie | Eine Studie der Young-Medical-Oncologists (YMO) |
| Studiennummer/ - Code | AIO-YMO/HEP-0315 - NIFE |
| Status: | 22 Patienten rekrutiert, 22 randomisiert, 18 Zentren offen, Initiierungen laufen |
| Rekrutierungszeitraum: | 2017 - 2019 |
| Weitere Zentren: | 2 Plätze frei, bei Interesse bitte bei der AIO-Studien-gGmbH melden |
| Letzte Aktualisierung: | Oktober 2018 |

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| Coordinating Investigator | Prof. Dr. med. Thomas Seufferlein<br>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<br>Tel.: 030-322932934, FAX:030-322932926<br>E-Mail: info@aio-studien-ggmbh.de |
| Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologists! | |

*Cholangiozelluläres Karzinom, Secondline*

**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)**

**AIO- Studie**

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| Studiennummer/-Code: | AIO-HEP-0116 - NALIRICC |
| Status: | Rekrutierung (45 Patienten rekrutiert, 41 randomisiert) 17 Zentren offen |
| Rekrutierungszeitraum | 2017 - 2019 |
| Weitere Zentren: | 2 Plätze frei, bei Interesse bitte bei der AIO-Studien-gGmbH melden |
| Letzte Aktualisierung | Oktober 2018 |

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| National Coordinating Investigator | Prof. Dr. med. Arndt Vogel<br>Klinik für Gastroenterologie, Hepatologie und Endokrinologie<br>Medizinische Hochschule Hannover<br>Carl-Neuberg-Str. 1, 30625 Hannover, Germany<br>Phone: +49 511-532-9590, FAX.: +49-511-532-8392<br>E-Mail: vogel.arndt@mh-hannover.de |
| Co-Coordinator: | Dr. med Martha Kirstein<br>Klinik für Gastroenterologie, Hepatologie und Endokrinologie<br>Medizinische Hochschule Hannover<br>Carl-Neuberg-Str. 1, 30625 Hannover, Germany<br>Phone:+49-511-532-0 Fax:+49-511-532-8392<br>E-mail: kirstein.martha@mh-hannover.de |
| Sponsor | AIO-Studien-gGmbH<br>Dr. Aysun Karatas (CEO)<br>Kuno-Fischer-Straße 8, 14057 Berlin, Germany<br>Phone: +49 30 814534435, Fax +49 30 322932926<br>E-Mail: info@aio-studien-ggmbh.de |
| Study design | open label, randomized, multicenter phase II trial |
| Start date | FPI Dec-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 | 1. Written informed consent incl. participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) |

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| | obtained from the subject prior to performing any protocol-related procedures, including screening evaluations<br>2. Age ≥ 18 years at time of study entry<br>3. Histologically or cytologically confirmed, non-resectable, locally advanced or metastatic cholangiocarcinoma or gall bladder carcinoma<br>4. Measurable or assessable disease according to RECIST 1.1<br>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:<br>a) Single agent gemcitabine<br>b) Any one gemcitabine-based regimen, with or without maintenance gemcitabine<br>6. ECOG performance status 0-1<br>7. Adequate blood count, liver-enzymes, and renal function:<br>• ANC > 1,500 cells/µL without the use of hematopoietic growth factors; and<br>• Platelet count ≥ 100 x 109/L (>100,000 per mm3) and<br>• Hemoglobin > 9 g/dL (blood transfusions are permitted for patients with hemoglobin levels below 9 g/dL)<br>• Serum total bilirubin ≤ 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):<br>• Albumin levels ≥ 3.0 g/dL<br>• Patients not receiving therapeutic anticoagulation must have an INR < 1.5 ULN and PTT < 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<br>• AST (SGOT)/ALT (SGPT) ≤ 5 x institutional upper limit of normal<br>• Serum Creatinine ≤ 1.5 x ULN and a calculated glomerular filtration rate ≥ 30 mL per minute<br>8. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of treatment.<br>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. |
| Exclusion criteria | 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<br>2. Clinically significant gastrointestinal disorder including bleeding, inflammation, occlusion, or diarrhoea > grade 1<br>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.<br>4. Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes or an unexplained fever > 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. |

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| | 5. Premalignant hematologic disorders, e.g. myelodysplastic syndrome<br>6. Pre-esxisting lung disease<br>7. Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment<br>8. History of hypersensitivity to any of the study drugs or any excipient (nal-IRI, other liposomal products, fluropyrimidines or leucovorin)<br>9. Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy<br>10. Severe non-healing wounds, ulcers or bone fractions<br>11. Evidence of bleeding diathesis or coagulopathy<br>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.<br>13. Medication that is known to interfere with any of the agents applied in the trial.<br>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].<br>15. Known Gilbert-Meulengracht syndrome<br>16. 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<br>17. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 5 half-lifes of previously used trial medication, whichever is of longer duration.<br>18. Previous enrollment or randomization in the present study (does not include screening failure).<br>19. Previous enrollment in the NIFE trial [AIO-YMO/HEP-0315]<br>20. Involvement in the planning and/or conduct of the study (applies to both Baxalta staff and/or staff of sponsor and study site)<br>21. Patient who might be dependent on the sponsor, site or the investigator<br>22. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |
| Investigational agents and active comparators | • IRINOTECAN LIPOSOME (MM-398, nal-IRI)<br>• 5-Fluorouracil,<br>• leucovorin (calcium folinate) |
| Treatment schedule | <u>Experimental intervention (Arm A):</u><br>• nal-IRI 80 mg/m$^2$ as a 1.5 hour infusion<br>• 5-FU 2400 mg/m$^2$ as 46 hour infusion<br>• leucovorin 400 mg/m$^2$ as 0.5 hour infusion<br>• Cycle q2w<br><br><u>Control intervention – standard arm (Arm B):</u><br>• 5-FU 2400 mg/m$^2$ as 46 hour infusion |

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| | • leucovorin 400 mg/m$^2$ as 0.5 hour infusion<br>• Cycle q2w<br>In both study arms treatment continues until progressive disease or intolerable toxicity or withdrawal of consent.<br><br>**Key study procedures (and routine procedures):**<br>• Tumor assessment according to standard of care Q6W<br>• Monitoring of serum tumor markers (Ca19-9, CEA, CRP) before and during therapy.<br>• Blood sampling of 35 mL Q6W for translational research |
| Primary endpoint | Progression-free survival |
| Secondary endpoints | • Overall survival<br>• Objective response rate (ORR)<br>• Safety (type, grade and frequency of AEs/SAEs)<br>• QoL – EORTC QLQ C30 |
| Exploratory objectives and endpoints | To assess prognostic biomarker in the serum and in tumor tissue and correlation with survival and response to treatment:<br>• Ca-19-9, CEA, CRP serum levels before the beginning of treatment and during treatment.<br>• Immunohistochemistry of Carboxylesterase (CES) 1 and 2 before treatment<br>• Whole blood and plasma will be collected to potentially identify factors that may correlate with tumour response, sensitivity or resistance to nal-IRI. |
| Randomization procedure | 1:1<br><br>Stratified permutated block randomization will be applied to ensure balanced prognostic groups.<br><br>The stratification parameter will be tumor localization:<br>• Intrahepatic CCA (ICCA)<br>• Extrahepatic CCA (ECCA)<br>• Gallbladder CA (GB) |
| Rationale<br>Hypothesis | 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 (Berqquist 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).<br>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).<br>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 |

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| | 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). 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).<br><br>**Research hypothesis:**<br>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. |
| Safety data | • Treatment Emergent Adverse Events according to CTC 4.03<br>• Frequency of abnormal laboratory parameters |
| Sample size estimation | 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 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.<br>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.<br>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).<br>In order to achieve balanced treatment arms it is proposed to recruit **N=100** patients into the study.<br>For the final efficacy analysis a total of 96 observed events are required. |
| Study plan / time lines | First Patient In (FPI): Q4/2017<br>Last Patient In (LPI): after approx. 24 months<br>Last Patient Last Visit (LPLV): after approx. 27 months<br>End of follow-up period after LPLV: after approx. 31 months<br>Study report: after approx. 42 months<br>Publication: after approx. 45 months |

*Cholangiokarzinom (intra- und extrahepatisch), Gallenblasenkarzinom, Secondline*

**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) |
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| Studiennummer: | AIO-YMO/HEP-0316 |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum: | 2017 – 2019 |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | Oktober 2018 |

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| Verantwortlicher Studienleiter nach AMG | Prof. Dr. Oliver Waidmann |
| Kontaktadresse/ Kontaktperson: | Prof. Dr. Oliver Waidmann<br>Universitätsklinikum Frankfurt<br>Medizinische Klinik 1<br>Theodor-Stern-Kai 7<br>60590 Frankfurt am Main<br>0049-69-6301-5122<br>0049-69-6301-6580<br>E-Mail: oliver.waidmann@kgu.de |
| 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 | |
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| Studiennummer: | AIO-HEP-0112 - ACTICCA-1 |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | ab 2014 |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | Oktober 2017 |

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| 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 |

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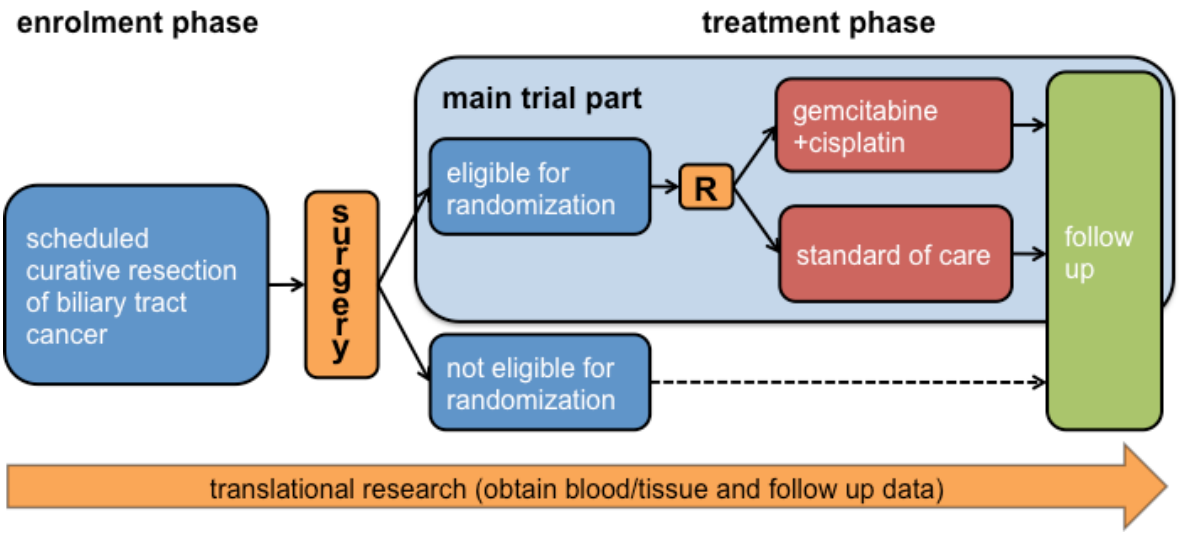
| Principle Investigator | Henning Wege, Hamburg |
| Sponsor | Universitätsklinikum Hamburg-Eppendorf<br>Funded by Deutsche Krebshilfe and medac GmbH (Germany)<br>International funding by Cancer Research UK, KWF Kanker Bestrijding The Netherlands, AGITG Australia |
| Contact | Studienkoordination:<br>Alexander Stein, Universitäres Cancer Center Hamburg<br>E-Mail: a.stein@uke.de E-Mail: acticca@uke.de |
| Endpoints | Primary endpoints:<br>• Disease free survival (DFS)<br>Secondary endpoints:<br>• Disease free survival rate at 24 months (DFSR@24)<br>• Recurrence free survival<br>• Overall survival (OS)<br>• Safety and tolerability of adjuvant chemotherapy<br>• Quality of life (QoL)<br>• Function of biliodigestive anastomosis (in terms of surgical revision, requirement of PTCD)<br>• Rate and severity of biliary tract infections<br>• Patterns of disease recurrence<br>• Locoregional control |
| Number of patients/sites | 781 patients to be randomized, 187 I in stage 1 and 594 in stage 2.<br>20 sites in Germany / 5 sites in the Netherlands / >20 sites in United Kingdom<br>8-10 sites in Australia / 2 sites in Denmark / 1 site in Austria |
| Start of recruitment | QII 2014 / Current status 18 OCT 2018: 334 pts included/304 pts randomized |
| Study duration | Duration of recruitment (stage 2): 48 months.<br>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 | 1. Histologically confirmed adenocarcinoma of biliary tract (intrahepatic, hilar or extrahepatic cholangicarcinoma or muscle invasive gallbladder cancer) after radical surgical therapy with macroscopically complete resection (mixed tumor entities (HCC/CCA) are excluded<br>2. Macroscopically complete resection (R0/1) within 6(-16) weeks before start of chemotherapy<br>3. No prior chemotherapy for CCA<br>4. Written informed consent<br>5. ECOG 0-1<br>6. Age >18 years<br>7. Adequat haematologic function: ANC ≥1.5 x $10^9$/L, platelets ≥100 x$10^9$/L, haemoglobin ≥9 g/dl or ≥5.59 mmol/L<br>8. Adequate liver function as measured by serum transaminases (AST and ALT) ≤5 x ULN and conjugated (direct) bilirubin ≤3 x ULN<br>9. Adequate renal function, i.e. serum creatinine ≤1.5 x ULN, glomerular filtration rate ≥50 mL/min |

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| Treatment, dosage and administration | 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.<br>**Arm A: Gemcitabine/cisplatin and observation**<br>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).<br>**Arm B: Capecitabine and observation**<br>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).<br>**Observation**<br>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.<br>**Duration of treatment**<br>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. |

*Registerstudie Gallenblasenkarzinom*

**AIO-HEP-0118/ass: Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone with or without adjuvant chemotherapy in incidentally detected gallbladder carcinoma after simple cholecystectomy or in front of radical resection of BTC (ICC/ECC) – A phase III study utilizing the German Registry of Incidental Gallbladder Carcinoma Platform (GR) – The AIO/ CALGP/ ACO- GAIN-Trial -**

| **AIO-assoziierte Studie** | |
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| Studiennummer/-Code: | AIO-HEP-0118/ass |
| Status: | in Vorbereitung; Förderantrag der DFG ist genehmigt, Einreichung 2018 |
| Rekrutierungszeitraum: | Studienstart 2018, 4 Jahre Rekrutierung |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | 25.05.2018 |

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| STUDY TYPE | Multicenter, randomized, open label phase III study |
| PRINCIPAL INVESTIGATOR | Priv.Doz. Dr. med. Thorsten Oliver Götze<br>Institute of Clinical Cancer Research (IKF)<br>UCT- University Cancer Center Frankfurt, Krankenhaus Nordwest<br>Steinbacher Hohl 2-26, 60488 Frankfurt am Main<br>Tel.: +49 69 7601-4187; Fax -3655<br>Email: goetze.thorsten@khnw.de |
| TRIAL OFFICE / SPONSOR | IKF Klinische Krebsforschung GmbH<br>at Krankenhaus Nordwest<br>Steinbacher Hohl 2-26<br>60488 Frankfurt am Main |
| CONDITION | Cholangiocarcinoma |
| DESIGN | This is a multicenter, randomized, controlled, open-label phase III study including patients with pT2-3 incidentally discovered gallbladder carcinomas (IGBC/ 70% of all GBC`s) after simple cholecystectomy and patients with resectable/ borderline resectable cholangiocarcinomas (ICC/ ECC) scheduled to receive perioperative chemotherapy or surgery alone.<br><br>Potential study participants will be assessed for eligibility during a 28-day screening period. Eligible patients will be enrolled and randomized to perioperative chemotherapy (Arm A) or immediate surgery alone with or without adjuvant chemotherapy (investigator's choice) (Arm B). Randomization will occur in a 1:1 ratio with stratification by clinical tumor stage (T1 and T2 vs. T3 and T4 (T1 and T4 not applicable for IGBC)), ECOG (0 and 1 vs. 2) and location of the primary (ICC vs. ECC vs. IGBC).<br><br>Neoadjuvant chemotherapy with gemcitabine plus cisplatin will be administered for 3 cycles preoperatively followed by radical liver resection versus immediate radical liver resection alone with or without adjuvant chemotherapy (investigator's choice) in incidentally detected T2-3 gallbladder carcinoma after simple cholecystectomy or in front of radical resection of Biliary Tract Cancer (ICC/ECC). After the radical tumor resection again 3 cycles postoperative chemotherapy will be administered in the experimental arm. In the standard (control) arm no perioperative chemotherapy will be administered. After surgery adjuvant chemotherapy can be administered by investigator's choice. |

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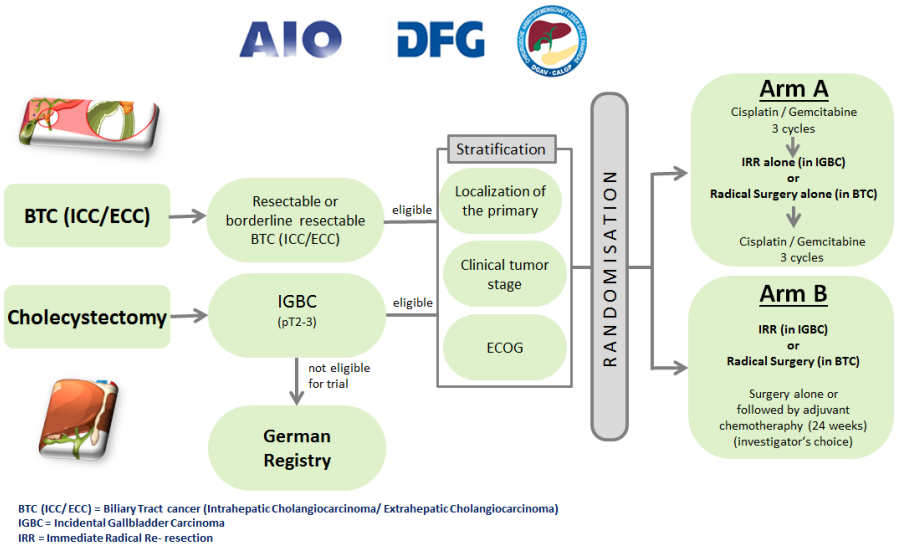
| | **Arm A (gemcitabine plus cisplatin)**<br><br>Patients assigned to arm A will receive gemcitabine (1000 mg/m$^2$) plus cisplatin (25 mg/m$^2$) every three weeks on days 1 and 8 intravenously. Treatment with gemcitabine plus cisplatin will be administered for 3 cycles preoperatively (neoadjuvant part) and for 3 cycles postoperatively (adjuvant part). In case of progressive or recurrent disease, unacceptable toxicity, or withdrawal of consent, treatment will be terminated.<br><br>**Arm B (standard postoperative management)**<br><br>Patients assigned to arm B will receive surgery immediately, without receiving perioperative chemotherapy (Standard of Care / SOC). After surgery adjuvant chemotherapy can be administered by investigator's choice.<br><br>In both of the treatment arms, tumor assessments (CT or MRI) are performed before randomization and prior to surgery. Therefore, in patients randomized to Arm A (surgery + chemotherapy) there will be an additional staging before the surgical procedure, after completing 3 cycles of chemotherapy. After surgery, tumor assessments are performed every 3 months 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.<br><br>During treatment, clinical visits (blood cell counts, detection of toxicity) occur prior to every treatment dose. Safety of Cis/ Gem will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.<br><br>  <br>**Figure 1: Study Scheme.** |
| INDICATION | Incidental gallbladder carcinoma (IGBC) or in front radical resection in biliary tract cancer (BTC) (intrahepatic cholangiocarcinoma (ICC)/ extrahepatic cholangiocarcinoma (ECC)) |
| OBJECTIVE(S) | The aim of the study is to investigate whether induction chemotherapy followed by radical re-resection (and - if possible - postoperative chemotherapy) in incidental gallbladder carcinoma (IGBC) or in front radical resection in biliary tract cancer (BTC) (intrahepatic cholangiocarcinoma (ICC)/ extrahepatic cholangiocarcinoma (ECC)) prolongs overall survival without impaired quality of life compared to immediate radical surgery alone with or without adjuvant chemotherapy (investigator's choice) in patients with IGBC, or BTC (ICC/ECC). One of the most important secondary objectives is to raise awareness for the necessity of a radical second surgery as well as to improve the adherence to the treatment guidelines in IGBC. Further secondary objectives are safety and tolerability of the treatment as well as quality of life.<br><br>Safety Objectives |

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| | • To evaluate the safety and tolerability of neoadjuvant, respectively perioperative chemotherapy plus surgery compared with immediate surgery alone with or without adjuvant chemotherapy (investigator's choice) in patients with incidentally detected T2-3 gallbladder carcinoma after simple cholecystectomy in front of radical re-resection in IGBC or in front of radical resection in BTC (ICC/ECC), focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities<br>• To evaluate the perioperative morbidity and mortality |
| INTERVENTION(S) | <u>Arm A (gemcitabine plus cisplatin)</u><br>Patients assigned to arm A will receive treatment with gemcitabine plus cisplatin. Chemotherapy will be administered for 3 cycles preoperatively (neoadjuvant part) and for 3 cycles postoperatively (adjuvant part). In case of progressive or recurrent disease, unacceptable toxicity, or withdrawal of consent, treatment will be terminated.<br>• Cisplatin (25 mg/m2) every three weeks on days 1 and 8 intravenously, in 1000 ml 0.9% saline with KCl 20 mmol and MgSO4 8 mmol during the one hour cisplatin infusion followed by 500 ml 0.9% saline over 30 minutes prior to gemcitabine; with adequate pre- and posthydration<br>• Gemcitabine (1000 mg/m2) in 250-500 ml 0.9% saline every three weeks on days 1 and 8 intravenously<br><br><u>Arm B (standard postoperative management)</u><br>Patients assigned to arm B will receive surgery directly, without receiving perioperative chemotherapy (Standard of Care / SOC). After surgery adjuvant chemotherapy can be administered by investigator's choice. In case of progressive or recurrent disease, unacceptable toxicity, or withdrawal of consent, adjuvant treatment will be terminated. |
| BACKROUND/RATIONALE | Currently, complete surgical resection represents the only potentially curative treatment option for Biliary tract cancer (BTC; Intrahepatic Cholangiocarcinoma/ Extrahepatic Cholangiocarcinoma) and Gallbladder Carcinoma, and is therefore the treatment of choice if the respective tumor is deemed resectable (Bridgewater et al., 2014).<br>However, more than 50% of patients already exhibit unresectable disease at the time of diagnosis (Glimelius et al., 1996; Sharma et al., 2010).<br>Even after curative resection, 5-year overall survival (OS) is only 20–40 % (Anderson & Kim, 2009; Choi et al., 2009; Guglielmi et al., 2009; Li et al., 2009; Murakami et al., 2011; Nuzzo et al., 2010; Saxena, Chua, Sarkar, Chu, & Morris, 2010; Tamandl et al., 2008). Van der Gaag and colleagues evaluated the long-term outcome of 175 consecutive patients with resected extrahepatic CCA (Cholangiocarcinoma) (van der Gaag et al., 2012). In this study, the 2-year OS was 50% and declined to 26% after five years. In summary, following complete resection of CCA, patients had DFS rates of 48 to 65% after one year and 23 to 35% after three years without adjuvant treatment (Choi et al., 2009; Takada et al., 2002; Tamandl et al., 2008). Patients with a positive nodal status (N1) and/or vascular invasion (V1) at time of resection had an even higher risk of disease recurrence.<br>Gallbladder carcinoma is relatively rare, but still the fifth most common neoplasm of the digestive tract and even the most frequent cancer of the biliary system (Goetze, 2015). Gallbladder carcinoma is suspected preoperatively in only 30% of all patients (Goetze & Paolucci, 2006; Paolucci, Neckell, & Goetze, 2003), while the majority of cases are discovered incidentally by the pathologist (IGBC) after cholecystectomy for a benign indication. All reported cases of IGBC in Germany are registered in the "German Registry of Incidental Gallbladder Carcinoma" also known as "CAES-/ CAMIC- Zentralregister", the largest casebook of gallbladder carcinomas in Europe, overseen by the principal investigator of this proposal |

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| | protocol (Goetze & Paolucci, 2006, 2008a, 2008b, 2009, 2010, 2012, 2013, 2014a, 2014b; C. N. Gutt et al., 2013; Paolucci et al., 2003). The GR shows that surgical management of gallbladder cancer remains inadequate despite widely published guidelines (Goetze & Paolucci, 2008a). Less than 50% of the patients received stage adjusted therapy according to the GR (Goetze & Paolucci, 2014c). Stage adjusted therapy according to the S3 Guidelines contains liver resection in the form of wedge resection of the gallbladder bed with a 3 cm margin in the liver, or a resection of liver segments 4b and 5, always combined with dissection of the regional lymph nodes along the hepatoduodenal ligament in cases of T2 (T1b, respectively – according to the new S3-Guidelines effective from 2017) or more advanced carcinomas (C. Gutt et al., 2018). Using the data of n = 930 IGBC patients contained in the GR, our group has shown that there is no need for an IRR in T1a- stage carcinomas. But – strikingly – in T1b-stage there is a significant improvement of OS (45% vs. 75%) after IRR. This applies also for T2- (22% vs. 38%) and T3- (12% vs. 18%) stages (Goetze & Paolucci, 2014a, 2014b). Gallbladder neoplasms shows a high incidence of locoregional failure after surgical resection, with early spread to celiac, retropancreatic, and aortocaval nodes and occult liver spread (Endo et al., 2004) in formally R0 patients after simple cholecystectomy (SC). The rate of positive lymphatic nodes is 31.2% in T2- and 45.5% in T3-stage carcinomas (Bartlett, Fong, Fortner, Brennan, & Blumgart, 1996; Endo et al., 2004). Lymphatic spread beyond the hepatoduodenal ligament generally represents distant metastatic disease, and a cure of such patients by a pure surgical concept does not seem to be achievable.<br>Therefore, there is a need for a systemic therapy as early as possible in the course of treatment in IGBC`s and also in BTC (ICC/ECC).<br>The landmark trial, UK ABC-02 by Valle et al. (Valle et al., 2010) compared gemcitabine/cisplatin with gemcitabine alone in locally advanced or metastatic cholangio- and gallbladder carcinomas and showed clear superiority of the combination, with significant improvements for PFS (8 vs. 5 months, p<0.001) and OS (8.1 vs. 11.7 months, P<0.001). Basically, the study indicates the sensitivity of this disease towards chemotherapy and provides a rationale for the use of this chemotherapeutic doublet in the present study.<br>For improving disease control and cure rates in BTC (ICC/ ECC) and of IRR in T2-3 IGBC`s, it is meaningful to implement early additional systemic therapy. The earliest moment to apply chemotherapy would be directly after simple cholecystectomy in IGBC`s and right before surgery in ICC/ECC. The encouraging results of neoadjuvant/perioperative concepts in esophagogastric, stomach, rectal, and other malignancies provide an additional rationale to use this treatment in the early phase of IGBC management and even ICC/ECC. However, due to the fact that 2/3 of gallbladder carcinomas are incidental findings after SC, an earlier start of a systemic therapy in IGBC will be not realizable. Furthermore, preoperatively discovered gallbladder carcinomas are usually too advanced for neoadjuvant/perioperative concepts.<br>Recently the results of two randomized trials were presented which evaluate the role of either gemcitabine and oxaliplatin (PRODIGE 12) or capecitabine (BILCAP) compared to observation alone. The primary endpoint of PRODIGE 12 trial was Relapse-Free Survival. The study showed no significant benefit according to Relapse-Free Survival and Overall Survival. Therefore, the authors conclude that there was no benefit for GEMOX over surveillance in the adjuvant setting and GEMOX chemotherapy was not recommended in the adjuvant setting (Edeline et al., 2017).<br>The most recent results of the BILCAP trial ("Capecitabine Extends Survival for Biliary Tract Cancer," 2017) in 447 patients showed a significantly improved OS again only in the PP-population. In a sensitivity analysis, adjusting for further prognostic factors (nodal status, disease grade and gender) there was a significant benefit for adjuvant chemotherapy. However, in the overall ITT-population the trial was negative and there was no |

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| | significance for the delta of 15 months even if the authors define a new standard, describing a gain in OS of 15 months due to adjuvant therapy.<br>To conclude there are trends for an improvement in OS due to adjuvant therapy, but data showing a significant improvement for adding adjuvant therapy after a curative resection are lacking.<br>Because of high rates of disease recurrence and poor survival rates in IGBC and ICC/ECC following surgical resection and the inadequacy of treatment modalities in the pure adjuvant therapy there is a need for an earlier intervention in the course of the disease. Due to the prognostic improvements of patients in other tumor entities (gastric, colorectal e.g. (Al-Batran et al., 2016; Cunningham et al., 2006) treated with neoadjuvant or perioperative therapy there is a strong rationale to use these concepts in biliary and gallbladder cancers. |
| KEY EXCLUSION CRITERIA | 1. Known hypersensitivity against gemcitabine or cisplatin<br>2. Other known contraindications to gemcitabine or cisplatin<br>3. Unresolved biliary tract obstruction<br>4. Clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV<br>5. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.<br>6. Clinically significant valvular defect<br>7. 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<br>8. Locally unresectabe tumor or metastatic disease:<br>- Radiological evidence suggesting inability to resect with curative intent whilst maintaining adequate vascular inflow and outflow, and sufficient future liver remnant<br>- Radiological evidence of direct invasion into adjacent organs<br>- Radiological evidence of extrahepatic metastatic disease<br>9. Other severe internal disease or acute infection<br>10. Chronic inflammatory bowel disease<br>11. Receiving chronic antiplatelet therapy, including aspirin (Once-daily aspirin use (maximum dose 325 mg/day) is permitted), nonsteroidal anti-inflammatory drugs (including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents.<br>12. 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 3 months prior to randomization.<br>13. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or ascites.<br>14. On-treatment participation in another clinical study 30 days prior to inclusion and during the study<br>15. Pregnant or breast feeding patient, or patient is planning to become pregnant within 7 months after the end of treatment.<br>16. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)<br>17. Any other concurrent antineoplastic treatment including irradiation |
| KEY INCLUSION CRITERIA | 1. Histologically/cytologically confirmed IGBC (T2-3 after Cholecystectomy) and BTC (intrahepatic, hilar or distal CCA) scheduled for complete resection (mixed tumor entities with hepatocellular carcinoma are excluded)<br>2. No prior partial or complete tumor resection for BTC (intrahepatic, hilar or distal CCA), for IGBC (T2-3) prior Cholecystectomy is allowed |

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| | 3. Exclusion of distant metastases by CT or MRI of abdomen, pelvis, and thorax, bone scan or MRI (if bone metastases are suspected due to clinical signs). Exclusion of the infiltration of any adjacent organs or structures by CT or MRI, indicating an unresectable situation<br>4. ECOG performance status of 0, 1, or 2<br>5. Estimated life expectancy > 3 months<br>6. Age >18 years.<br>7. Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures<br>8. No previous or preceding cytotoxic or targeted therapy for BTC or IGBC.<br>9. No previous malignancy within three years or concomitant malignancy, except non-melanomatous skin cancer or adequately treated in situ cervical cancer.<br>10. No severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction in the last three months, significant arrhythmia).<br>11. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent.<br>12. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to participate in the trial.<br>13. Fertile women (<1 year after last menstruation) and procreative men willing and able to use effective means of contraception during the study and 7 months after the end of the study (appropriate contraception is defined as surgical sterilization (e.g., bilateral tubal ligation, vasectomy), and hormonal contraception (implantable, patch, oral). Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.<br>14. No pregnancy or lactation.<br>15. Adequate hematologic function: ANC ≥ 1.5 × 109/L, platelets ≥ 100 × 109/L, hemoglobin ≥ 9 g/dl or ≥ 5.59 mmol/L. *prior transfusions for patients with low haemoglobin are allowed<br>16. Adequate liver function as measured by serum transaminases (AST and ALT) ≤ 5 x ULN and bilirubin ≤ 3 x ULN.<br>17. Adequate renal function, i.e. serum creatinine ≤ 1.5 x ULN, glomerular filtration rate ≥ 60 mL/min determined with the MDRD formula.<br>18. Adequate coagulation functions as defined by International Normalized Ratio (INR) ≤ 1.5, and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin/ phenprocoumon must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to randomization.<br>19. No active uncontrolled infection, except chronic viral hepatitis under antiviral therapy (patients on long-term antibiotics are eligible provided signs of active infection have been resolved).<br>20. No concurrent treatment with other experimental drugs or other anti-cancer therapy, treatment in a clinical trial within 30 days prior to randomization.<br>21. Negative serum pregnancy test within 7 days of starting study<br>treatment in pre-menopausal women and women <1 year after the onset of menopause |
| OUTCOME(S) | <u>Primary efficacy endpoint</u><br>• Primary efficacy endpoint is overall survival (OS)<br><u>Secondary efficacy endpoints</u><br>• Quality of life (EORTC QLQ- C30) |

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| | • PFS rates at 3 and 5 years<br>• OS rates at 3 and 5 years<br>• progression free survival (PFS)<br>• R0- resection rate<br>• Toxicity, graded using CTC adverse events criteria version CTCAE V 5.0<br>• perioperative morbidity and mortality (30 days and 90 days mortality/morbidity) |
| SAMPLE SIZE | A total of n = 333 patients with IGBC or ICC/ECC will be included in the study with 10% drop out expected. Therefore, 300 patients will be allocated to the trial and analyzed as intention-to-treat basis. |
| TRIAL DURATION | Recruitment period (months): 4 years (48 months)<br>Duration of follow-up: overall 2 years (24 months), every 3 months<br>Duration of the entire trial (first patient in to last patient out): 6 years (72 months). The study can be analyzed earlier or later depending on the number of events. |
| PARTICIPATING CENTERS | Up to 50 sites in Germany |
| NUMBER of PATIENTS | N=330 |

# Interdisziplinäre Arbeitsgruppe Hodentumoren

*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**

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| Studiennummer/-Code: | AIO-GC-0716/ass |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2016 – 2018 |
| Weitere Zentren: | sind erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Art der Studie<br>Study Type | Retrospektive Registerstudie |
| Verantwortlicher Studienleiter nach AMG | Prof. Dr. med. Carsten Bokemeyer |
| Kontaktadresse/<br>Kontaktperson: | PD Dr. med. Christoph Seidel<br>II. Medizinische Klinik & Poliklinik<br>Universitätsklinikum Hamburg-Eppendorf<br>Tel.: (+49) 040 7410 0<br>Fax: (+49) 040 7410 55234 |
| Studienziele/<br>Objectives | Primärer Endpunkt: Verteilung und Charakteristika einer Tumormarkererhöhung<br>Sekundäre Endpunkte: Zusammenhänge zwischen Tumormarker und Patienten- sowie Krankheitscharakteristika |
| Zielparameter/<br>Objectives | ß-HCG Wert, Tumorgröße, Metastasierungsmuster, Primärtumorlokalisation, Stadium, Therapieansprechen, Restvitalität, Rezidivrate, PFS und OS |
| Patientenzahl<br>Number of patients | Geplant: ca. 1000 Patienten |
| Haupt-Einschlusskriterien /<br>Key inclusion criteria | Histologisch nachgewiesenes reines Seminom, ß-HCG Wert über Normbereich bei Erstdiagnose, männliches Geschlecht, Alter > 18 Jahre, alle Tumorstadien, keine AFP-Erhöhung nachweisbar. |
| Therapieschema<br>Scheme of therapy | Retrospektive Datenerhebung anhand von CRFs, keine Vorgabe eines Therapieregimes |
| Tumorevaluierung<br>Criteria for evaluation | Retrospektive Erfassung des Krankheitsverlaufs und Überlebens |
| Rationale | Mäßiggradige Erhöhungen des Tumormarkers ß-HCG finden sich bei etwa 30% aller Patienten mit reinem Seminom. Bisher existieren keinerlei Daten dazu, wie der ß-HCG Wert mit spezifischen Charakteristika dieser Patienten korreliert und welche therapeutischen und prognostischen Konsequenzen dadurch entstehen könnten.<br>Durch dieses Register sollen diese Fragen beantwortet werden. |

*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**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | AIO-GC-0416/ass |
| Status: | Studienstart in Deutschland im Mai 2018 erfolgt (1. Studienzentrum eröffnet) |
| Rekrutierungszeitraum | Aktuell bis vorausichtlich 2022 |
| Weitere Zentren: | sind erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Art der Studie | Phase-III; international, multizentrisch |
| Verantwortlicher Studienleiter nach AMG | Sponsor USA: Alliance; Darren Feldman; New York<br>Sponsor Europa: EORTC; Thomas Powles MD; London<br>Weiterer Sponsor: Movember<br>Deutschland gefördert durch die Deutsche Krebshilfe<br>PI für Deutschland: Prof. Dr. med. Anja Lorch, Düsseldorf |
| Kontaktadresse/ Kontaktperson: | Univ.-Prof. Dr. med. Anja Lorch<br>FÄ Hämatologie und Onkologie<br>Leitung Bereich kons. urolog. Onkologie<br>Klinik für Urologie<br>Universitätsklinikum Düsseldorf<br>Tel.: 0211- 81 08776<br>Fax: 0211- 81 04640<br>anja.lorch@med.uni-duesseldorf.de |
| Studienziele/ Objectives | Primäres Studienziel: Overall survival<br>Sekundäres Studienziel: Progression-Free Survival (PFS)<br>Favorable Response Rate (CR + PR-neg markers); Toxicity<br>Prospective Evaluation of the IPFSG Prognostic Model |
| Zielparameter/ Objectives | OS, PFS, Favorable Response Rate (CR + PR-neg markers); Toxicity<br>Prospective Evaluation of the IPFSG Prognostic Model<br>Biologic correlates |
| Patientenzahl Number of patients | Geplant Gesamtstudie: 420 Patienten, pro Arm jeweils 210 Patienten<br>Aus Deutschland: geplanter Einschluß von etwa 70-75 Patienten<br>Studie in den USA in 08/16 gestartet, Studienstart in Europa im Sommer 2017 erfolgt. Start in Deutschland im Mai 2018 erfolgt (erstes Studienzentrum eröffnet; bislang noch keine Patienten eingeschlossen) |
| Rekrutierungzeitraum von/bis period of | Initial 08/16 – 08/20 für alle Zentren weltweit, jedoch Verlängerung bis 2022 geplant, auf Grund verspäteter Initiierungen an allen europäischen Zentren incl. Deutschland. |
| Weitere teilnehmende Zentren erwünscht? | Folgende Zentren in Deutschland sind derzeit bereits initiiert:<br>UK Düsseldorf, UK Hamburg-Eppendorf, Rot-Kreuz Klinikum München<br>Folgende Zentren in Deutschland werden noch initiiert:<br>Berlin Charite, UK Dresden, UK Essen, Städtisches Klinikum Koblenz, UK Marburg, UK Nürnberg, UK Ulm |
| Haupt-Einschlusskriterien / Key inclusion criteria | Male gender<br>Age ≥ 18 years for Germany<br>ECOG Performance Status 0 to 2 |

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| | GCT histology (Seminoma and Nonseminoma)<br>Unequivocal progression of measurable disease following one line of cisplatin-based chemotherapy<br>Unequivocal progression of non-measurable disease with consecutive elevated markers following one line of cisplatin-based chemotherapy<br>A minimum of three and maximum of six cisplatin-based treatment cycles<br>No more than one prior line of chemotherapy for GCT<br>Patients with late relapses who have unresectable disease<br>Completion of a full informed consent |
| Therapieschema<br>Scheme of therapy | 4 Zyklen konventionelle Chemotherapie TIP **versus**<br>3 Zyklen CE- Hochdosischemotherapie |
| Tumorevaluierung<br>Criteria for evaluation | Marker und Bildgebung Baseline, unter Therapie und im Rahmen der Nachsorge, Lebensqualitätsbogen QLQ-C30 |
| Rationale | 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).<br>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.<br>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.<br>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.<br>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 Gesamtüberleben. Allerdings wurden die Daten wegen des retrospektiven Ansatzes von kritischen Experten nicht als ausreichenden Beleg erachtet.<br>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. 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.<br>Die Studie wird in internationaler Zusammenarbeit als „Intergroup Trial“ durchgeführt.<br>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. |

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| | 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.<br>Die Durchführung des Forschungsvorhabens in Deutschland wird in Kooperation mit einem Koordinierungszentrum für Klinische Studien (KKS) als CRO erfolgen. |

*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")**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | AIO-GC-0516/ass |
| Status: | aktiv |
| Rekrutierungszeitraum | 2017 – 2019 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Art der Studie<br>Study Type | Retrospektive Registerstudie |
| Verantwortlicher Studienleiter nach AMG | Prof. Dr. med. Carsten Bokemeyer |
| Kontaktadresse/ Kontaktperson: | Dr. med. Christoph Oing<br>II. Medizinische Klinik & Poliklinik<br>Universitätsklinikum Hamburg-Eppendorf<br>Fax: (+49) 040 7410 55139<br>Email: c.oing@uke.de |
| Studienziele/ Objectives | Primärer Endpunkt: PFS und OS unter palliativer Systemtherapie<br>Sekundäre Endpunkte: Therapieanprechen, Tumormarkerverlauf, Organfunktionen, Todesursachen, Symptome, Vortherapien |
| Zielparameter/ Objectives | Vortherapien, Therapieansprechen (CR/PR/SD/PD), PFS, OS, Tumormarkerverlauf, Organfunktionen, Todesursachen, Symptomlast |
| Patientenzahl<br>Number of patients | Geplant: ca. 250 Patienten |
| Rekrutierungzeitraum von/bis<br>period of | 12/2016 bis voraussichtlich 03/2019 |
| Weitere teilnehmende Zentren erwünscht? | Ja |
| Haupt-Einschlusskriterien / | Männliches Geschlecht; metastasierter Keimzelltumor; Cisplatin-refraktäre Erkrankung; Systemtherapie (Mono- und Kombinationschemotherapie) in |

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| Key inclusion criteria | palliativer Intention; Versagen von mindestens 2 Vortherapien (inkl. Hochdosischemotherapie) |
| Therapieschema<br>Scheme of therapy | Retrospektive Datenerhebung anhand von CRFs, keine Vorgabe eines Therapieregimes |
| Tumorevaluierung<br>Criteria for evaluation | Retrospektive Erfassung des radiologischen Ansprechens nach RECIST (CR/PR/SD/PD) sowie des Tumormarkerverlaufs (AFP, ßHCG) 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. |

*Registerstudie*

**Erfassung von Leydigzelltumoren und noch selteneren Sertolizelltumoren**

| **AIO**-assoziierte Studie | |
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| Kontaktadresse/<br>Kontaktperson: | Prof. Dr. med. Sabine Kliesch<br>Chefärztin der Klinischen Andrologie<br>Centrum für Reproduktionsmedizin und Andrologie<br>WHO Kollaborationszentrum, EAA Ausbildungszentrum<br>Universitätsklinikum Münster<br>Domagkstraße 11<br>48149 Münster<br>E-Mail: sabine.kliesch@ukmuenster.de<br>Tel. 02 51/83-5 60 96, -5 60 97<br>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**

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| 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 | Oktober 2018 |

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| 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<br>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: | • 88 Study Sites initiated<br>• 300 Patients enrolled<br>• 202 Patients randomized<br>• Interested Sites might be considered | |
| 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 | |

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| 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 | To compare maintenance arms with respect to:<br>• Time from randomization until failure of treatment strategy (death/ progression)<br>• Progression-free survival of re-induction<br>• Objective response after 12 weeks of induction chemotherapy<br>• Objective best response during maintenance and re-induction<br>• Overall survival measured from time of randomization and from time of registration<br>• Safety<br>• Health and skin related Quality of life |
| Exploratory objectives | • Translational research parameters as defined in the respective section<br>• Central review of CT/MRI scans<br>• Depth of response (during induction and maintenance therapy) |
| Planned sample size | Approx. 380 patients will be enrolled to reach the planned number of 252 randomizations. |
| Inclusion criteria | • Signed written informed consent<br>• Male or female ≥ 18 years of age<br>• Histologically proven metastatic colorectal cancer<br>• Molecular testing showing RAS wild-type in colorectal carcinoma cells<br>• Life expectancy > 12 weeks<br>• At least one measurable lesion according to RECIST 1.1<br>• Adequate bone marrow, liver, kidney, organ and metabolic function<br>- Bone marrow function<br>o leukocyte count $\geq$ 3.0 x $10^9$/L<br>o ANC $\geq$ 1.5 x $10^9$/L<br>o platelet count ≥ 100 x $10^9$/L<br>o hemoglobin ≥ 9 g/dL or 5.59 mmol/L (may be transfused or treated with erythropoietin to maintain/ exceed this level)<br>- Hepatic function<br>o Total bilirubin ≤ 1.5 x UNL<br>o ALT and AST ≤ 2.5 x UNL (or ≤ 5 x UNL in presence of liver metastases)<br>o AP ≤ 5 x UNL<br>- Renal function<br>o Creatinine clearance ≥ 50 mL/ according to Cockroft-Gault formula or serum creatinine ≤ 1.5 x UNL<br>- Metabolic function<br>o Magnesium ≥ lower limit of normal<br>o Calcium ≥ lower limit of normal<br>• ECOG performance status 0 - 1<br>• Women of child-bearing potential must have a negative pregnancy test |
| Exclusion criteria | • Previous treatment for colorectal cancer in the metastatic setting<br>• Previous EGFR-targeting therapy<br>• < 6 months after end of adjuvant therapy<br>• Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids<br>• Chronic inflammatory bowel disease<br>• Peripheral neuropathy ≥ NCI-CTCAE V 4.03 grade 2<br>• Other previous malignancies with the exception of a history of previous curatively treated basal cell carcinoma of the skin or pre-invasive carcinoma |

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| | of the cervix or other curatively treated malignant disease without recurrence after at least 5 years of follow-up<br>• Significant disease that, in the investigator's opinion, would exclude the patient from the study<br>• History of cardiac disease; defined as:<br>- Congestive heart failure > New York Heart Association (NYHA) class 2<br>- Active coronary artery disease (myocardial infarction more than 6 months prior to start of study treatment is allowed)<br>- Cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)<br>- Uncontrolled hypertension (defined as blood pressure ≥ 160 mmHg systolic and/or ≥ 90 mmHg diastolic on medication)<br>• Patients with interstitial lung disease, e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan<br>• Known HIV, hepatitis B or C infection<br>• Known hypersensitivity reaction to any of the study components<br>• Radiotherapy, major surgery or any investigational drug 21 days before registration<br>• Pregnancy or lactation or planning to be pregnant during treatment and within 6 months after the end of treatment<br>• 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<br>• Known alcohol or drug abuse<br>• Any condition that is unstable or could jeopardize the safety of the patient and his compliance in the study |
| Treatment scheme | Induction chemotherapy<br>6 cycles mFOLFOX6 plus panitumumab for 12 weeks<br><br>Panitumumab 6mg/kg BW<br><br>mFOLFOX6:<br>85 mg/m² Oxaliplatin 2h d1<br>400 mg/m² folinic acid 2h d1<br>2400mg/m² 5-FU over 46 h d1 -2<br>Q2w<br><br>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.<br><br>Maintenance<br>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.<br>Patient with curative resection within 12 weeks of induction therapy do not qualify for randomization.<br><br>Re-induction:<br>After tumor progression, a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression<br><br>Concomitant therapy:<br>Prophylactic management program for panitumumab-related acute and late skin toxicities (see section 6.5.2, 6.5.3) |
| Primary parameter | Progression-free survival during maintenance therapy defined as time from randomization until disease progression or death, whatever occurs first. |

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| Secondary parameters | • Time from randomization until failure (death/ progression) of treatment strategy<br>• Progression-free survival of re-induction<br>• Objective response after 12 weeks of induction chemotherapy<br>• Objective best response during maintenance and re-induction<br>• Overall survival measured from time of randomization<br>• Safety<br>• Health and skin related Quality of life |
| Exploratory parameters | 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).<br><br>Central review of CT/MRI scans for resectability, volumetry and further related parameters (i.e. depth of response etc.) |
| Study procedures | After the initial screening procedure, eligible patients will be registered for study participation.<br><br>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.<br><br>After tumor progression a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression.<br><br>Tumor assessments will be performed 12 weeks after treatment start with induction therapy and every 8 weeks during maintenance therapy and re-induction.<br><br>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. |
| Randomization procedure | 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<br>1. Response to induction therapy at time of randomization (CR/PR vs. SD)<br>2. Prior oxaliplatin-containing adjuvant therapy (yes vs. no)<br>3. Planned starting dose of panitumumab for maintenance therapy, if patient will be assigned to arm A (full dosage vs. reduced dosage)<br><br>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. |
| Sample size calculation | 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. |
| Planned interim analysis | No confirmatory interim analyses for efficacy with the aim to stop the trial prematurely are foreseen within this study protocol. |

**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**

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| Studiennummer/-Code: | AIO-KRK-0116 - FIRE-4.5 |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2016 - 2020 |
| Weitere Zentren: | Aktuell keine neuen Zentren benötigt |
| Letzte Aktualisierung | Oktober 2018 |

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| Study Type | Randomisierte, multizentrische Phase-II Studie |
| Verantwortlicher Studienleiter nach AMG | Klinikum der Universität München<br>Marchioninistraße 15, 81377 München<br>Vertreten durch: Prof. Dr. med. Volker Heinemann |
| Objectives | Primäres Studienziel:<br>Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 under treatment with FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab.<br>Sekundäre Studienziele:<br>• Progression-free survival (PFS) from randomisation<br>• Overall survival (OS) from randomisation<br>• Investigation of early tumour shrinkage (ETS) and depth of response (DpR)<br>• 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)<br>• Investigation of progressive analysis of tumour marker evolution (CEA and CA 19-9)<br>• Recording of the safety and tolerance (NCI-CTCAE version 5.01 criteria) of the treatment |
| Objectives | - Objective response rate (ORR)<br>- Progression-free Survival (PFS) and Overall Survival (OS)<br>- Safety and Toxicity |
| Number of patients | Geplant: 99 Patienten<br>Bereits eingeschlossen: 42 (Oktober 2018) |
| Key inclusion criteria | - 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<br>- RAS wild-type tumour status (KRAS and NRAS exons 2, 3, 4) (proven in the primary tumour or metastasis)<br>- BRAF-mutated (V600E) tumour (proven in primary or metastasis)<br>o Age ≥18 years<br>o ECOG performance status 0-1<br>- Patient's written declaration of consent obtained<br>- 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)<br>- Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of the tumour material.<br>- Adequate haematopoietic function:<br>o Leukocytes ≥ 3.0 x $10^9$/L with neutrophils ≥ 1.5 x $10^9$/L |

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| | o Thrombocytes ≥ 100 x $10^9$/L,<br>o Haemoglobin ≥ 5.6 mmol/L (equivalent to 9 g/dL)<br>- Adequate hepatic function:<br>o Serum bilirubin ≤ 1.5 x upper limit of normal (ULN),<br>o ALAT and ASAT ≤ 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT ≤ 5 x ULN)<br>- INR < 1.5 and aPTT < 1.5 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.<br>- Adequate renal function:<br>o Serum creatinine ≤ 1.5 x ULN or creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50ml/min.<br>- Adequate cardiac function: ECG and echocardiogram with a LVEF of ≥55%<br>- No previous chemotherapy for metastatic disease. One cycle (cycle 0) of either FOLFOX, FOLFIRI, or FOLFOXIRI is allowed prior to randomisation.<br>- Time since last administration of any previous adjunctive chemotherapy >6 months<br>- Any significant toxicities of previous treatments must have subsided to grade 0 |
| Key exlusion criteria | - Grade III or IV heart failure (NYHA classification)<br>- Myocardial infarction, unstable angina pectoris, balloon angioplasty (PTCA) with or without stenting within the past 12 months before randomisation<br>- Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study<br>- 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).<br>- Previous chemotherapy for the colorectal cancer with the exception of adjunctive treatment, completed at least 6 months before entering the study.<br>- 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<br>- 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<br>- Known hypersensitivity to CHO (Chinese hamster ovary cells) - cellular products or other recombinant human or humanised antibodies<br>- 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.<br>- History of acute or subacute intestinal occlusion or chronic inflammatory bowel disease or chronic diarrhoea.<br>- Symptomatic peritoneal carcinosis<br>- Severe, non-healing wounds, ulcers or bone fractures<br>- 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.<br>- Requirement for immunisation with live vaccine during the study treatment.<br>- Uncontrolled hypertension<br>- Marked proteinuria (nephrotic syndrome)<br>- Arterial thromboemboli or severe haemorrhage within 6 months prior to randomisation (with the exception of tumour bleeding before tumour resection surgery)<br>- Haemorrhagic diathesis or tendency towards thrombosis<br>- Known DPD deficiency (specific screening not required)<br>- Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required) |

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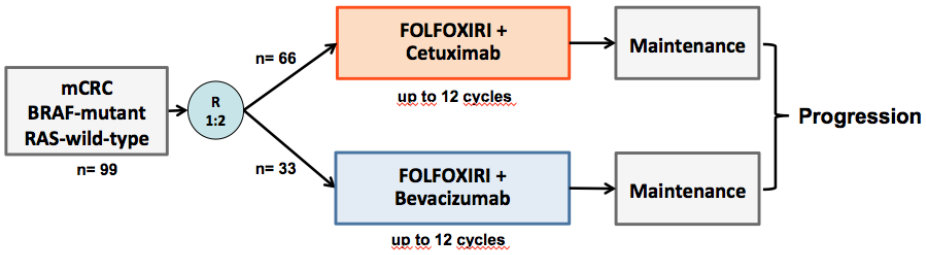
| | - History of a second malignoma during the 5 years before inclusion in the study or during participation in the study, with the exception of a basalioma, spinalioma or cervical carcinoma in situ, if these were treated curatively.<br>- Known history of alcohol or drug abuse<br>- A significant concomitant 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<br>- Absent or restricted legal capacity |
| Scheme of therapy | **FOLFOXIRI plus bevacizumab up to 12 cycles**<br>one cycle (cycle duration 14 days) consists of:<br>• Irinotecan 150 mg/m² iv, 30 - 90 min. day 1<br>• Folinic acid (racemic) 400 mg/m² iv, 120 min. day 1<br>• Oxaliplatin 85mg/m² day 1<br>• 5-FU 3000 mg/m² iv over 48 h days 1-2<br>• Bevacizumab 5 mg/kg BW iv over 30 to 90* min day 1<br><br>**FOLFOXIRI plus cetuximab up to 12 cycles**<br>one cycle (cycle duration 14 days) consists of:<br>• Irinotecan 150 mg/m² iv, 30 - 90 min. day 1<br>• Folinic acid (racemic) 400 mg/m² iv, 120 min. day 1<br>• Oxaliplatin 85mg/m² day 1<br>• 5-FU 3000 mg/m² iv over 48 h days 1-2<br>• Cetuximab initially 400 mg/m² with infusion rate of ≤5 mg/min., subsequently 250 mg/m² iv with infusion rate of ≤10 mg/min.days 1+8<br><br>**Study design**<br>  <br><br>**Primary Objective:**<br>Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 during treatment with FOLFOXIRI plus bevacizumab versus FOLFOXIRI plus cetuximab. |
| Criteria for evaluation | After treatment week 8, 16, 24 and every 12 treatment weeks thereafter tumor response evaluation according to RECIST 1.1 |
| Rationale | 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%, median PFS times of 7.5 months versus 5.5 months and median OS times of 19.0 months versus 10.7 months, repectively [Cremolini C et al Lancet Oncol 2015]. However, none of the differences reached the significance level, owing to the small number of |

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| | cases. Given the study design, it is not possible to make any statement concerning the additional benefit of bevacizumab in combination with FOLFOXIRI.<br>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 Annaös of Oncology (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. |
| Statistik | 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.<br><br>The efficacy of FOLFOXIRI plus cetuximab will be assessed as promising if:<br>• The null hypothesis (ORR in the FOLFOXIRI plus cetuximab arm ≤ 55%) can be rejected at a significance level of 0.1 and<br>• Response (ORR) in the FOLFOXIRI plus cetuximab arm is greater than in the FOLFOXIRI plus bevacizumab arm.<br>Hence, the hypotheses to be tested are:<br>• H0: ORR (arm B) ≤ 55%<br>• H1: ORR (arm B) ≥70%<br><br>Since an ORR of ≥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).<br>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”.<br><br>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. |

**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**

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| Studiennummer/-Code: | AIO-KRK-0117 |
| Status: | Rekrutiert |
| Rekrutierungszeitraum: | 09/2018 – 09/2020 (geplant) |
| Weitere Zentren: | nur noch wenige Plätze |
| Letzte Aktualisierung: | 22. Oktober 2018 |

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| Phase | Randomized phase II |
| Coordinating Investigators | Prof. Dr. Ralf-Dieter Hofheinz<br>Tagestherapiezentrum am ITM & III. Med. Klinik<br>Universitätsmedizin Mannheim<br>Theodor-Kutzer-Ufer 1-3<br>68167 Mannheim, Germany<br>Phone: +49 - 621 – 3832855<br>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<br>Total number of sites | Germany<br>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 1st line treatment. |
| Secondary objectives | To compare the treatment arms with respect to:<br>**Safety**<br>- Dose intensities of study medication<br>- Type, incidence and severity of AEs and SAEs<br>- Laboratory parameters<br><br>**Efficacy**<br>- Response rate assessed by the local investigators<br>- Overall and progression-free survival<br><br>**Patient reported outcomes**<br>- Quality of life<br>- Geriatric assessment<br>- Overall treatment utility |
| 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 | **Safety**<br>• Dose intensities of study medication<br>• Type, incidence and severity of AEs, SAEs (CTCAE version 4.03)<br>• Dose reduction or discontinuation of study drug due to adverse events<br>• Rate of treatment discontination due to toxicity<br>• Type, incidence and severity of laboratory abnormalities |

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| | **Efficacy**<br>• 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)<br>• Overall and progression-free survival (OS)<br><br>**Patient reported outcomes**<br>• Quality of life using EQ5D<br>• Geriatric assessment using G8, ADL and IADL<br>• Overall treatment utility (as defined in FOCUS2 trial) |
| 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 1st line chemotherapy |
| Inclusion Criteria | 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 (<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 ≤14, indicating a geriatric risk profile.<br>2. Patients have to have histologically confirmed mCRC with unidimensionally measurable inoperable advanced or metastatic disease<br>3. ECOG performance status of 2 or better.<br>4. Life expectancy of 3 months or longer at enrolment<br>5. Patients >70 years with no upper age limit<br>6. Previous adjuvant chemotherapy is allowed if completed more than 6 months before randomisation<br>7. Previous rectal (chemo)radiotherapy is allowed if completed more than 6 months before randomisation<br>8. Hematological status:<br>• Neutrophils (ANC) ≥ 1.5 x $10^9$/L<br>• Platelets ≥ 100 x $10^9$/L<br>• Hemoglobin ≥ 9 g/dL<br>9. Adequate renal function:<br>• Serum creatinine level ≤ 1.5 x upper limit normal (ULN)<br>10. Adequate liver function:<br>• Serum bilirubin ≤ 1.5 x upper limit normal (ULN)<br>• Alkaline phosphatase < 5 x ULN<br>• AST and ALT < 3 x ULN (unless liver metastases are present then < 5 x ULN in that case)<br>11. Proteinuria < 2+ (dipstick urinalysis) or ≤ 1 g/24hour<br>12. Signed and dated informed consent, and willing and able to comply with protocol requirements<br>13. Regular follow-up feasible<br>14. Male patients with a partner of childbearing potential must agree to use effective contraception (Pearl Index < 1) during the course of the trial and at least 3 months after last administration of the study drug. |
| Exclusion Criteria | 1. Prior systemic chemotherapy for mCRC<br>2. Other concomitant or previous malignancy, except:<br>• Adequately treated in-situ carcinoma of the uterine cervix<br>• Basal or squamous cell carcinoma of the skin<br>• Cancer in complete remission for > 5 years |

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| | 3. Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 Days<br>4. History or evidence upon physical examination of CNS metastasis unless adequately treated (irradiation and no seizure with appropriate treatment)<br>5. Uncontrolled hypercalcemia<br>6. Pre-existing peripheral neuropathy (NCI grade ≥2)<br>7. Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy),<br>8. Treatment with any other investigational medicinal product within 28 days prior to study entry.<br>9. Significant cardiovascular disease:<br>• Cardiovascular accident or myocardial infarction or unstable angina ≤6 months before start of study treatment<br>• Severe cardiac arrhythmia<br>• New York Heart Association grade ≥2 congestive heart failure<br>• Uncontrolled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), or history of hypertensive crisis, or hypertensive encephalopathy.<br>• History of stroke or transient ischemic attack ≤6 months before start of study treatment<br>• Coronary/peripheral artery bypass graft ≤6 months before start of study treatment.<br>• Deep vein thrombosis or thromboembolic events ≤1 month before start of study treatment<br>10. Patients with known allergy to any excipient to study drugs,<br>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.<br>12. Bowel obstruction.<br>13. Treatment with CYP3A4 inducers unless discontinued > 7 days prior to randomization<br>14. Known dihydropyrimidine dehydrogenase (DPD) deficiency<br>15. Involvement in the planning and/or conduct of the study (applies to both Sanofi staff and/or staff of sponsor and study site)<br>16. Patient who might be dependent on the sponsor, site or the investigator<br>17. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |

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| Treatment schedule after randomization | **Arm A (mFOLFOX7):**<br>Patients in the 5-FU / oxaliplatin arm receive modified (m) FOLFOX 7: Levofolinate 320 mg/m² and oxaliplatin 68 mg/m² by concurrent 2-h intravenous infusion, 5-fluorouracil 1920 mg/m² 46-h intravenous infusion.<br>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.<br><br>**Arm B (Aflibercept + mLV5FU2):**<br>Patients in the 5-FU / aflibercept arm receive aflibercept 4mg/kg as 1-h infusion followed by levofolinate 320 mg/m² by 2-h intravenous infusion, 5-fluorouracil 1920 mg/m² 46-h intravenous infusion (mLV5FU2).<br>The decision to use reduced doses of 5-FU and levofolinate was made to have comparable doses to the reduced FOLFOX 7. |
| Scientific rationale | 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.<br>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. |
| Randomization and stratification procedures | After the initial screening procedure, eligible patients will be randomized in a ratio of 1:1 to receive either mFOLFOX7 or Aflibercept + mLV5FU2.<br>Permuted block randomization will be applied.<br>Stratification factors: G8 score ≤14 versus 15-17 & ECOG 0/1 versus 2 |
| Statistical considerations and sample size calculation | **Sample Size Estimation:**<br>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.<br>Sample size calculation was done using R version 2.15.2 (R Core Team (2014). http://www.R-project.org/.).Assumptions:<br>• Uniform recruitment of patients during randomized phase II-part<br>• PFS exponential distribution PFS(t)=exp(rt)<br>• Median $PFS_{5FU\text{-}Aflibercept}$=6 months equivalent to a mean $PFS_{5FU\text{-}Aflibercept}$=8.7 months<br>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.<br>Assuming a 10% drop out rate a total of 196 patients need to be recruited.<br>Stratification factors: G8 score ≤14 versus 15-17 & ECOG 0/1 versus 2 |
| | **Safety**<br>The dose intensities of study medication will be calculated over the whole study duration and will be summarized descriptively by summary statistics.<br>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 |

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| | be presented for AEs by severity and relationship to study medication. Tables will be broken down by study arm.<br><br>All deaths and serious adverse events will be listed and briefly described.<br><br>Laboratory evaluations will be analyzed by summary statistics per parameter, visit and treatment group.<br><br>**Others**<br>Vital signs will be analyzed using summary statistics broken down per treatment group and visit.<br>Physical examination as well as ECOG will be analyzed by calculating frequencies and percentages broken down per treatment group and visit. |
| Number of patients, and location | Total number of patients: 196<br>Location of sites: Germany |
| Anzahl eingeschl. Pat. | 1 |
| 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]**

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| **AIO**-assoziierte Studie | |
| Studiennummer/-Code: | AIO-KRK-0316/ass - RAMTAS |
| Status: | Voten vorliegend; wird in QIV/2019 initiiert |
| Rekrutierungszeitraum | 2018 - 2019 |
| Weitere Zentren: | es sind noch wenige Plätze frei |
| Letzte Aktualisierung | 19.10.2018 |

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| Condition | metastatic colorectal cancer (mCRC) |
| Principal Investigator | Prof Dr. med. Stefan Kasper<br>University Hospital Essen, West German Cancer Center<br>Hufelandstr. 55, 45147 Essen, Germany<br>Tel.: +49 201 723 3449<br>Fax.: +49 201 723 5549<br>Email: stefan.kasper@uk-essen.de |
| Study group | Arbeitsgemeinschaft Internistische Onkologie in der<br>Deutschen Krebsgesellschaft e.V. |
| CRO | Institut für Klinisch-Onkologische Forschung<br>Krankenhaus Nordwest, Steinbacher Hohl 2-26<br>60488 Frankfurt am Main, Germany |
| Objectives | Primary objective:<br>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.<br>Secondary objectives:<br>Overall Response Rate (ORR) (complete remission and partial remission)<br>Disease control rate (DCR) (complete remission, partial remission and stable disease)<br>Progression Free Survival (PFS) |

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| | OS rate at 6 and 12 months<br>Efficacy (ORR, PFS, OS) in patients who develop neutropenia ≥ grade 2 (ANC≤1500/µl) in cycle 1<br>Toxicity/safety<br>Quality of life (QoL)<br>Tanslational research program |
| Study type | An interventional, prospective, randomized (1:1), controlled, open label, multicenter phase IIb study with run in safety phase |
| Rational | Patients with mCRC who have progressed on/after Fluoropyrimidins, Oxaliplatin, Irinotecan, anti-angiogenic and anti-EGFR therapies have limitied therapeutic options with a dismal prognosis and a median overall survial below 6 months (1,2). Recently TAS102, an oral agent that combines trifluridine and tipiracil hydrochloride significantely 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. |
| Key inclusion criteria | Metastatic and inoperable, colorectal cancer who have progressed on/after or did not tolerate:<br>Fluoropyrimidins, Oxaliplatin, Irinotecan, anti-angiogenic therapies (Bevacizumab, Aflibercept, Regorafenib or Ramucirumab) and when indicated anti-EGFR antibodies (Cetuximab or Panitumumab)<br>signed informed consent before start of specific protocol procedure<br>age>18 years<br>histologically or cytologically documented diagnosis of adenocarcinoma of the colon or rectum<br>presence of at least one measurable site of disease following RECIST 1.1 criteria<br>ECOG performance 0-1<br>known *RAS* mutational status<br>life expectancy of at least 3 months<br>adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening<br>absolute neutrophil count (ANC)≥1500/µl<br>platelet count ≥100,000/µl<br>total bilirubin <1.5xULN<br>ALT and AST <3xULN, <5xULN if liver metastasis present<br>PT-INR/PTT<1.5xULN, patients therapeutically anticoagulated with LMWH, heparin or NOACs (dabigatran, rivaroxaban, abixaban) are allowed to participate, patients anticoagulated with phenoprocoumon or warfarin should be switched to LMWH, heparin or NOACs<br>creatinine clearance ≥30ml/min and serum creatinine ≤2.0xULN<br>confirmed menopause or negative pregnancy test within 7 days of the start of treatment and willingness to use highly effective methods of contraception<br>willingness and able to comply with the protocol for the duration of the study |
| Key exclusion criteria | prior therapy with TAS102<br>investigational drug therapy within 4 weeks of study entry<br>major surgery within 4 weeks of starting therapy within this study<br>symptomatic brain metastasis<br>clincially significant cardiovascular disease (NYHA>II°, LV-EF<45%, myocardial infarction within 6 months prior study entry)<br>active clinically serious infections (>grade 2 NCI-CTC version 4.0)<br>history of uncontrolled HIV infection or chronic hepatitis B or C<br>patients with evidence of bleeding diathesis<br>arterial thromboemblic events <6 months prior study entry<br>patients with second primary cancer within 5 years, exept adequately treated basal skin cancer or carcinoma in-situ of the cervix or bladder, or low/intermediate risk prostate cancer (Gleason score ≤ 7) with normal PSA levels |

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| | any condition that could jeopardize the safety of the patient and their compliance of the study<br>breast-feeding patients<br>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 ≥ or <12 months in total |
| Interventions | Run in phase with safety analyses after 20 and 40 patients:<br>Arm A:<br>Ramucirumab 8 mg/kg d1+15, q4w<br>TAS102 35mg/m$^2$ BID d1-5, 8-12, q4w<br>Arm B<br>TAS102 35mg/m$^2$ BID d1-5, 8-12, q4w |
| Sample Size and Statistical Analyses | According to results of the RECOURSE 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 IV/2018<br>Last patient in (LPI) Q IV/2019<br>LPLV (last patient last visit) date QIV/2020<br>Recruitment period (months): 12 months<br>Minimum follow-up-period: 12 months |
| Participating centers | 30 in total |

1: Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M,Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372:1909-19.

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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4: Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30(28):3499-506.

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6. Garcia-Carbonero R, Rivera F, Maurel J, Ayoub JP, Moore MJ, Cervantes A, Asmis TR, Schwartz JD, Nasroulah F, Ballal S, Tabernero J. An open-label phase II study evaluating the safety and efficacy of ramucirumab combined with mFOLFOX-6 as first-line therapy for metastatic colorectal cancer. Oncologist. 2014;19:350-1.

**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**

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| Studiennummer/-Code: | AIO-KRK-0114 - FIRE-4 |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2015 - 2020 |
| Weitere Zentren: | Aktuell keine neuen Zentren benötigt |
| Letzte Aktualisierung | Oktober 2018 |

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| Art der Studie | Randomisierte, multizentrische Phase-III Studie |
| Verantwortlicher Studienleiter nach AMG | Klinikum der Universität München<br>Marchioninistraße 15<br>81377 München<br>Vertreten durch: Prof. Dr. med. Volker Heinemann |
| Kontaktadresse/ Kontaktperson: | Prof. Dr. V. Heinemann<br>Medizinische Klinik III<br>Sekr. Matthias Wolff<br>Klinikum Großhadern<br>LMU München<br>Marchioninistr. 15<br>81377 München<br>Tel: 089 4400 -72208<br>Fax: 089 4400 -75256<br><br>Dr. B. Deuß<br>ClinAssess GmbH<br>Abteilung Projektmanagement<br>Birkenbergstr. 82<br>51379 Leverkusen<br>Tel.: +49 (0) 2171 / 36 336 0<br>Fax: +49 (0) 2171 / 36 336 55 |
| Studienziele | <u>Primäres Studienziel:</u><br>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 >6 Monate angesprochen haben<br><br><u>Sekundäre Studienziele:</u><br>• Ansprechrate ORR<br>• Progressions-freie Zeit PFS<br>• Gesamtüberleben (OS1) ab Beginn der Erstlinientherapie<br>• Early tumor shrinkage und der Remissionstiefe<br>• Untersuchung von molekularen Biomarkern zur Prädiktion von Sensitivität und sekundärer Resistenz einer anti-EGFR Therapie mit Cetuximab<br>• Prospektive Validierung eines Biomarker Scores<br>• Prospektive Analyse des Tumormarkerverlaufs (CEA und CA 19-9)<br>• Erfassung der Sicherheit und Verträglichkeit |
| Zielparameter | - Gesamtüberleben in der Drittlinientherapie (OS3)<br>- Progressionsfreies Überleben im Rahmen der Erstlinientherapie (PFS1) |
| Patientenzahl | Geplant: 550 Patienten<br>Bereits eingeschlossen: 414 Patienten (Stand: Oktober 2018) |
| Haupt-Einschlusskriterien | Haupteinschlusskriterien:<br>• Adenokarzinom des Kolons oder Rektums im UICC Stadium IV, primär nicht resektabel<br>• RAS - Wildtyp-Status (KRAS und NRAS Exone 2-4) des Tumors (nachgewiesen in Primärtumor oder Metastase)<br>• Alter ≥18<br>• ECOG 0-1 |

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| | • Vorliegen mindestens einer messbaren Referenzläsion entsprechend der RECIST 1.1 –Kriterien (CT Thorax und Abdomen 4 Wochen oder weniger vor Randomisation)<br>• Adäquate Knochenmarksfunktion:<br>- Leukozyten ≥ 3,0 x $10^9$/L mit Neutrophilen ≥ 1,5 x $10^9$/L<br>- Thrombozyten ≥ 100 x $10^9$/L,<br>- Hämoglobin ≥ 5,6 mmol/L (entspr. 9 g/dL)<br>• Adäquate Leberfunktion:<br>- Serumbilirubin ≤ 1,5 x obere Normwertgrenze,<br>- ALAT und ASAT ≤ 2,5 x obere Normwertgrenze (bei Vorliegen von Lebermetastasen ALAT und ASAT ≤ 5 x obere Normwertgrenze)<br>• INR < 1,5 und aPTT < 1,5 x obere Normwertgrenze (Patienten ohne Antikoagulation).<br>• Adäquate Nierenfunktion:<br>- Serumkreatinin ≤ 1,5 x obere Normwertgrenze oder Kreatinin Clearance (berechnet nach Cockroft und Gault) ≥ 50ml/min<br>• adäquate Herzfunktion: EKG und Echokardiogram mit einer LVEF von ≥55%<br>**Einschlusskriterium nur für Eingang 1:**<br>• Zeit zur letzten Gabe einer vorangegangenen adjuvanten Chemotherapie >6 Monate<br>**Zusätzliche Einschlusskriterien nur für Eingang 2:**<br>• Stattgehabte Erstlinientherapie mit FOLFIRI und Cetxuximab;<br>• Stattgehabte Zweitlinientherapie *ohne* FOLFIRI, Irinotecan oder eine gegen EGFR gerichtete Substanz<br>• Letzte Gabe einer gegen den EGFR gerichteten Substanz ≥ 4 Monate vor Randomisation 2<br>• Nachweis eines RAS-Wildtyp Tumors innerhalb von 4 Wochen vor Randomisation<br>• CT Untersuchungen mit dem Nachweis vonPR oder CR oder SD ≥6 Monate nach RECIST Version 1.1 Kriterien als bestes Ansprechen im Rahmen der Erstlinientherapie mit FOLFIRI und Cetuximab |
| Haupt-Ausschlusskriterien | **Hauptausschlusskriterien**<br>• Nachweis einer RAS-Mutation oder fehlende Untersuchung auf RAS-Mutation<br>• Primär resektable Metastasen und Patient wünscht Resektion<br>• Herzinsuffizienz Grad III oder IV (NYHA-Klassifikation)<br>• Myokardinfarkt, instabile Angina pectoris, Ballonangioplastie (PTCA) mit oder ohne Stenting innerhalb der letzten 6 Monate vor Studieneinschluss<br>• Medizinische oder psychologische Beeinträchtigungen, die mit eingeschränkter Einwilligungsfähigkeit einhergehen oder die Durchführung der Studie nicht erlauben<br>• 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)<br>• Teilnahme an einer klinischen Studie oder experimentelle medikamentöse Behandlung innerhalb von 30 Tagen vor Aufnahme oder während der Studienteilnahme<br>• Bekannte Hypersensitivität oder allergische Reaktion gegen eine der folgenden Substanzen: 5-Fluorouracil, Cetuximab, Oxaliplatin, Irinotecan, Bevacizumab und chemisch verwandte Substanzen<br>• Bekannte oder klinisch vermutete Hirnmetastasen<br>• Akuter oder subakuter Darmverschluss oder chronisch-entzündliche Darmerkrankung in der Anamnese oder chronische Diarrhoe<br>• Arterielle Thromboembolien oder schwere Blutungen innerhalb von 6 Monaten vor Aufnahme in die Studie (Ausnahme Tumorblutung vor der Tumorresektionsoperation)<br>• Bekannter DPD-Mangel (spezielles Screening nicht erforderlich) |

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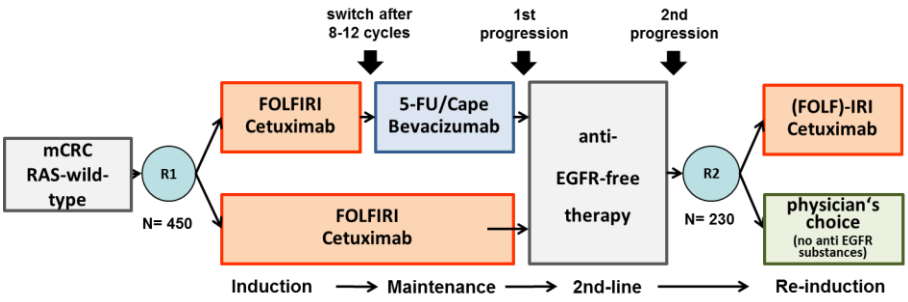
| | • Bekannter Glukuronidierungsdefekt (Gilbert-Meulengracht-Syndrom) (spezielles Screening nicht erforderlich)<br>• Zweitmalignom in der Anamnese während der letzten 5 Jahre vor Studieneinschluss oder während der Studienteilnahme, mit Ausnahme eines Basalioms, Spinalioms oder eines in-situ-Karzinoms der Cervix uteri, soweit diese kurativ behandelt wurden.<br>• Fehlende oder eingeschränkte juristische Geschäftsfähigkeit |
| Therapieschema | **FOLFIRI plus Cetuximab**<br>ein Zyklus (Zykluslänge 14 Tage) besteht aus:<br>• Irinotecan 180 mg/m² iv, 30 - 90 min Tag 1<br>• Folinsäure (racemisch) 400 mg/m² iv, 120 min Tag 1<br>• 5-FU 400 mg/m² Bolus Tag 1<br>• 5-FU 2400 mg/m² iv über 46 h Tag 1-2<br>• Cetuximab initial 400 mg/m² als 120 min Infusion, danach jeweils 250 mg/m² iv als 60 min Infusion Tag 1 + 8<br>**FUFA plus Bevacizumab**<br>Ein Zyklus (Zykluslänge 21 Tage) besteht aus:<br>• Folinsäure (racemisch) 400 mg/m² iv, 120 min Tag 1<br>• 5-FU 400 mg/m² Bolus Tag 1<br>• 5-FU 2400 mg/m² iv über 46 h Tag 1-2<br>• Bevacizumab 7,5 mg/kg KG iv<br>**Capecitabine plus Bevacizumab**<br>Ein Zyklus (Zykluslänge 21 Tage) besteht aus:<br>• Capecitabin 1250 mg/m2 2 x tgl p.o. Tag 1-14<br>• Bevacizumab 7,5 mg/kg KG i.v<br><br>**Irinotecan plus Cetuximab (2. Teil)**<br>Ein Zyklus (Zykluslänge 42 Tage) besteht aus:<br>• Irinotecan 125 mg/m² iv, 60 - 90 min wöchentlich (D1, D8, D15, D22) d.h. über 4 Wochen gefolgt von einer 14 tägigen Pause<br>• Cetuximab initial 400 mg/m² als 120 min Infusion, danach jeweils 250 mg/m² iv als 60 min Infusion wöchentlich (D1, D8, D15, D22, D29, D36)<br><br>**Windowtherapie:**<br>Nach Maßgabe des Prüfarztes z.B. XELOX/FOLFOX plus Bevacizumab, Capecitabin plus Bevacizumab<br><br>**Studiendesign:**<br>  <br> |
| Tumorevaluierung | • Ansprechen nach RECIST 1.1 (nach 8, 16 und 24 Wochen, danach alle 12 Behandlungswochen)<br>• Untersuchung des Primärtumors (erweiterte Mutations- und Expressionsanalysen)<br>• Liquid Biopsies (Baseline und zum jeweiligen Progress)<br>• Pharmakogenomische Untersuchungen an einer Vollblutprobe |
| Rationale | 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 |

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| | Cetuximab eine Tumorreduktion nach RECIST oder eine Krankheitsstabilisierung über > 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. |
| Statistik | Für das primäre Studienziel (OS3 ) werden folgende Annahmen gemacht:<br>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.<br>Bei 196 benötigten Ereignissen und einer angenommenen Dropout-Rate von 15% sind damit 230 Patienten (115 Patienten pro Therapiearm) erforderlich. |

**AIO KRK-0118: Avelumab added to FOLFIRI plus Cetuximab followed by Avelumab maintenance in patients with previously untreated RAS wild-type colorectal cancer. The phase II FIRE-6-Avelumab study**

**AIO-Studie**

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| Studiennummer/-Code: | AIO-KRK-0118 - FIRE-6 |
| Status: | Start der Rekrutierung für Q1/2019 geplant |
| Rekrutierungszeitraum | 2019 - 2020 |
| Weitere Zentren: | erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Study Type | Einarmige, multizentrische Phase-II Studie |
| Verantwortlicher Studienleiter nach AMG | Klinikum der Universität München<br>Marchioninistraße 15, 81377 München<br>Vertreten durch: Prof. Dr. med. Sebastian Stintzing |
| Objectives | <u>Primäres Studienziel:</u><br>Progression Free Survival (PFS) according to RECIST v1.1<br><br><u>Sekundäre Studienziele:</u><br>• Safety and tolerability (acc. to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters (oxygen saturation) and feasibility of the regimen)<br>• Progression-free survival (PFS) according to immune-modified RECIST (imRECIST)<br>• Response Rate (RR) according to RECIST v1.1 and (imRECIST)<br>• Progression Free Survival Rate after 12 months of treatment (PFSR@12) (acc. to RECIST v1.1)<br>• Overall survival (OS)<br>• Translational research (PD-L1, PD-1 expression, TIL´s within the tumor specimen, neutrophil/leukocyte ratio and use of antibiotics as predictive marker for avelumab) |
| Objectives | - Progression-free Survival (PFS)<br>- Objective response rate (ORR) and Overall Survival (OS) |

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| | - Safety and Toxicity |
| Number of patients | Geplant: 55 Patienten<br>Bereits eingeschlossen: 0 (Rekrutierungsstart Q1/19) (Oktober 2018) |
| Key inclusion criteria | - Histologically confirmed, UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer), metastases primarily non-resectable or surgery refused by the patient<br>- RAS wild-type tumour status (KRAS and NRAS exon 2, 3, 4) (proven in the primary tumour or metastasis)<br>- Age ≥18<br>- ECOG performance status 0-1<br>- Patients suitable for chemotherapy administration<br>- Patient's written declaration of consent obtained<br>- Estimated life expectancy > 3 months<br>- Presence of at least one measurable reference lesion according to the RECIST 1.1 criteria<br>- Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of tumour material. Molecular profiling of blood samples is optionally performed.<br>- Females of childbearing potential (FCBPs) and men must agree to use highly effective contraceptive measures (Pearl index <1) or practice true abstinence from any heterosexual intercourse (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject) for the duration of the study treatment and for at least 6 months after the last administration of study medication. A woman will be considered as being of childbearing potential unless she is at least 50 years old and moreover has gone through menopause for at least 2 years or has been surgically sterilised.<br>- Adequate bone marrow function:<br>- Leukocytes ≥ 3.0 x 109/L with neutrophils ≥ 1.5 x 109/L<br>- Thrombocytes ≥ 100 x 109/L<br>- Haemoglobin ≥ 5.6 mmol/L (equivalent to 9 g/dL)<br>- Adequate hepatic function:<br>- Serum bilirubin ≤ 1.5 x upper limit of normal (ULN)<br>- ALAT and ASAT ≤ 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT ≤ 5 x ULN)<br>- INR < 1.5 and aPTT < 1.5 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.<br>- Adequate renal function:<br>- Creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50 mL/min<br>- Adequate cardiac function: ECG and echocardiogram with a LVEF of ≥ 55%<br>- No previous chemotherapy for metastatic disease. Patient with need of immediate treatment (high tumour load, symptoms) may have received one application of FOLFIRI prior to study entry.<br>- Time interval since last administration of any previous neoadjuvant/adjuvant chemotherapy or radiochemotherapy of the primary tumour in curative treatment intention ≥ 6 months.<br>- Any relevant toxicities of prior treatments must have resolved<br>- Patient affiliated to a public health insurance coverage |
| Key exlusion criteria | - Proof of a RAS mutation (KRAS or NRAS, exons 2, 3, 4 in the tumor (proven in the primary tumor or metastasis) or absence of testing for RAS mutation<br>- Primarily resectable metastases and the patient wishes for resection<br>- ≥ Grade II heart failure (NYHA classification)<br>- Myocardial infarction, balloon angioplasty (PTCA) with or without stenting, and cerebral vascular accident/stroke within the past 12 months before start of study treatment, unstable angina pectoris, serious cardiac arrhythmia according to investigator’s judgement requiring medication.<br>- Pre-existing pulmonary fibrosis or immune pneumonitis |

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| | - Active autoimmune disease that might be negatively affected by an immune checkpoint inhibitor. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.<br>- Prior organ transplantation, including allogeneic stem cell transplantation<br>- Current use of immunosuppressive medication, except for the following:<br>- Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);<br>- Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent;<br>- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).<br>- Pregnancy (absence of pregnancy to be ascertained by a negative beta hCG test) or breast feeding<br>- Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study<br>- Additional cancer treatment (chemotherapy, radiation, immunotherapy or hormone treatment) during the study treatment in first-line (treatments that are conducted as part of an anthroposophic or homeopathic treatment approach, e.g. mistletoe therapy do not represent an exclusion criterion)<br>- Previous chemotherapy for the colorectal cancer with the exception of adjuvant treatment, completed at least 6 months before entering the study<br>- Toxicity > Grade 1 that has not yet resolved, attributed to a previous treatment or measure for treatment of the CRC. However, alopecia (all grades) and oxaliplatin-induced neurotoxicity ≤ Grade 2 are acceptable.<br>- 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 study while taking part in the study<br>- Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, capecitabine, cetuximab, irinotecan, avelumab and chemically related substances and/or hypersensitivity to any of the components in the formulations of the aforementioned substances, including known hypersensitivity reactions to monoclonal antibodies NCI CTCAE Grade ≥ 3.<br>- Known hypersensitivity to Chinese hamster ovary cell (CHO) – cellular products or other recombinant human or humanised monoclonal antibodies<br>- Patients with known brain metastases. In case of clinical suspicion of brain metastasis a cranial CT or MRI must be performed to rule out brain metastasis before study inclusion.<br>- History of acute or subacute intestinal occlusion, inflammatory bowel disease, immune colitis or chronic diarrhoea<br>- Symptomatic peritoneal carcinosis<br>- Severe, non-healing wounds, ulcers or bone fractures<br>- Patients with active infection requiring systemic therapy<br>- Known history of testing positive for HIV or known acquired immunodeficiency syndrome.<br>- Active or chronic Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive; serologic tests required).<br>- Requirement for immunisation with live vaccine under the study treatment.<br>- Haemorrhagic diathesis or known thrombophilia<br>- Known DPD deficiency (specific screening not required)<br>- Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required)<br>- History of a second primary malignancy during the past 5 years before inclusion in the study or during participation in the study, with the exception of a basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ, if these were treated curatively.<br>- Known history of alcohol or drug abuse<br>- Any other severe acute or chronic concomitant disease or medical condition including psychiatric conditions (including recent i.e. within the past year or |

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| | active suicidal ideation or behavior) or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.<br>- Absent or restricted legal capacity |
| Scheme of therapy | All eligible patients will receive cetuximab and FOLFIRI until the first follow up examination for the first 4 cycles (2 months). Patients with a cycle 0 of FOLFIRI will also receive 4 cycles of FOLFIRI plus cetuximab within the study. Patients that have not progressed will receive FOLFIRI and cetuximab in combination with avelumab from the fifth cycle onwards for a total of 4 cycles until the second follow up examination. Having not progressed for a total of 8 cycles, patients will then switch to avelumab single agent maintenance until progression of the disease. Study treatment will therefore be discontinued if one of the following events occur:<br>• Progressive disease (according to RECIST 1.1)<br>• Intolerable toxicity<br>• Withdrawal of consent<br><br>**Initial regimen (4 cycles):**<br>**FOLFIRI plus cetuximab (administration to local standard)**<br>One cycle (cycle duration 14 days) consists of:<br>Irinotecan 180 mg/m² iv — day 1<br>Folinic acid (racemic) 400 mg/m² iv — day 1<br>5-FU 400 mg/m² bolus — day 1<br>5-FU 2400 mg/m² iv over 46h — day 1-2<br>Cetuximab initially 400 mg/m²; subsequently 250 mg/m² iv — day 1 + 8<br><br>**Switch after 4 cycles:**<br>**FOLFIRI Cetuximab (administration to local standard) plus Avelumab (for 4 cycles)**<br>One cycle (cycle duration 14 days) consists of:<br>Irinotecan 180 mg/m² iv — day 1<br>Folinic acid (racemic) 400 mg/m² iv — day 1<br>5-FU 400 mg/m² bolus — day 1<br>5-FU 2400 mg/m² iv over 46h — day 1-2<br>Cetuximab 250 mg/m² iv — day 1 + 8<br>Avelumab at a dose of 10mg/kg IV — day 1<br><br>**Maintenance (starting at cycle 9) until progression:**<br>Avelumab at a dose of 10mg/kg IV day 1 (repeat every 14 days)<br>Study design |

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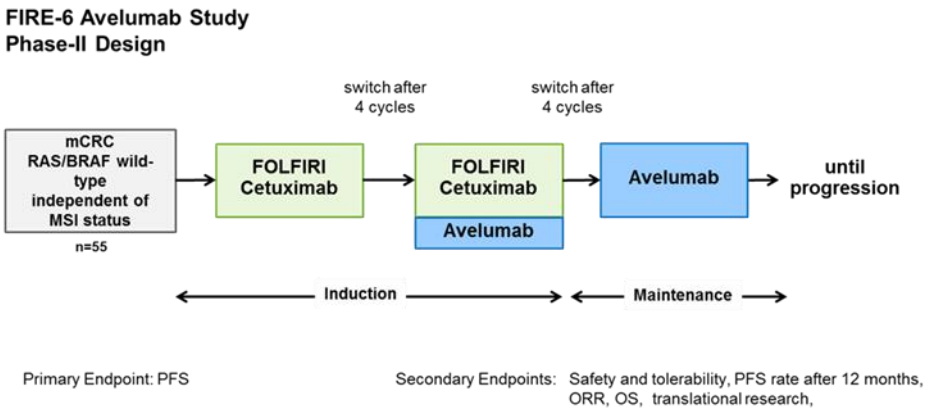
| |  |
| Criteria for evaluation | During treatment tumor response will be assessed by the investigator according to RECIST v1.1 (MRI (or CT scan if MRI is unavailable) of the chest, abdomen, pelvis and all other sites of disease) every 4 cycles (8 weeks ±7 days) CT and/or MRI scans will be independently reviewed. The results ot the central review will not have an impact on the study treatment. |
| Rationale | 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).<br><br>After 4-6 months of doublet chemotherapy a de-escalation to a less toxic regimen is needed for most of the patient with mCRC. The addition of Avelumab to a cytotoxic chemotherapy regimen with FOLFIRI plus cetuximab followed by Avelumab maintenance has not been investigated so far. It is known that FOLFIRI plus cetuximab leads to necrosis and therefore tumor antigens that usually are not presented to the host immune system become recognizable. This effect of a triggered immune response after induction treatment with chemotherapy is currently investigated in other trials. The ongoing IMPALA trial (Cunningham, Zurlo et al. 2015) is testing the toll-like receptor (TLR)-9 agonist MGN1703 as maintenance treatment in patients that have responded to an induction doublet chemotherapy. This effect may be enhanced by the fact that Cetuximab in Combination with 5-FU and Irinotecan triggers immunogenic cell death (Pozzi, Cuomo et al. 2016).<br><br>The lately published data from the interim analysis of the PACIFIC trial using the anti-PD L1 antibody durvalumab after chemoradiation in stage II non-small cell lung cancer (NSCLC) proofed the concept of an anti-PD L1 antibody as a maintenance treatment after chemoradiation. Durvalumab prolonged PFS significantly (HR 0.52, $p<0.001$) (Antonia, Villegas et al. 2017).<br><br>The study is not limited to MSI-h and should be able to demonstrate Avelumab efficacy in MSS tumors when used in combination with cetuximab plus FOLFIRI. The lately presented data on the use of atezolizumab plus cobimetinib (NCT01988896, IMblaze370) (Bendell, Bang et al. 2018) in in heavily pretreated MSS mCRC patients showed a 12-month OS rate of 43% which was higher than the 24% seen for Regorafenib in the pivotal CORRECT trial. But its primary endpoint, a benefit in median OS, was not met (Bendell, Ciardiello et al. 2018). As the IMblaze370 trial was conducted in heavily pretreated patients without the combination of chemotherapy, it is worthwhile to test this concept in MSS and MSI-h mCRC.<br><br>Furthermore part of the cetuximab as of the avelumab effect can be attributed to ADCC (antibody derived cellular cytotoxicity) with again leads to necrosis of tumor cells and the release of antigens. Both effects together may be able to |

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| | present enough tumor-neo-antigens. To boost the effect, Avelumab is able to inhibit the PD-1 derived inhibition of cytolysis and other tumor cells within the body may be attacked by the immune system which leads to an anti-tumor effect represented by a prolonged PFS and finally OS of the patients.<br><br>Patients will be included independent of microsatellite instability (MSI) status. It is expected that within the trial population the MSI rate will be as reported in stage IV MCRC with about 5% (Venderbosch, Nagtegaal et al. 2014). |
| Statistik | It is intended to study the progression-free survival within the context of the first-line treatment and maintenance trial. The goal of this phase-II study is to detect non-sufficient treatment timely. With regard to FOLFIRI plus cetuximab a median PFS of 10 months has been reported before (FIRE-3 study)<br><br>Thereby a median PFS of at most 8 months will be rated as non-sufficient, in contrast a median PFS of 12.88 months as sufficient..<br><br>Hence the hypotheses to be tested are:<br><br>H0: median PFS ≤ 8 months<br>H1: median PFS ≥ 12.88 months<br><br>PFS = period between start of treatment and progression or death.<br><br>According to this hypothesis formulation, the tests of the objective (PFS) will be performed in line with a one-sided logrank test.<br><br>Since a median PFS of ≥12.88 months is expected, 47 patients are required in order to reject the null hypothesis with a power of 80% at a one-tailed significance level of 0.025 (one sample testing using log-rank test) if an accrual period of 18 months and a minimum follow-up of 18 months is assumed. Due to possible drop-outs, a total of 55 patients (15% drop-out rate) are going to be included into this trial. |

**AIO-KRK-0218: Body-surface adapted versus pharmacokinetically guided dosing of 5-fluorouracil in patients with metastatic colorectal cancer harboring RAS mutations: A randomized phase III trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO) (RAS MUT)**

**AIO-Studie**

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| Studiennummer/-Code: | AIO-KRK-0218 - RAS MUT |
| Status: | in Vorbereitung<br>Förderantrag beim BMBF wurde gestellt. Bewilligung steht noch aus. |
| Rekrutierungszeitraum: | Studienstart offen |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | 18.07.2018 |

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| Sponsor | University of Heidelberg |
| Study Chairmen | Prof. Dr. Ralf-Dieter Hofheinz, Mannheim<br>Prof. Dr. Thomas Seufferlein, Ulm<br>Priv.-Doz. Dr. Alexander Stein, Hamburg |
| Study Statistician | Prof. Dr. Iris Burkholder, Zweibrücken |
| Clinical chemistry | Sonani Mindt, Mannheim |
| Rationale | Metastatic colorectal cancer (mCRC) is still a threatening disease accounting for about 25.000 cancer deaths in Germany per year. Chemotherapy in combination with monoclonal antibodies (anti-EGFR antibodies and anti-VEGF) is the treatment of choice for patients not amenable to surgery for metastases. About 50-55% of the colorectal cancers exhibit RAS mutations. Patients with RAS mutations have a worse prognosis (median survival of about 20-22 months; e.g. Modest et al. 2016). In contrast to those patients suffering from tumors without RAS mutations, antibodies targeting EGFR are ineffective. Moreover, it has been shown that also drugs targeting VEGF have only minor effects in tumors with RAS mutations in terms of increasing the efficacy of chemotherapy (Wirapati et al. 2017; Hofheinz et al. 2016) and even triple chemotherapy only marginally improves overall survival (Cremolini C et al. Lancet Oncol 2015). Thus, there is a huge medical need in order to improve the treatment of patients with RAS mutated colorectal cancer as they will (i) not derive significant benefit from monoclonal antibodies and (ii) treatment outcome will consequently depend on the efficacy of chemotherapy (namely 5-FU, irinotecan, and oxaliplatin).<br><br>One strategy to increase the efficacy of combination chemotherapy is using pharmaco-kinetically (PK) guided 5-FU instead of determining the dose of chemotherapy based on body-surface area (BSA). It has been repeatedly shown in several investigations that up to 60% of patients receiving BSA guided infusional 5-FU have 5-FU levels below the target AUC (Wilhelm et al. 2016; Hofheinz, data on file). During the past years it was shown that PK-guided dose adjustment of 5-FU was feasible, and PK-based dosing can significantly improve clinical outcomes by reducing toxicities and improving efficacy in terms of response rates and even overall survival. For instance, by using PK-guided 5-FU, Gamelin and coworkers found a significantly higher response rate and improved toxicity along with a numerical 6-months survival benefit in comparison with BSA-guided 5-FU dosing in patients with metastatic colorectal cancer receiving weekly 8-h infusional 5-FU monotherapy in a phase-III trial (Gamelin et al. 2008). Phase-II studies have employed a PK-based approach to dose 5-FU also within the context of modern chemotherapy regimens such as FOLFOX or FOLFIRI (Wilhelm et al. 2016; Capitain et al. 2012). Comparable to the study by Gamelin, survival benefit of about 6 months |

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| | has been reported by using PK-guided 5-FU treatment in non-randomized studies (Capitain et al. 2012).<br>The aim of the current study is to compare the use of PK-guided 5-FU with BSA-guided 5-FU in patients with RAS mutated mCRC in order to improve overall survival. Patients treated with chemotherapy doublets (FOLFIRI or FOLFOX) or infusional 5-FU, will be randomized between the use of PK- or BSA-guided 5-FU on a regular basis during 1st and 2nd line treatment. |
| Study type and study design | Investigator-driven, academic, multicentre, randomized phase III study |
| Primary objective and endpoint | The primary endpoint of this randomized trial is overall survival defined as the time between randomisation and death of any cause.<br>We hypothesize that the median overall survival would improve by six months from 21 months in the control arm to 27 months in the investigational arm corresponding to a Hazard ratio (HR) of 0.78. Assuming a recruitment period of 48 months and a follow-up of 48 months, and using a power of 80% and a two-sided type I error of 5%, the sample size required to obtain a statistically significant difference is 610 patients (including 5% of drop-outs). |
| Secondary objectives and endpoints | • Toxicity assessment according to NCI CTCAE v. 5.0<br>• Investigator assessed progression-free survival in 1st and 2nd line treatment.<br>• R0 resection rate of metastases<br>• Percentage of patients receiving all active drugs<br>• Quality of life as assessed with EORTC QLQ C30 and CR29 |
| Key inclusion criteria | • Signed written informed consent<br>• Male or female ≥ 18 years of age<br>• WHO/ECOG Performance Status ≤2<br>• Histologically proven metastatic colorectal cancer<br>• Molecular testing showing RAS mutation (KRAS or NRAS exon 2, 3, or 4 mutations as per local pathological testing)<br>• Metastatic disease not amenable to potentially curative resection of distant metastases<br>• Adequate haematological, hepatic, and renal function parameters allowing for the use of chemotherapy according to label<br>• Women of child-bearing potential must have a negative pregnancy test |
| Key exclusion criteria | • Previous treatment for colorectal cancer in the metastatic setting<br>• < 6 months after end of oxaliplatin-based adjuvant therapy<br>• Chronic inflammatory bowel disease<br>• Peripheral neuropathy ≥ NCI-CTCAE V 4.03 grade 2<br>• Other previous malignancies within the past 5 years with the exception of a history of previous curatively treated basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix or other curatively treated malignant disease<br>• Significant disease that would exclude the patient from the study according to the respective SmPCs of the drugs used<br>• History of significant cardiac disease; defined as:<br>Congestive heart failure > New York Heart Association (NYHA) class 2<br>Active coronary artery disease (myocardial infarction more than 6 months prior to start of study treatment is allowed)<br>Cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)<br>Uncontrolled hypertension (defined as blood pressure > 160 mmHg systolic and/or > 90 mmHg diastolic on medication)<br>• Known HIV, hepatitis B or C infection<br>• Any condition that is unstable or could jeopardize the safety of the patient and his compliance in the study<br>• Previous or current drug or alcohol abuse<br>• Known dihydropyrimidine dehydrogenase deficiency<br>• Known microsatellite instability of the primary tumor |
| Treatment | In the control arm (BSA-dosing of 5-FU), patients receive bi-weekly FOLFOX or FOLFIRI or infusional 5-FU +/- bevacizumab as 1st line treatment for a |

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| | maximum of 6 months. Maintenance treatment may be administered at the discretion of the local investigator. Upon progression a switch from FOLFIRI to FOLFOX or vice versa is foreseen. Patients receiving infusional 5-FU monotherapy as 1st line may be switched to either of these regimens. Antiangiogenic treatment is used as per label and at the discretion of the investigator. Anti-angiogenic treatment may be continued in the 2nd line treatment (i.e. bevacizumab or aflibercept or ramucirumab, as per label and according to the preference of the local investigator)<br><br>Patients in the investigational arm receive the same regimens (including switch in the 2nd line setting) but starting with cycle 1 the AUC of 5-FU will be assessed and the dose of 5-FU for subsequent cycles will be adjusted according to the scheme established by Kaldate et al. 2012. AUC will be tested twice during the first month of treatment and at least monthly thereafter, including maintenance treatment (provided 5-FU is used) and 2nd line treatment.<br><br>The following 1st line regimens will be used:<br><br>FOLFIRI +/- Bevacizumab:<br>Bevacizumab 5 mg/kg KG d1 30-90 min.<br>Irinotecan 180 mg/m² d1 30-90 min.<br>Folinic acid 400 mg/m² d1 120 min.<br>5-Fluorouracil 400 mg/m² d1 Bolus followed by<br>5-Fluorouracil 2.400 mg/m² d1 46h infusion.<br>Cycle is repeated d 15.<br><br>FOLFOX +/- Bevacizumab:<br>Bevacizumab 5 mg/kg KG d1 30-90 min.<br>Oxaliplatin 85 mg/m² d1 120 min.<br>Folinic acid 400 mg/m² d1 120 min.<br>5-Fluorouracil 400 mg/m² d1 Bolus followed by<br>5-Fluorouracil 2.400 mg/m² d1 46h infusion.<br>Cycle is repeated d 15.<br><br>Infusional 5-FU + Bevacizumab:<br>Bevacizumab 5 mg/kg KG d1 30-90 min.<br>Folinic acid 400 mg/m² d1 120 min.<br>5-Fluorouracil 400 mg/m² d1 Bolus followed by<br>5-Fluorouracil 2.400 mg/m² d1 46h infusion.<br>Cycle is repeated d 15. |
| Sample size and justification | The sample size is driven by the primary efficacy outcome overall survival. Recruitment will be over 4 years and all patients will be followed up for at least 4 years. For the planning of the study we assume that the event times and times to study withdrawal follow exponential distributions and are independent. Median survival in patients with RAS mutated colorectal cancer treated with chemotherapy doublets + bevacizumab has been reported in the range of 20.1 months (n=188; Stintzing et al. Eur J Cancer 2017) and 21.0 months (n=500; Modest et al. Ann Oncol 2016). Thus, we anticipate a median overall survival of about 21 months in the standard arm. A survival gain of about six months has been observed in previous trials and is expected also in the current trial (i.e. from 21 to 27 months). |
| Biostatistical methods | All primary analyses will follow the ITT principle, i.e. all randomized patients will be included in the analyses and in the treatment groups they were randomized to. Primary analysis of OS will be performed using stratified log-rank test as well as using a stratified Cox regression model for estimation of |

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| | HR and 95% CI. Two stratification factors will be used: (i) Sidedness of primary tumor (i.e. right versus left sided primary tumor), and (ii) doublet chemotherapy versus 5-FU chemotherapy in 1st. The treatment effect will be reported as hazard ratio with 95% confidence intervals and p-value testing the null hypothesis that the hazard ratio < 1. Patients withdrawing from study medication will be followed up for the endpoints. Withdrawal from the study will be dealt with as independent right censoring in the primary analysis. The primary endpoint will be displayed by treatment group as Kaplan-Meyer curves with 95% confidence bands. The analyses of the time-to-event outcomes among the secondary endpoints will follow the same lines as the analyses of the primary endpoint. |
| Planned interim analyses | No interim analysis is planned. |
| Estimated number of sites | Approximately 75 centers |
| Study duration | Start of preparation: Q4 2018<br>Start of recruitment: Q2 2019<br>Planned termination of recruitment: Q2 2023<br>Planned termination of follow-up: Q2 2026<br>Final study report: Q4 2026 |

**AIO-KRK-0318ass: A randomized, double blinded, phase 2, efficacy and safety study of abituzumab (EMD 525797) in combination with cetuximab and FOLFIRI versus placebo in combination with cetuximab and FOLFIRI in first-line RAS wild-type, left-sided, metastatic colorectal cancer patients with high αvβ6 integrin expression (AMELION)**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | AIO-KRK-0318/ass - AMELION |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum: | Studienstart noch offen |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| STUDY TYPE | Metastasiertes kolorektales Karzinom |
| PRINCIPAL INVESTIGATOR | To be determined |
| SPONSOR | SFJ Pharmaceuticals, Inc.<br>c/o Chief Financial Officer<br>5000 Hopyard Road, Suite 330<br>Pleasanton, CA 94588, U.S. |
| DESIGN | This is a multi-national, multicenter, double-blind, randomized, placebo-controlled, Phase 2 study comparing the efficacy and safety of abituzumab 1000 mg IV in combination with cetuximab + FOLFIRI versus placebo IV in combination with cetuximab + FOLFIRI, in patients newly diagnosed with RAS wild-type (WT), left-sided, metastatic colorectal cancer (mCRC) with high αvβ6 integrin expression and eligible for first-line treatment.<br>Confirmation of RAS WT mCRC by the local laboratory is required prior to screening for all patients. Determination of a high αvβ6 integrin expression (histoscore >70) by the central laboratory is required at screening. |
| INDICATION | First line treatment for RAS wild-type, left-sided, metastatic colorectal cancer patients with high αvβ6 integrin expression |
| OBJECTIVE(S) | To demonstrate that abituzumab treatment added to cetuximab + FOLFIRI is superior to placebo added to cetuximab + FOLFIRI with respect to Progression Free Survival (PFS) by investigator. |
| BACKROUND/RATIONALE | Abituzumab is a recombinant, humanized monoclonal IgG2 antibody antagonist directed against the alpha-beta sub-unit of human integrin receptors. Abituzumab is a pan-integrin inhibitor specific for αv integrins, inhibits all αv heterodimers (αvβ1, β3, β5, β6 and β8). Specifically, abituzumab inhibits αvβ6 which displays enhanced activity in metastatic colorectal cancer (mCRC). It has been demonstrated that members of the αvβ6 integrin family play a direct role in tumor progression, tumor angiogenesis, and metastasis.<br>Abituzumab has therefore the potential to inhibit tumor progression by inhibiting tumor induced angiogenesis, inhibiting tumor growth by targeting tumor cells directly, and affecting metastatic tumor cell migration and extravasation.<br>In a retrospective exploratory analysis in the POSEIDON study patients with a high αvβ6 integrin expression had a poorer outcome than patients with a low integrin expression in 2nd line RAS WT mCRC, indicating that patients with a high αvβ6 integrin expression benefit from treatment by abituzumab added to cetuximab and irinotecan. This benefit was higher in patients with left-sided colon tumors.<br>Therefore this study was designated to prospectively select for first-line RAS WT left-sided mCRC patients with high αvβ6 integrin expression and confirm the clinical benefit of treated by abituzumab in combination with cetuximab and FOLFIRI. |
| KEY EXCLUSION CRITERIA | 1. Demonstrated any RAS or BRAF mutation;<br>2. Prior anti-EGFR or other targeted therapy; |

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| | 3. Prior chemotherapy of the colorectal cancer, except for (neo) adjuvant therapy completed at least 6 months before randomization;<br>4. Radiotherapy (localized radiotherapy for pain relief is allowed to non-target lesions);<br>5. Investigational drug treatment for the treatment of malignancies in the past;<br>6. Concurrent participation in another interventional clinical study;<br>7. Pregnancy (exclusion confirmed with beta-hCG test) or lactation;<br>8. Any history or evidence of brain metastases or leptomeningeal metastases;<br>9. History of secondary malignancy within the past 5 years, except for basal cell carcinoma or carcinoma in situ of the cervix uteri, if treated with curative intent;<br>10. Concomitant chronic systemic immune or hormone therapy not indicated in this study protocol (except for physiologic replacement; steroids up to 10 mg per day of prednisone equivalent or topical and inhaled steroids are allowed);<br>11. Clinically relevant coronary artery disease (New York Heart Association [NYHA] functional angina classification III/IV), congestive heart failure (NYHA III/IV), or clinically relevant cardiomyopathy;<br>12. Uncontrolled hypertension defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg under resting conditions;<br>13. History of myocardial infarction in the last 12 months, or a high risk of uncontrolled arrhythmia, coagulation disorder associated with bleeding or recurrent thrombotic events, with the exception of arterial fibrillation treated with anti-coagulants;<br>14. Recent peptic ulcer disease (endoscopically proven) within 6 months of randomization, chronic inflammatory bowel disease, or acute/chronic ileus;<br>15. Active infection (requiring IV antibiotics and/or antiviral therapy), including active tuberculosis, active or chronic Hepatitis B or C, or ongoing HIV infection, AIDS;<br>16. Presence of any contra-indications or known hypersensitivity to treatment with abituzumab, cetuximab, and FOLFIRI, or to any of the excipients of these drugs;<br>17. Concomitant treatment with prohibited medications refer to section Error! Reference source not found.;<br>18. Medical or psychological conditions that would not permit the patient to complete the study. |
| KEY INCLUSION CRITERIA | 1. Signed and dated written informed consent prior to any study specific procedure;<br>2. Age: ≥18 years;<br>3. Evidence of newly diagnosed stage IV metastatic colorectal cancer. Primary tumor location on the left side of the Colon (including left splenic flexure) or rectum;<br>4. Demonstrated wild-type RAS mutation status in the tumor (primary tumor or metastasis) by local assessment;<br>5. Tumor tissue specimen shows high αvβ6 integrin expression (histoscore >70), as determined by central laboratory assessment;<br>6. Tumor tissue specimen (formalin-fixed, paraffin-embedded block) preferably from primary resection and/or if available from a surgical sample from metastatic site must be available for central laboratory based αvβ6 integrin expression analysis. (No Fine Needle Aspiration [FNA] will be accepted);<br>7. At least 1 radiographically documented measurable lesion in a previously non-irradiated area according to RECIST (Version 1.1), i.e., this lesion must be adequately measurable in at least 1 dimension (longest diameter to be recorded) as ≥2 cm by conventional techniques or ≥1 cm by spiral CT scan;<br>8. Eastern Cooperative Oncology Group (ECOG) performance status 0-1;<br>9. White blood cell count ≥3.0 x 109/L with neutrophils ≥1.5 x 109/L;<br>10. Platelets ≥100 x 109/L, hemoglobin ≥5.6 mmol/L or 9 g/dL (without transfusions);<br>11. Serum bilirubin ≤1.5 x upper limit of normal;<br>12. ALT and AST ≤2.5 x upper limit of normal. ALT and AST ≤5 x upper limit of normal in the presence of liver metastases; |

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| | 13. Serum creatinine ≤1.5 x upper limit of normal;<br>14. INR, and PTT within normal limits;<br>15. Sodium and potassium within normal limits or ≤10% above or below (supplementation permitted);<br>16. Surgery must have been performed more than 4 weeks before, fine needle biopsy more than 1 week before randomization. Surgical wounds must have healed completely. No need for major surgery during the course of the study is expected, unless the underlying tumor becomes resectable during study treatment;<br>17. Ability to comply with the study and follow-up procedures;<br>18. Female patients of childbearing potential (defined in Appendix 3) must have a negative pregnancy test at screening and be willing to have additional pregnancy tests during the study;<br>19. Female patients of childbearing potential and male patients with female partners of childbearing potential are eligible to participate if they agree to one of the following:<br>• A female patient of childbearing potential must agree to use highly effective contraception (i.e., methods with a failure rate of less than 1% per year) as detailed in Appendix 3 of this protocol 14 days before start of first dose of study treatment, during the treatment period, and for at least 90 days after the last dose of study treatment.<br>• A male patient must agree to use and to have their female partners agree to use highly effective contraception (i.e., methods with a failure rate of less than 1% per year) as detailed in Appendix 3 of this protocol during the treatment period, and for at least 90 days after the last dose of study treatment.<br>• In addition, male patients must refrain from donating sperm for the duration of the study and for 6 months after study treatment completion. |
| STATISTICAL ANALYSIS | The primary endpoint of the study is PFS as determined by investigator assessment. It is estimated that approximately 230 randomized patients and a minimum of 113 PFS events will be required to achieve a 80% power to detect Hazard ratio (HR) of 0.67 (this HR translates to a improvement in median PFS from 10 months to 14.9 months) in patients receiving abituzumab versus those receiving placebo, using a stratified log-rank test at 1-sided α=0.10).<br>The analysis of PFS will take place when a minimum of 113 PFS events per investigator assessment are observed, which is anticipated around 17.5 months after study start. |
| TRIAL DURATION | Patient Recruitment: 11 months<br>Patient treatment: 16 months<br>Follow Up: Up to 68 months after FPI |
| PARTICIPATING CENTERS | 100 – 125 |
| NUMBER of PATIENTS | Total 230 CURRENT NUMBER of PATIENTS: |

*Kolonkarzinom, frühe Stadien*

## AIO-KRK-0317: Randomized trial of FOLFOX alone or combined with Atezolizumab as adjuvant therapy of patiens with stage III colon cancer with deficient DNA mismatch repair or microsatellite instability (ATOMIC)

**AIO-Studie**

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| Studiennummer/-Code: | AIO-KRK-0317 - *ATOMIC*-Trial |
| Status: | in Vorbereitung, geplanter Studienstart (FPI) Q2 2019 |
| Rekrutierungszeitraum: | geplant 2019 – 2020 |
| Weitere Zentren: | weitere Zentren auf Anfrage |
| Letzte Aktualisierung | Oktober 2018 |

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| 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 deficient MMR (dMMR) via IHC
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 ≥ 2 peripheral motor or sensory neuropathy
Non-pregnant, non-nursing
Age ≥ 18 years
ECOG PS≤ 2

**Required Initial Laboratory Values**

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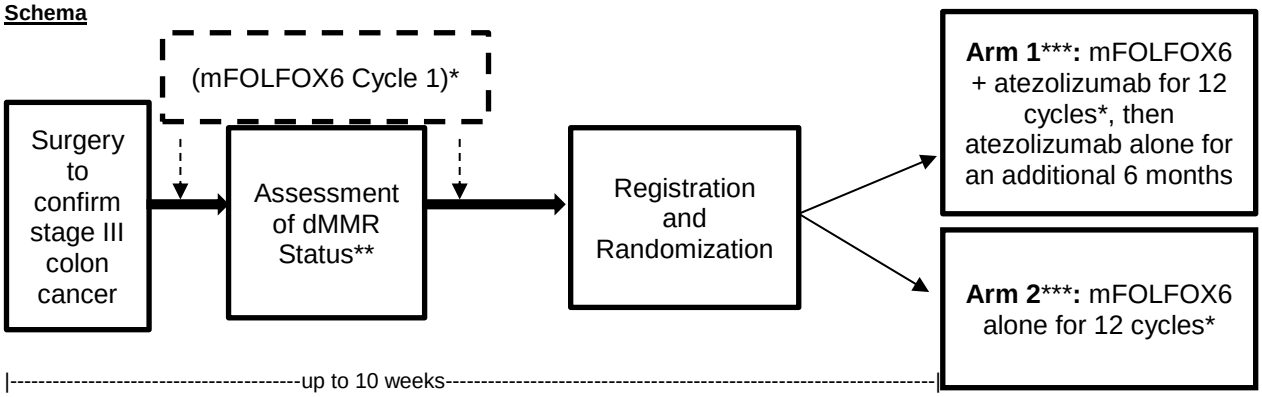
| Absolute Neutrophil Count (ANC) | ≥ 1500/mm$^3$ |
| Platelet Count | ≥ 100,000/mm$^3$* |
| AST/ALT | ≤ 2.5 x ULN |
| Bilirubin | ≤ 1.5 x ULN** |
| TSH | WNL*** |
| Creatinine | ≤ 1.5 x ULN |
| **OR** | |
| Calculated Creatinine Clearance | ≥ 45 mL/min |

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

**Schema**




* 1 cycle = 14 days. One cycle of mFOLFOX6 is allowed prior to registration. If Cycle 1 of mFOLFOX6 is started prior to registration, then the first post-registration cycle will be mFOLFOX6 Cycle 2. For patients who received Cycle 1 of mFOLFOX6 prior to registration and who are randomized to Arm 1, atezolizumab will start with Cycle 2 of mFOLFOX6.

** Assessment of dMMR status for eligibility may be performed locally or at a site-selected reference laboratory. Retrospective central confirmation of dMMR testing is required for all patients to gauge the false-positive rate in local testing (not for eligibility).

*** The standard of care for the time window between the end of mFOLFOX6 Cycle 1 and the start of mFOLFOX6 Cycle 2 is 14 days; however, up to 28 days are allowed between the end of Cycle 1 and the start of Cycle 2 if delays are made due to toxicity.

*Patients will be followed for recurrence and survival every 6 months for the first two years after registration, then survival every 6 months and recurrence once annually for years 3-5 after registration, and then survival every 6 months for years 5-8 after registration.*

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

**AIO-Studie**

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| Studiennummer/-Code: | AIO-KRK-0217 - CIRCULATE |
| Status: | in Vorbereitung<br>Förderantrag beim BMG wurde im April 2017 gestellt, ist genehmigt<br>Finanzierung geklärt |
| Rekrutierungszeitraum: | Studienstart voraussichtlich 5/2019 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | PD Dr. med. Gunnar Folprecht<br>University Hospital Carl Gustav Carus<br>University Cancer Center / Medical Department I<br>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.<br>Primary:<br>- 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<br>Secondary:<br>- 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<br>- 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 |
| 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.<br>Experimental intervention: Chemotherapy (oxaliplatin / fluoropyrimidine, in pts who are positive for postoperative ctDNA; elderly pts: fluoropyrimidine)<br>Control intervention: Follow up (no chemotherapy)<br>Duration of intervention per patient: 6 months (chemotherapy cohort)<br>Follow-up per patient: 5 years |
| KEY INCLUSION AND EXCLUSION CRITERIA | Key inclusion criteria:<br>- Histologically proven colon cancer stage II, microsatellite stable<br>- Resection of the primary 3 – 8 weeks before randomization<br>- Age > 18 years<br>Key exclusion criteria:<br>- Clinical high risk situation, if it is regarded as certain indication for adjuvant therapy by the treating physician and the patient<br>- Contraindication to chemotherapy (inadaequate bone marrow, hepatic, renal function)<br>- Comorbidity influencing the prognosis of the patients (i.e. secondary cancer) |

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| | - Participation at another interventional study for postoperative therapy |
| OUTCOME(S) | Primary efficacy endpoint:<br>- DFS of patients with positive postoperative ctDNA at study enrolment by treatment arm<br>Key secondary endpoint(s):<br>- OS of pts with positive postoperative ctDNA by treatment arm<br>- DFS and OS of untreated pts by postoperative ctDNA<br>Assessment of safety:<br>- Toxicity |
| STUDY TYPE | Investigator intiated, prospective, controlled, randomized, confirmatory study |
| STATISTICAL ANALYSIS | Efficacy:<br>- DFS in pts positive for postoperative ctDNA by treatment arm<br>Description of the primary efficacy analysis and population:<br>- Stratified log rank test for DFS in all randomized pts positive for postoperative ctDNA treated with or without chemotherapy<br>Safety:<br>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<br>Secondary endpoint(s):<br>- Overall survival by treatment arm<br>- DFS and OS of untreated pts by presence/absence of postoperative ctDNA |
| SAMPLE SIZE | To be assessed for eligibility: n = 3500 (screened for ctDNA, MSI)<br>To be allocated to trial: n = 231 (randomized pts)<br>To be analysed: n = 231 |
| TRIAL DURATION | Time for preparation of the trial (months): 9<br>Recruitment period (months): 36<br>First patient in to last patient out (months): 60<br>Time for data clearance and analysis (months): 8 (primary analysis)<br>Duration of the entire trial (months): 77 (including preparation);<br>plus 3 years long term follow-up for overall survival |

*Lebermetastasen*

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

**AIO-assoziierte Studie**

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

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| Studienleitung | Prof. Dr. med. Volker Heinemann, Ludwig-Maximilians-Univ. München |
| Studienkoordination | PD Dr. med. Dominik P. Modest<br>Medizinische Klinik III, Klinikum Großhadern<br>Ludwig-Maximilians-Univ. München, Marchioninistr. 15<br>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 | • Verträglichkeit und Nebenwirkungen<br>• Gesamtüberleben |
| Explorative Endpunkte | • Translationale Forschung<br>• Biomarkerprogramm |
| Studientyp und Studiendesign | Randomisierte, open-label, multizentrische Phase II Studie, in mehreren Ländern durchgeführte Studie (Deutschland und Österreich) |
| Patientenanzahl | 111 geplante Patienten<br>Rekrutierungsstand: 104 rand. Pat. (Stand: (Oktober 2018) |
| Geschätzte Anzahl der Zentren | bis zu 70 Zentren in Deutschland und Österreich (davon bis zu 15 Zentren) |
| Stratifizierung | 1. FONG-Score 0-2 verglichen mit 3-5<br>2. R0 versus R1<br>3. Vorbehandlung mit einem gegen EGFR gerichteten Wirkstoff |
| Einschlusskriterien | 1. Patient hat seine schriftliche Einverständniserklärung gegeben.<br>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)<br>3. Histologisch bestätigte Diagnose eines metastierten Kolorektalkarzinoms mit Beschränkung auf die Leber<br>4. RAS- Wildtyp des Tumors, getestet in: |

<table>
<tr>
<td></td>
<td>
<ul>
<li>KRAS exon 2 (codons 12/13)</li>
<li>KRAS exon 3 (codons 59/61)</li>
<li>KRAS exon 4 (codons 117/146)</li>
<li>NRAS exon 2 (codons 12/13)</li>
<li>NRAS exon 3 (codons 59/61)</li>
<li>NRAS exon 4 (codons 117/146)</li>
</ul>
5. Alter ≥ 18 Jahre<br>
6. ECOG Performance-Status 0-1<br>
7. Frauen im gebärfähigen Alter müssen geeignete Verhütungsmethoden anwenden<br>
8. Ausschluss einer Schwangerschaft<br>
9. Relevante Toxizitäten vorheriger Behandlungen müssen abgeklungen sein<br>
10. Magnesium ≥ untere Normwertgrenze; Kalzium ≥ untere Normwertgrenze<br>
11. Durch EKG und Echokardiogramm bestätigte normale kardiale Funktion (LVEF ≥ 55%)
<ul>
<li>Keine symptomatische kongestive Herzinsuffizienz</li>
<li>Keine instabile Angina pectoris</li>
<li>Keine kardialen Arrhythmien</li>
</ul>
12. Adäquate Organfunktion wie in Tabelle 1 definiert:<br><br>
Table 1: Adäquate Leber- und Nierenfunktionswerte
<table>
<tr><th>SYSTEM</th><th>LABORWERTE</th></tr>
<tr><td colspan="2">Hämatologisch</td></tr>
<tr><td>Neutrophile</td><td>≥1,5 G/L</td></tr>
<tr><td>Leukozyten</td><td>>3,0 G/L</td></tr>
<tr><td>Hämoglobin</td><td>≥9 g/dL</td></tr>
<tr><td>Thrombozyten</td><td>≥100 G/L</td></tr>
<tr><td colspan="2">Hepatisch</td></tr>
<tr><td>Albumin</td><td>≥2,5 g/dL</td></tr>
<tr><td>Serumbilirubin</td><td>≤2 mg/dL</td></tr>
<tr><td>AST und ALT</td><td>≤3 × ULN</td></tr>
<tr><td colspan="2">Renal</td></tr>
<tr><td>Serumkreatinin</td><td>≤1,5 mg/dL</td></tr>
</table>
</td>
</tr>
<tr>
<td>Ausschlusskriterien</td>
<td>
Ein Teilnehmer ist nicht geeignet für den Studieneinschluss, falls eines der folgenden Kriterien zutrifft:<br>
1. Bekannte Manifestation von Metastasen<br>
2. Progression während der präoperativen Behandlung<br>
3. RAS-Mutation des Tumors<br>
4. Kontraindikation gegen eine Behandlung mit 5-Fluorouracil/ Folinsäure oder Oxaliplatin<br>
5. Bekannte Unverträglichkeit von Panitumumab<br>
6. Bekannter DPD-Mangel<br>
7. Polyneuropathie > Grad 1 (NCI-CTCv4), welche die Anwendung von Oxaliplatin ausschließt<br>
8. Nachweis von Aszites oder Zirrhose<br>
9. Patient ist schwanger oder stillt oder plant innerhalb von 6 Monaten nach Ende der Behandlung schwanger zu werden<br>
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<br>
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.<br>
12. Klinisch signifikante kardiovaskuläre Erkrankung (einschließlich Myokardinfarkt, instabile Angina pectoris, symptomatische kongestive
</td>
</tr>
</table>

| | |
|---|---|
| | Herzinsuffizienz, schwerwiegende unkontrollierte kardiale Arrhythmien)<br>≤1 Jahr von Einschluss/Randomisierung<br>13. Anamnese einer interstitiellen Lungenerkrankung z.B. Pneumonitis oder pulmonale Fibrose oder Nachweis einer interstitiellen Lungenerkrankung in der Baseline-Thorax-Aufnahme<br>14. Gleichzeitige Erkrankung oder Zustand, durch welchen der Teilnehmer nicht geeignet ist für die Studienteilnahme oder welcher sich auf die Sicherheit des Teilnehmers auswirkt.<br>15. Psychologische, familiäre, soziologische oder geographische Bedingungen, die eine Einhaltung des Protokolls nicht erlauben.<br>16. Gleichzeitige Krebstherapie (Chemotherapie, Bestrahlung, biologische Therapie, Immuntherapie oder hormonale Therapie) während der Studie.<br>17. Gleichzeitige Behandlung mit einem Prüfpräparat, Teilnahme an einer anderen klinischen Studie oder jegliche ausdrücklich verbotene Medikation während der Studie.<br>18. Bekannte sofortige oder verzögerte Überempfindlichkeitsreaktion oder Idiosynkrasie auf chemisch verwandte Arzneimittel zu 5-Fluorouracil, Folinsäure, Oxaliplatin oder Panitumumab.<br>19. Andere aktive Malignität<br>20. Bekannter Alkoholabusus oder Drogensucht<br>21. Unfähigkeit die Einwilligungserklärung zu erteilen |
| Behandlungsschema | mFOLFOX6<br>Folinsäure 400 mg/m$^2$, 2-h-Infusion, d1<br>5-FU 400 mg/m$^2$ Bolus i.v., d1<br>5-FU 2400 mg/m$^2$ 46-h-Infusion, d1-2<br>Oxaliplatin 85 mg/m$^2$ 2-h-Infusion d1<br>Wiederholung des Zyklus nach 2 Wochen<br><br>Panitumumab initial 3 Monate (+ mFOLFOX6)<br>6 mg/kg KG alle 2 Wochen<br><br>Panitumumab-Erhaltungstherapie Phase (3 Monate)<br>9mg/kg KG alle 3 Wochen<br><br>Dauer der postoperativen Chemotherapie<br>FOLFOX wird für 3 Monate gegeben.<br>Panitumumab wird gleichzeitig mit der FOLFOX-Chemotherapie (3 Monate) und als zusätzliche Einzelmedikament-Erhaltungstherapie für weitere 3 Monate im experimentellen Arm verabreicht.<br><br>Die Behandlung innerhalb der Studie wird bei Diagnose des Wiederauftretens beendet |
| Deeskalation der Chemotherapie | Bei Patienten, die während der Therapie eine Unverträglichkeit von Oxaliplatin aufgrund von allergischen Reaktionen oder Polyneuropathie entwickeln, kann FOLFOX zu 5-Fluorouracil/Folinsäure deeskaliert werden. |
| Baseline-Untersuchungen | Innerhalb von 2 Wochen vor erster Verabreichung der Studienmedikation<br>• Einverständniserklärung<br>• RAS-Status<br>• Anamnese (einschließlich Tumorstatus, vorherige Tumortherapien, vorherige/begleitende Erkrankungen, Begleitmedikation)<br>• Körperliche Untersuchung<br>• Versand der Blutproben (10ml PAXGene) und Gewebeproben der resezierten Lebermetastasen an das Labor des Leiters der klinischen Prüfung<br>• Gewicht<br>• Größe<br>• Urinuntersuchung mittels Streifentest<br>• Vitalzeichen (einschließlich Blutdruck und Puls)<br>• ECOG-Performance-Status<br>• Großes Blutbild (einschließlich Differentialblutbild) |

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| | • 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<br>• Tumormarker (CEA, CA 19-9)<br>• Schwangerschaftstest (bei gebärfähige Frauen)<br>• EKG<br>• Echokardiographie<br>• CT Thorax/Abdomen (zum Ausschluss von Metastasen, innerhalb von 6 Wochen vor der ersten Gabe von Studienmedikation durchzuführen) |
| Untersuchungen während der FOLFOX-Chemotherapie (beide Arme) | An Tag 1 jedes FOLFOX-Zyklus (beide Arme)<br>• Anamnese (Symptome, Toxizitäten, Begleitmedikation)<br>• Körperliche Untersuchung<br>• Gewicht<br>• Urinuntersuchung mittels Streifentest (nur in monatlichen Intervallen)<br>• Vitalzeichen (einschließlich Blutdruck und Puls)<br>• ECOG-Performance-Status<br>• Großes Blutbild (einschließlich Differentialblutbild)<br>• 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<br>• Tumormarker (CEA, CA 19-9) |
| Untersuchungen während Panitumumab-Erhaltung (experimenteller Arm) | An Tag 1 jedes 3-wöchigen Behandlungszyklus<br>• Anamnese (Symptome, Toxizitäten, Begleitmedikation)<br>• CT Thorax/Abdomen (nur Zyklus 1 Tag 1 der Erhaltungstherapie)<br>• Gewicht<br>• Körperliche Untersuchung<br>• ECOG-Performance-Status<br>• Tumormarker (CEA, CA 19-9)<br>• Großes Blutbild (einschließlich Differentialblutbild)<br>• 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 |
| Untersuchungen <u>zum</u> Ende der Studienbehandlung | • Die Behandlung endet nach 6 Monaten für den experimentellen Arm und nach 3 Monaten für den Kontrollarm<br>• Anamnese (Symptome, Toxizitäten, Begleitmedikation)<br>• Körperliche Untersuchung<br>• Gewicht<br>• Vitalzeichen (einschließlich Blutdruck und Puls)<br>• ECOG-Performance-Status<br>• Großes Blutbild (einschließlich Differentialblutbild)<br>• 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<br>• Tumormarker (CEA, CA 19-9)<br>• EKG<br>• Echokardiographie<br>• CT Thorax/Abdomen |
| Follow-Up Untersuchungen für mindestens 36 Monate <u>nach</u> Randomisierung | Alle 3 Monate für mindestens 36 Monate nach Randomisierung<br>• Serumchemie (einschließlich Kreatinin, Elektrolyte (Natrium, Kalium, Kalzium), AST, ALT, gamma-GT, LDH, CRP, AP, Gesamtbilirubin, Gesamteiweiß, Albumin) |

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| | • Großes Blutbild<br>• Tumormarker (CEA und CA19-9)<br>• CT Thorax/Abdomen alle 3 Monate bis 2 Jahre nach Randomisierung, danach alle 6 Monate bis zu 36 Monate nach Randomisierung<br>• Informationen zum Überleben<br>• Anhaltende Toxitzitäten (nur beim ersten Follow up) |
| 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 | 2:1 Randomisierung von Patienten mit RAS-Wildtyp<br>Ziel: einen Nachweis für eine Verbesserung des 2-Jahres-PFS um 15% zu erhalten.<br>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.<br>Die Fallzahl ist durch die folgenden Annahmen begründet:<br>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.<br>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).<br>In einer großen Kohorte von Patienten mit Lebermetastasen eines kolorektalen Karzinoms, die sich einer Leberteilresektion 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.<br>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.<br>Aus diesen Gründen nehmen wir an, dass die alleinige Chemotherapie ein 2-Jahres-PFS von ≤50% in unserer Zielpopulation verursacht.<br>Eine 2-Jahres PFS-Rate ≤50 % 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 (>65%), obwohl die wahre Rate erfolglos ist (<50%), unter 5% halten. |
| Studiendauer | Vergleichsarm:<br>FOLFOX: 3 Monate (6 Zyklen)<br>Experimenteller Arm: |

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| | FOLFOX: 3 Monate (6 Zyklen)<br>Panitumumab: 6 Monate<br><br>Follow-up-Zeitraum: Der minimale Follow-up-Zeitraum wird 36 Monate nach Randomisierung betragen, um eine adäquate Beurteilung des progressionsfreien Überlebens zu ermöglichen |
| Rationale | 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.<br>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).<br>Diese Studie untersucht die Wirksamkeit der postoperativen Chemotherapie kombiniert mit einer gegen EGFR gerichteten Behandlung unter Verwendung von Panitumumab.<br>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.<br>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).<br>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).<br>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).<br>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.<br>Nach der Operation wird ein behandlungsfreier Zeitraum von mindestens 4 Wochen, aber nicht länger als 8 Wochen gestattet.<br>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 |

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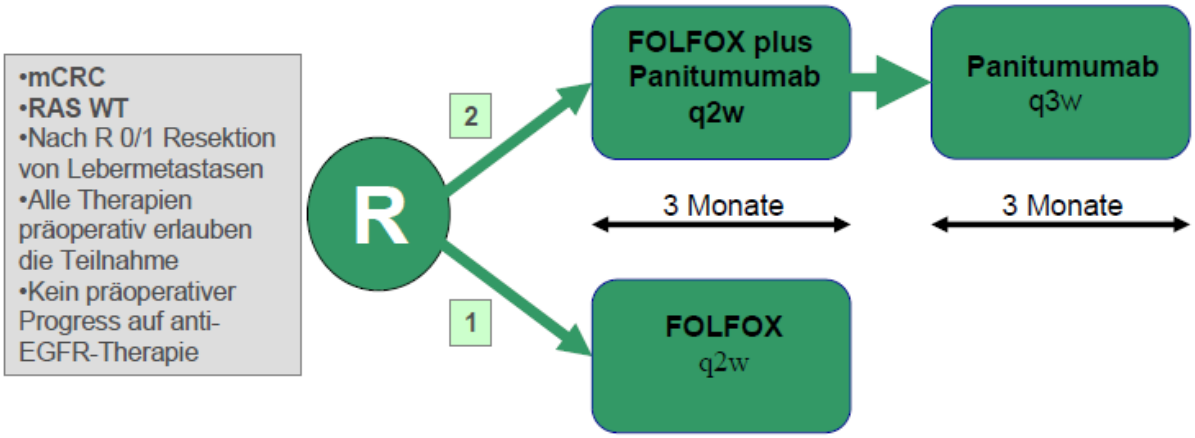
| | Vergleichsarm wird die Behandlung jedoch nach 3 Monaten beendet (Abbildung 1). |

Figure 1: Studien Design




**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**

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

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|---|---|
| COORDINATING INVESTaGATOR | PD Dr. Gunnar Folprecht, University Cancer Center<br>Prof. Dr. Jürgen Weitz, Dpt. of Surgery<br>University Hospital Carl Gustav Carus, Fetscherstr. 74, 01307 Dresden<br>Gunnar.Folprecht@uniklinikum-dresden.de<br>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) | Experimental intervention / index test:<br>Resection of all metastases (with or without ablation),<br>systemic therapy in case of progression according to local standard<br>Control intervention / reference test:<br>No resection / ablation unless changes in medical findings,<br>systemic therapy according to local standard<br>Follow-up per patient:<br>- Resections to be completed within 6 months<br>- Chemotherapy will be performed according to local standard<br>(not as pharmaceutical trial)<br>Duration of intervention per patient:<br>6 years or until end of study whatever occurs first |

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| | Experimental and / or control off label or on label in Germany:<br>Not applicable (chemotherapy follows local standard, resection not off-label) |
| KEY INCLUSION AND EXCLUSION CRITERIA | Key inclusion criteria:<br>The patients are included if they:<br>1. Have technically resectable metastases of colorectal cancer (multistep approaches, ablation, portal vein embolization allowed) AND<br>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<br>3. Have unfavourable prognosis defined as:<br>a. more than 10 metastases OR<br>b. disease free survival after the last resection shorter than 6 months and more than 3 metastases OR<br>c. Basingstoke score 20 or more OR<br>d. Basingstoke score 15 or more in patients with<br>i. Age ≥ 70 and ECOG > 0 or significant co-morbidity (Charlson Co-Morbidity index > 2)<br>ii. disease free survival after the last resection shorter than 6 months<br>iii. More than three operations planned<br>4. Are discussed in the multidisciplinary tumour board confirming criteria 1-3<br>5. Have a WHO performance status 0-1<br>6. Are generally operable<br>7. Have a signed informed consent<br><br>Key exclusion criteria:<br>Patients are excluded if they:<br>1. Are younger than 18 years, pregnant, breast-feeding or have a severe psychiatric disease<br>2. Are legally dependent or cannot understand the informed consent<br>3. Have brain metastases |
| OUTCOME(S) | Primary efficacy endpoint:<br>1. Overall survival in the intention-to-treat (ITT) population (primary endpoint)<br>Key secondary endpoint(s):<br>1. Quality of life<br>2. Overall survival in patients as per protocol analysis<br>3. Safety of resection<br>4. Rate of resection and pathological outcome (margins)<br>5. Disease free survival in resected patients<br>6. Duration / protocols of subsequent chemotherapies<br><br>Assessment of safety:<br>90 day mortality |
| STUDY TYPE | Randomized, controlled, open, interventional, confirmatory trial |
| STATISTICAL ANALYSIS | Description of the primary efficacy / test accuracy analysis and population:<br>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%.<br>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 |

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| | 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.<br>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.<br>Safety:<br>Descriptive analysis of mortality in both arms, perioperative morbidity. Chemotherapy toxicity (QoL).<br>Data will be supervised by a Data Safety Monitoring Board.<br>Secondary endpoints:<br>Descriptive analysis (DFS), multivariate analysis |
| SAMPLE SIZE | 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.<br>To be assessed for eligibility (n = 650)<br>To be allocated to trial (n = 366)<br>To be analysed (n = 366) |
| TRIAL DURATION | First patient in to last patient out (months): 12<br>*Duration of the entire trial (months): 60*<br>*Recruitment period (months): 48* |
| PARTICIPATING CENTERS | *To be involved (n): 80* |

**AIO-KRK-0418: Post-resection therapy with mFOLFOXIRI in patients with colorectal cancer *(PORT)***

| **AIO-Studie** | |
|---|---|
| Studiennummer/-Code: | **AIO-KRK-0418 - PORT** |
| Status: | in Vorbereitung, Finanzierung noch nicht gesichert |
| Rekrutierungszeitraum: | Studienstart noch offen - geplante Rekrutierungszeit: 48 Monate |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | November 2018 |

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| STUDY TYPE | **Interventional trial**: [X]<br>**Key elements:** open label, randomised, controlled phase II trial |
| PRINCIPAL INVESTIGATOR | • Prof. Dr. med. Volker Heinemann, Klinikum der Universität Muenchen, Medizinische Klinik III, Marchioninistrasse 15, 81377 München;<br>• Prof. Dr. med. Johann Pratschke, Chirurgische Klinik, Campus Charité Mitte \| Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin. |
| TRIAL OFFICE | Studienzentrale AG Onkologie Prof. Heinemann, München |
| CONDITION | After removal or ablation of metastases from colorectal cancer |

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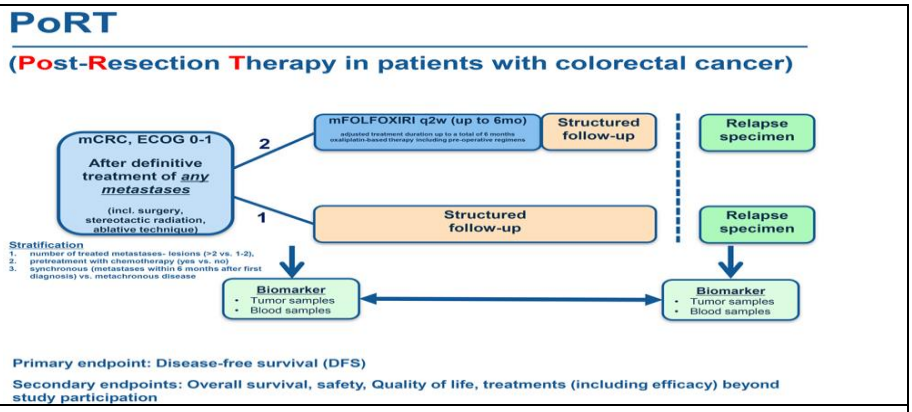
| DESIGN |  |
| OBJECTIVE(S) | The study will pragmatically recruit all patients with definitely treated metastases from colorectal cancer, as the underlying question, what to do after treated metastases, applies to all sorts of disease spread in a variety of clinical settings. Furthermore, it is not realistic to recruit a trial limited to “after lung metastases” or “without prior treatment” or similar rarer constructs, as this will inevitably result in recruitment-failure. Besides this selection, the indicated criteria represent standard and take into account that patients were fit enough to undergo an intervention. |
| INTERVENTION(S) | **Experimental procedure**:<br>Additive therapy with up to 12 cycles of modified FOLFOXIRI, adjusted individually for the total dose of oxaliplatin, i.e. a maximum of 12 cycles for patients pretreated with biweekly FOLFOX, or a corresponding limitation for CAPOX-pretreated patients. Thereafter, treatment may be deescalated to FOLFIRI or single-agent fluoropyrimidine (depending on tolerability) to reach a total postoperative treatment duration of 6 months.<br>**mFOLFOXIRI:**<br>(d1: 2.4g 5-FU in 46 hours, 400mg/qm leucovorin, 85mg/qm oxaliplatin, 150mg/qm irinotecan)<br><br>**Control intervention:** structured oncological observation (no chemotherapy)<br><br>**Follow-up per patient:** 36 months<br>**Duration of intervention per patient:** 6 months |
| BACKROUND/RATIONALE | In Germany, colorectal cancer has a prevalence of 65-80/100.000 and a current 5-year mortality of appr. 50% (Robert-Koch-Institut: Krebsdaten 2015; www.krebsdaten.de). In Western Europe, the burden of colorectal cancer is reported to be 211 (female) and 298 (male) diability adjusted life years (DALYs) on a population of 100.000 [1]. Given the available screening-programs, no severe socioeconomic impact within the incidence appears present. Life-style attitudes however may effect individual risk.<br>Patients with metastates from colorectal cancer (appr. 40-50% of all patients develop metastases) benefit from the resection or ablation of metastates, although relapse occurs in the majority (appr. 70-80%) of these patients [2-4]. Clearly, a reduction in relapse rates would improve the long term outcome of these patients. Unfortunately, additive/adjuvant therapy after local treatment of metastases is not established by phase III trials. Accordingly, no standard of care treatment to improve the relapse rates is available and the current S3-guidline for colorectal cancer does not recommend additive chemotherapy due to insufficient evidence on its benefit (http://www.awmf.org/leitlinien/detail/ll/021-007OL.html), explicitly.<br><br>The present clinical trial aims to generate evidence that additive therapy after resection or ablation of metastases may improve DFS and OS in patients with colorectal cancer. This is of specific importance since both improvements in in localized, but also systemic therapies [5, 6] have resulted in increasing numbers of mCRC patients undergoing resection and/or ablation of metastases [7-9]. Optimal oncological management after |

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| | removal of metastases is unclear. The result of this trial may be therefore be practice-changing. To support the purely clinical information a supporting translational study will help to identify subgroups (if present) of patients that benefit/ or not from systemic therapy after removal of metastases.<br><br>The translational study-program consists of the following steps:<br>1. Characterization of the initial resected/ablated tumor (primary and/or metastases) for DNA mutations and RNA expressions (for example oncomine panel plus nanostring)<br>2. Sequential central assessment of tumor markers and circulating tumor DNA (according to initial tumor characteristics), two assessments during study (q2m).<br>3. Characterisation of tumor specimen obtained after relapse of disease during or after study (if occurring and available) for DNA mutations and RNA expressions.<br>4. Correlation of 1) with 3) and eventually also correlation of relapse with acquired changes in samples of 2)<br><br>This paired sample collection including relapse specimen plus the longitudinal assessment of circulating tumor DNA will be performed in order to inform about early detection of relapse (potentially prior to radiographic correlate), relapse patterns (based on initial spread and the ablative technique) and molecular background of relapse (tumor evolution, secondary mutations, expressions). Necessary platforms for DNA/RNA alterations are availaible at both universities. It is anticipated that tumor samples will be availaible for 400 patients and about 400 linear blood samles can be completed (3-4 samples per patient). With six samples from roughly 400 patients, ~2400 probes will be characterized for DNA/RNA. |
| KEY EXCLUSION CRITERIA | **Key exclusion criteria:**<br>• Other previous malignancies within 3 years prior to study start,<br>• History of severe cardiac disease,<br>• Previous palliative chemotherapy with >6 cycles of FOLFOX or >4 cyles of CAPOX<br>• Radiotherapy, major surgery or any investigational drug 21 days before randomization,<br>Conditions prohibiting the use of study drugs |
| KEY INCLUSION CRITERIA | **Key inclusion criteria:**<br>• Resected and/or ablated metastases (all techniques allowed) of colorectal cancer within 3-10 weeks before randomisation AND resected primary tumor (synchronous or metachronous)<br>• No radiographic evidence of metastatic disease at study entry according to RECIST 1.1 scan no older than 4 weeks).<br>• Signed written informed consent,<br>• Adequate bone marrow, liver, kidney, organ and metabolic function,<br>• ECOG performance status 0 – 2. |

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| OUTCOME(S) | Disease-free survival (DFS) is defined as time from randomisation to progression (new metastases) or death from any cause. DFS is an established surrogate endpoint in trials promoting adjuvant or additive therapy and correlates with overall survival (randomisation to death from any cause). Quality of life is assessed by EORTC QLQC30 and EDEQ5L. Treatments (including efficacy) beyond study participation are analyzed descriptively.<br>Blood samples are collected during follow-up to create a biobank of patients with and without relapse. Moreover the relapses will be recorded as part of the study protocol, including the collection of tumor tissue and blood samples, if possible at relapse. The patterns of relapse will be correlated with the initially resected/ablated metastases clinically and in terms of tumor characteristics (mutations, expressions). |
| STATISTICAL ANALYSIS | Dr. Ingrid Ricard, IBE, Marchioninistrasse 15, Ludwig-Maximilians-Universität, München<br><br>**Statistical methods used to compare groups for primary and secondary outcomes:**<br>Cumulative incidence of DSF will be estimated by Kaplan-Meier procedure, while comparison of treatment arms will be done by log-rank test, adjusted for stratification factors. Sensitivity analysis will be performed using Cox regression to adjust for relevant prognostic factors. Both analyses will be stratified according to respective criteria (see randomisation). The above analyses will be repeated for overall survival (OS).<br>The influence of treatments received after the period of intervention on (DFS and) OS will be assessed.<br>Specific post-study treatments will be included in a Cox model as time-dependent explanatory variables.<br><br>**Methods for additional analyses, such as subgroup analyses and adjusted analyses:**<br>Safety analyses will consist of comparisons of AEs, SAEs, event rates of grade 3 and 4 toxicities<br>(NCI-CTCAE) and abnormal laboratory values/ increase/decrease between treatment arms during the 4<br>months of intervention. Descriptive tables will be created; Fisher exact tests will be performed to<br>compare the number of patients with a specific characteristic between the 2 arms; longitudinal models will be fitted to examine the evolution over time of the 2 arms and to test potential differences between them. Biomarkers and quality of life/ patient reported outcomes will be evaluated exploratorily. |
| SAMPLE SIZE | To be assessed for eligibility: (n ~ 550)<br>To be assigned to the trial: (n = 445) corresponding to 294/147 per arm<br>To be analysed: (n = 445) 279 events needed |
| TRIAL DURATION | First patient in to last patient out (months): 52<br>Duration of the entire trial (months): 58 (or until 80% of DFS events will have taken place)<br>Recruitment period (months): 48<br>It is intended to apply for a second funding period |
| PARTICIPATING CENTERS | No. of cities to be involved: 80<br>No. of centres to be involved: 80<br>Names of cities and centres: FIRE-Study Group (Germany) |
| NUMBER of PATIENTS | ~ 550 CURRENT NUMBER of PATIENTS: |

*Rektumkarzinom*

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

**AIO-Studie**

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| Studiennummer/-Code: | AIO-KRK-0214 |
| Status: | Rekrutierung (37 Patienten registriert / 34 randomisiert) |
| Rekrutierungszeitraum: | Juli 2017 – Q 3 2020 |
| Anzahl initiierter Sites: | 30 |
| Weitere Zentren: | Erwünscht, bei Interesse bitte bei der AIO-Studien-gGmbH melden |
| Letzte Aktualisierung: | Oktober 2018 |

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| 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<br>Tagestherapiezentrum am ITM & III. Med. Klinik<br>Universitätsmedizin Mannheim<br>Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany<br>Phone: +49 - 621 – 38 32 855, Fax: +49 - 621 – 38 32 488 |
| Sponsor | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8, 14057 Berlin, Germany<br>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<br>Total number of sites | Germany, Austria<br>40 sites |
| Randomised patients | 34 |
| Primary objective | To investigate the ***pathological tumor response*** 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:<br><br>**Safety**<br>- Dose intensities of study medication<br>- Type, incidence and severity of AEs and SAEs<br>- Laboratory parameters<br><br>**Efficacy**<br>- Survival, disease-free survival, relapse-free survival<br>- Downstaging and downsizing using a standardized regression grading (Dworak regression grading)<br><br>**Surgical morbidity and mortality**<br>- Perioperative in-hospital morbidity and mortality within 28 days after surgery<br><br>**Others**<br>- Vital signs, Physical examination, WHO/ECOG |

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| | The following secondary objectives will be considered beyond the clinical study report:<br>**Quality assurance of MRI (central read)**<br>- Comparison of the local read of:<br>• T, N, M Staging<br>• Heigh localization<br>• Distance to circumferential resection margin (CRM) |
| Planned sample size | 209 patients total (70 Arm A, 139 Arm B) |
| Inclusion Criteria | 1. Age ≥ 18 years<br>2. Signed and dated informed consent, and willing and able to comply with protocol requirements<br>3. WHO/ECOG Performance Status (PS) 0-1<br>4. Diagnosis of rectal adenocarcinoma<br>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.<br>6. Clinical staging is based on the combination of the following assessments:<br>• Physical examination by the primary surgeon<br>• CT scan of the chest/abdomen<br>• Pelvic MRI<br>• Rigid rectoscopy / endoscopic ultrasound (ERUS)<br>• Both examinations (MRI + ERUS) are mandatory<br>7. The tumor has to fulfill the following criteria:<br>• No symptomatic bowel obstruction<br>• Locally advanced rectal and rectosigmoid cancer, i.e. lower border of tumor > 5 cm and < 16 cm from anal verge as determined by rigid rectoscopy<br>• MRI criteria:<br>a. Lower border of tumor below a line defined by promontorium and symphysis, regardless of the criterion "< 16 cm from anal verge as determined by rigid rectoscopy".<br>b. No evidence that tumor is adjacent to (defined as within 2 mm of) the mesorectal fascia on MRI (i.e. CRM > 2 mm)<br>c. Only T3-tumors are included, i.e infiltration into perirectal fat < 10 mm provided CRM > 2 mm<br>d. ***Note:*** MRI criteria are used for the definition of T3 tumor (i.e. exclusion of T2 and T4 situation).<br>8. Hematological status:<br>• Neutrophils (ANC) ≥ 2 x $10^9$/L<br>• Platelets ≥ 100 x $10^9$/L<br>• Hemoglobin ≥ 9 g/dL (previous transfusion of packed blood cells allowed)<br>9. Adequate renal function:<br>• Serum creatinine level ≤ 1.5 x upper normal limit (ULN) or ≤ 1.5 mg/dl<br>• Creatinine clearance ≥ 30 ml/min<br>10. Adequate liver function:<br>• Serum bilirubin ≤ 1.5 x upper normal limit (ULN)<br>• Alkaline phosphatase < 3 x ULN<br>• AST and ALT < 3 x ULN<br>11. Proteinuria < 2+ (dipstick urinalysis) or ≤ 1 g/24hour or ≤ 500 mg/dl<br>12. Regular follow-up feasible<br>13. For female patients of childbearing potential, negative serum pregnancy test within 1 week (7 Days) prior of starting study treatment<br>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 |

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| | 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.<br>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. |
| Exclusion Criteria | 1. Distant metastases (CT scans of thorax and abdomen are mandatory)<br>2. cT2 and cT4 tumors (defined by MRI criteria)<br>3. Exclusion of potentially compromised CRM as defined by MRI criteria (i.e. > 2 mm distance from CRM)<br>4. Prior antineoplastic therapy for rectal cancer<br>5. History or evidence upon physical examination of CNS metastasis<br>6. Uncontrolled hypercalcemia<br>7. Pre-existing permanent neuropathy (NCI-CTCAE grade ≥ 2)<br>8. Uncontrolled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), or history of hypertensive crisis, or hypertensive encephalopathy<br>9. Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy, radiotherapy)<br>10. Treatment with any other investigational medicinal product within 28 Days prior to study entry<br>11. Known dihydropyrimidine dehydrogenase (DPD) deficiency<br>12. Treatment with CYP3A4 inducers unless discontinued > 7 Days prior to randomization<br>13. Any of the following in 3 months prior to inclusion:<br>• Grade 3-4 gastrointestinal bleeding (unless due to resected tumor)<br>• Treatment resistant peptic ulcer disease<br>• Erosive esophagitis or gastritis<br>• Infectious or inflammatory bowel disease<br>• Diverticulitis<br>14. Any active infection within 2 weeks prior to study inclusion<br>15. Vaccination with a live, attenuated vaccine within 4 weeks prior to the first administration of the study medication<br>16. Other concomitant or previous malignancy, except:<br>• Adequately treated in-situ carcinoma of the uterine cervix<br>• Basal or squamous cell carcinoma of the skin<br>• Cancer in complete remission for > 5 years<br>17. Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 Days<br>18. Pregnant or breastfeeding women<br>19. Patients with known allergy to any excipient to study drugs<br>20. History of myocardial infarction and/or stroke within 6 months prior to randomization, NYHA class III and IV congestive heart failure<br>21. Severe renal insufficiency (creatinine clearance < 30ml/min)<br>22. Bowel obstruction<br>23. Contra-indication to the assessment by MRI<br>24. Involvement in the planning and/or conduct of the study (applies to both Sanofi staff and/or staff of sponsor and study site)<br>25. Patient who might be dependent on the sponsor, site or the investigator<br>26. Patients who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |
| Investigational Product | Aflibercept (Zaltrap®) 4 mg/kg BW i.v. |

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| Treatment schedule after randomization | **Arm A:**<br>Oxaliplatin 85 mg/m², Leucovorin 350 mg/m² i.v. as 2 h infusion on Day 1, 5-FU 400 mg/m² i.v. as bolus on Day 1 and 2400 mg/m² as 46 h infusion q2w<br><br>**Arm B:**<br>Oxaliplatin 85 mg/m², Leucovorin 350 mg/m² i.v. as 2 h infusion on Day 1, 5-FU 400 mg/m² i.v. as bolus on Day 1 and 2400 mg/m² as 46 h infusion q2w, Aflibercept 4 mg/kg BW i.v. on Day 1 q2w |
| 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 | **Safety**<br>• Dose intensities of study medication<br>• Type, incidence and severity of AEs, SAEs and AESIs<br>• Dose reduction or discontinuation of study drug due to adverse events<br>• Rate of treatment discontinuation due to toxicity<br>• Type, incidence and severity of laboratory abnormalities<br><br>**Efficacy**<br>• Rate of R0-wide, R0-narrow (according to CRM definitions in S3-guideline Version 1.1 August 2014), R1 and locoregional R2 resection<br>• Disease-free survival (DFS) rate<br>• Relapse-free survival (RFS) in resected patients<br>• Overall survival (OS)<br>• Downstaging and downsizing using a standardized regression grading (Dworak regression grading)<br><br>**Surgical morbidity and mortality**<br>• Type, incidence and severity of perioperativ medical events<br>• Mortality within 28 days after surgery<br><br>**Others**<br>• Vital signs<br>• Physical examination<br>• WHO/ECOG |
| Randomization procedure | After the initial screening procedure, eligible patients will be randomized in a ratio of 1:2 to receive either mFOLFOX6 or Aflibercept+mFOLFOX6.<br>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. |

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| Statistical considerations and sample size calculation | **Sample Size Estimation:**<br>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).<br><br>**Statistical Considerations:**<br>An observed cases approach will be applied, and missing data will not be imputed. |
| Statistical analysis | STABIL – Statistische und Biometrische Lösungen<br>Pistorstr. 7, 66482 Zweibrücken, Germany |
| Study plan | FPI: Q1/2017<br>LPI: Q1/2020<br>Duration of treatment: up to 5.5 months<br>Follow-up: 3 years<br>Follow-up for LPI: 12 months after EOT visit<br>LPO: Q3/2021<br>Study report: Q3/2022 |

*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**

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

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| Verantwortlicher Studienleiter nach AMG | Prof. Dr. med. Andrea Tannapfel (molekulare Diagnostik/ Gewebebank)<br>Institut für Pathologie der Ruhr-Universität Bochum<br>Zentrale Gewebebank<br>Bürkle-de-la-Camp-Platz 1, 44789 Bochum<br>Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809<br>E-Mail: Andrea.tannapfel@rub.de |
| Projektkoordination | Prof. Dr. med. Anke Reinacher-Schick<br>(Leitung klinische Registerdaten)<br>Abteilung für Hämatologie, Onkologie und Palliativmedizin<br>St. Josef-Hospital Bochum<br>Klinikum der Ruhr-Universität<br>Tel.: 0234-509-3591, Fax:-Nr.: 0234-509-3592<br>E-Mail: onkologie@klinikum-bochum.de |

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| Kontaktadresse/ Kontaktperson | Institut für Pathologie der Ruhr-Universität Bochum<br>Bürkle-de-la-Camp-Platz 1, 44789 Bochum<br>Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809<br>Ansprechpartner:<br>S. Westphal, A. Remmel (0234-302-4924, stephanie.westphal@pathologie-bochum.de; anna.remmel@rub.de) |
| Studienziele | Primäres Studienziel: 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).<br><br>Sekundäre Studienziele:<br>• Rolle von MSI und KRAS auf die Prognose von Patienten mit Kolonkarzinomen im Stadium II mit Risikofaktoren<br>• Prognose von Patienten im Stadium III A, B und C (UICC 7. Auflage) unter Standardchemotherapie<br><br>Explorativ:<br>• 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-Profilinguntersuchungen<br>• Identifizierung von Patienten für mögliche Therapiestudien über bestimmte genetische oder andere molekulare Tumoreigenschaften (fakultativ) |
| Geplante Patientenzahl | 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.<br>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. |
| Anzahl eingeschlossene Patienten | Aktuell 2865, Erweiterung auf 8000 geplant |

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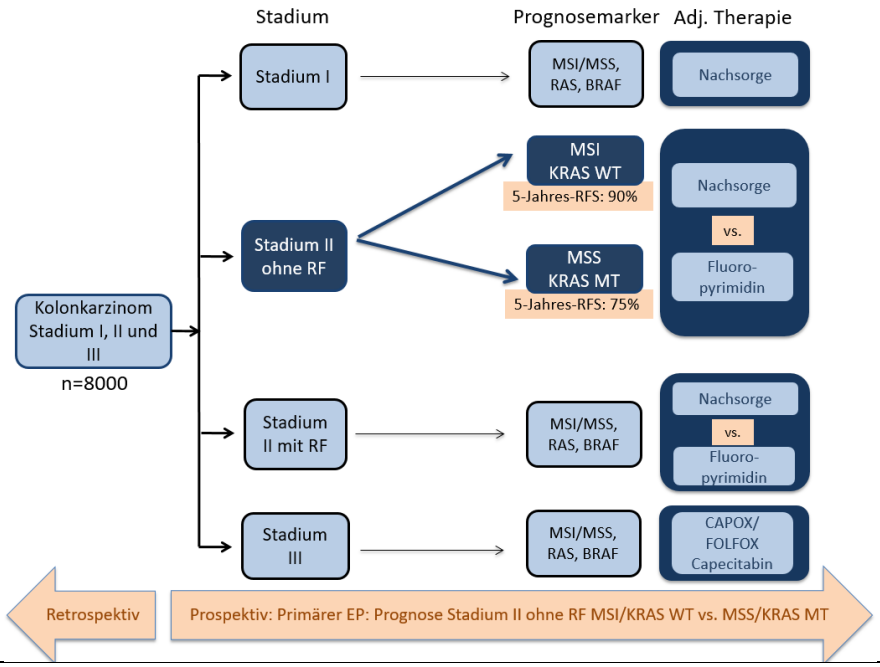
| Flow-Chart |  |
| Anzahl teilnehmende Zentren | Die Registerstudie soll vor allem, aber nicht ausschließlich innerhalb der Darmkrebszentren der DKG durchgeführt werden. 10 Stadium I/II/III Patienten pro Zentrum pro Jahr, 200 Zentren sollten rekrutiert werden. 4 Jahre Rekrutierungszeit. |
| Start des prospektiven Registers<br>Amendment 3 | September 2013<br><br>August 2018 |
| Haupt-Einschlusskriterien | Patienten, die sich in den Behandlungskontext des teilnehmenden Zentrums begeben haben und die folgende Kriterien erfüllen:<br>• männliche und weibliche Patienten mit der Diagnose eines Kolonkarzinoms im Stadium I, II oder III<br>• Bereitschaft der mit dem Studienzentrum kooperierenden Pathologie, Gewebeblöcke gemäß der Protokollanforderungen für die wissenschaftlichen Analysen zur Verfügung zu stellen<br>• Alter ≥ 18 Jahre und in Besitz der Fähigkeit, die Anforderungen des Registers und die Aufklärung dazu zu verstehen, zu hinterfragen und zu bemessen<br>• gemäß ICH-GCP unterschriebene Einwilligungserklärung zur Teilnahme an dem Register<br>• unterschriebene Schweigepflichtsentbindung der behandelnden Ärzte für die Zwecke der Studienerhebungen |
| Haupt-Ausschlusskriterien | Patienten, die<br>• die Einschlusskriterien nicht erfüllen<br>• ihr Einverständnis zur Studienteilnahme zurückziehen |
| Therapie | 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. |
| Zielparameter | Primär:<br>• 5-Jahres Rückfall-freies Überleben von MSI/KRAS WT Patienten versus MSS/KRAS MT Patienten im Stadium II ohne RF<br>Sekundär:<br>• 5-Jahres Rückfall-freies Überleben von MSI/KRAS WT Patienten versus MSS/KRAS MT Patienten im Stadium II mit RF |

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| | • OS, DFS im Stadium II<br>• RFS, DFS und OS im Stadium III<br>• Identifizierung einer Prognosesignatur für Patienten im Stadium II ohne RF<br>• Identifizierung von Patienten für mögliche Therapiestudien über bestimmte genetische oder andere molekulare Tumoreigenschaften (fakultativ)<br><br>Ausblick: Etablierung einer PEF- Strategie (Partizipative Entscheidungsfindung) |
| Statistik | 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.<br>Für die explorative Beurteilung anderer prognostischer Faktoren/molekularer Marker werden explorative Subgruppenanalysen durchgeführt. |

# 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**

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| Studiennummer/-Code: | AIO-KHT-0115 - ELDORANDO |
| Status: | Rekrutierung |
| Rekrutierungszeitraum | 2018 – 2020 |
| Weitere Zentren: | aktuell nicht erforderlich |
| Letzte Aktualisierung | Oktober 2018 |

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| National Coordinating Investigator | Prof. Dr. med. Viktor Grünwald<br>Universitätsklinikum Essen (AöR), Westdeutsches Tumorzentrum, Innere Klinik (Tumorforschung), Hufelandstraße 55, 45147 Essen<br>Tel: +49 201 - 723 2011, Fax: +49 201 - 723 5547<br>E-Mail: viktor.gruenwald@uk-essen.de |
| Sponsor | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>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<br>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:<br>• predictive value of PD-L1 expression<br>• exploration of molecular-genetic pro-inflammatory markers in archival tumor specimen |
| Planned sample size | A total of 100 patients will be randomized, 50 per treatment arm,<br>Recruiting. |
| Inclusion criteria | 1. Cooperation and willingness to complete all aspects of the study including participation in the translational research<br>2. Signed and dated written informed consent must be given prior to study inclusion<br>3. Histological or cytological confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC) not amenable to local therapies<br>4. Progressive disease at study entry<br>5. At least 1 measurable lesion according to RECIST 1.1<br>6. No previous systemic treatment for metastatic disease<br>7. Not eligible for cisplatin-based chemotherapy, defined as:<br>- ECOG 2 and/or<br>- calculated CrCl <60 mL/min (measured by MDRD)<br>8. Age ≥18 years<br>9. ECOG performance status 0 - 2<br>10. Brain metastases require completion of local therapy with discontinuation of steroids prior to start of treatment |

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| | 11. If of childbearing potential, willingness to use effective contraceptive method (double barrier method) for the duration of the study and 2 months after last dose<br>12. Adequate bone marrow function, liver and renal function:<br>a. Absolute neutrophil count ≥ 1.5 x $10^9$/L<br>b. Thrombocytes ≥ 100 x $10^9$/L<br>c. Hemoglobin ≥ 9 g/dL<br>d. INR ≤ 1.5 and PPT ≤ 1.5 x upper limit during the last 7 days before therapy<br>e. Bilirubin < 1.5 x lower limit and<br>f. AST (GOT) and ALT (GPT) < 3 x lower limit (5 x lower limit in case of liver metastases)<br>13. Tumor block must be available at study inclusion for central pathology testing |
| Exclusion criteria | 1. Live expectancy less than 3 months<br>2. Nasopharynx carcinoma<br>3. Anticancer treatment during the last 30 days prior to start of treatment, including systemic therapy, radiotherapy or major surgery<br>4. Participation in a clinical trial within the last 30 days prior to study treatment<br>5. History of allogeneic tissue/solid organ transplant<br>6. History of pneumonitis that has required oral or i.v. steroids<br>7. Evidence of interstitial lung disease<br>8. Minor surgery ≤ 24 hours prior first dose of study treatment<br>9. Symptomatic acute cardiovascular or cerebrovascular disease<br>10. Known active HBV, HCV or HIV infection<br>11. Has any other active infection requiring systemic therapy.<br>12. Patients with active tuberculosis<br>13. 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)<br>14. 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.<br>15. 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<br>16. Patient has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse eventsany toxicities due to agents administered more than 4 weeks earlier. [Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.]<br>17. 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<br>18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.<br>19. Has known hypersensitivity to methotrexate or pembrolizumab or any of constituent of the productsits.<br>20. Other active malignancy requiring treatment<br>21. 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 β-hCG) at Screening. |

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| | 22. Any psychiatric illness that would affect the patient's ability to understand the demands of the clinical trial<br>23. Patient has already been recruited in this trial (does not include screening failures)<br>24. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |
| Randomization criteria | Randomization will be performed 1:1<br>Strata:<br>• ECOG performance status (PS 0-1 vs. 2)<br>• HN-CCI index (<2 vs. ≥2) |
| Investigational drug | Pembrolizumab at fixed dose |
| Treatment phase | Arm A: Pembrolizumab 200 mg q3w i.v. until disease progression or non-tolerable toxicity (maximum 2 years)<br>Arm B: Methotrexate (MTX) 40 mg/m$^2$ weekly i.v. until disease progression or non-tolerable toxicity (maximum 2 years) |
| Study rationale | 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% >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).<br><br>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&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 (>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).<br><br>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.<br><br>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 >30 but <60 mL/min) (De Santis JCO 2012), which may serve as a backbone for the definition of cisplatin-ineligible patients.<br><br>Criteria for cisplatin-ineligibility:<br>• ECOG 2 and/or<br>• CrCl <60 mL/min |

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| | The modulation of the immune system has been identified as a promising 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.<br><br>We test the hypothesis that pembrolizumab is superior to methotrexate treatment in patients unfit to receive cisplatin-based chemotherapy. |
| 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 | **Primary endpoint and hypothesis:** 1-year overall survival rate<br>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)).<br><br>**Key secondary:**<br>• 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<br>• objective response rate (ORR) according to modified RECIST 1.1<br><br>**other secondary:**<br>• progression free survival (PFS)<br>• median overall survival (OS)<br>• ORR according to RECIST 1..1<br>• duration of response<br>• duration of treatment beyond progression<br>• treatment discontinuation rate<br>• safety and tolerability<br><br>Exploratory:<br>• predictive value of PD-L1 expression<br>• prognostic value of tumor shrinkage<br>• QoL response, defined as improvement of 5-10 points in QLQC30 and HN35 |
| Study plan | Study start (FPI): Q1/2018<br>Recruitment end (LPI): Q4/2020<br>Reaching the primary endpoint: Q4/2021<br>Planned analysis of primary endpoint: Q1/2022<br>Publication date: Q4/2021<br>End of maximum treatment period for last patient [24 months]: Q4/2022<br>Follow up period for the last patient: 12 months<br>Study end (LPLV): Q4/2023<br>Data base lock: Q4/2024-Q1/2025<br>Completion of Clinical Study Report (CSR): Q3/2023<br>Publication date: Q2/2024 |

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

| **AIO-Studie** | |
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| Studiennummer/-Code | AIO-KHT-0117 - OPTIM |
| Status | In der Rekrutierung |
| Rekrutierungszeitraum | 2018 - 2020 |
| Weitere Zentren | Sind erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| National Coordinating Investigator | Professor Dr. med. Viktor Grünwald<br>Universitätsklinikum Essen (AöR)<br>Klinik und Poliklinik für Urologie, Kinderurologie und Uroonkologie<br>Hufelandstraße 55<br>45147 Essen<br>E-Mail: Viktor.Gruenwald@uk-essen.de |
| Sponsor | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8<br>14057 Berlin<br>Phone: +49 30 814534431<br>Fax +49 30 322932926<br>E-Mail: info@aio-studien-ggmbh.de |
| Study design | Open label, randomized, multicenter phase II trial |
| Duration of study | Enrollment: 24 month<br>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 |
| Further sites desired | yes |
| 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:<br>• to assess efficacy, feasibility and safety of an intensified immunotherapy regimen. |
| Planned number of patients | N=280 enrolled to receive nivolumab mono-therapy<br>N=154 randomized |
| Current number of patients | 1 |
| 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<br>2. Age ≥ 18 years at time of study entry<br>3. Histological or cytological confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC) or nasal sinus not amenable to local therapies<br>4. Availability of tumor tissue from biopsy for determination of PD-L1 and HPV status according to the following priority ranking: i) recent biopsy (≤3 month old) without intervening therapy; ii) any recent biopsy (≤3 month old); iii) any |

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| | archival tumor tissue (> 3 month old) [Biopsy should be excisional, incisional or core biopsy. Fine needle aspiration is not allowed.]<br>5. Progression or recurrence during or after cetuximab+platinum-based 1st line palliative chemotherapy for relapsed or metastatic disease<br>OR<br>progression within 6 months after completion of definitive platinum-containing radiochemotherapy for locally advanced disease<br>6. At least 1 measurable lesion according to RECIST 1.1<br>7. ECOG performance status 0-1<br>8. Completion of local therapy for brain metastases with discontinuation of steroids prior to start of study treatment<br>9. Adequate blood count, liver-enzymes, and renal function:<br>• neutrophil count > 1.5 x $10^6$/mL<br>• Platelet count ≥ 100 x $10^9$/L (>100,000 per $mm^3$)<br>• hemoglobin ≥ 9 g/dL<br>• INR ≤ 1.5 and PPT ≤ 1.5 x lower limit during the last 7 days before therapy<br>• AST (SGOT)/ALT (SGPT) < 3 x institutional upper limit of normal (5 x lower limit in case of liver metastases)<br>• bilirubin < 1.5 x ULN<br>• Serum Creatinine ≤ 1.5 x institutional ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):<br>Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$<br>Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$<br>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.<br>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.]<br>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).<br>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.<br>**Inclusion criteria for randomization**<br>1. progressive disease according to RECIST 1.1<br>2. successful biospy of tumor tissue at time of disease progression (if feasible, biopsy from the progressive lesion is preferred)<br>3. known PD-L1 expression of most recent tumor tissue (primary, recurrence or metastasis)<br>4. known HPV-status in oropharyngeal disease<br>5. ECOG: 0-1<br>6. adequate organ function, defined as:<br>• neutrophil count > 1.5 x $10^6$/mL<br>• Platelet count ≥ 100 x $10^9$/L (>100,000 per $mm^3$)<br>• hemoglobin ≥ 9 g/dL<br>• INR ≤ 1.5 and PPT ≤ 1.5 x lower limit during the last 7 days before therapy<br>• AST (SGOT)/ALT (SGPT) < 3 x institutional upper limit of normal (5 x lower limit in case of liver metastases)<br>• bilirubin < 1.5 x ULN<br>• Serum Creatinine ≤ 1.5 x institutional ULN or creatinine clearance (CrCl) ≥ 40 mL/min<br>7. Immune related adverse events to prior nivolumab therapy have to resolve to grade ≤1 and may not require active treatment (prednisolone doses ≤10mg or equivalent doses of steroids are allowed) |

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| Global Exclusion criteria.<br><br>Assessments at screening and re-assessment before randomization | **Medical criteria:**<br>10. Nasopharynx carcinoma or carcinoma of salivary glands<br>11. Live expectancy less than 3 months<br>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:<br>a) Minor surgery ≤ 24 hours prior first dose of nivolumab monotherapy<br>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]<br>c) known active HBV, HCV or HIV infection<br>d) active tuberculosis<br>e) any other active infection requiring systemic therapy<br>f) history of allogeneic tissue/solid organ transplant<br>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.<br>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.<br>i) live vaccine within 30 days prior to the first dose of nivolumab-monotherapy treatment or during study treatment.<br>j) Other active malignancy requiring treatment<br>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<br>l) History or clinical evidence of CNS metastases<br>Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:<br>I. are asymptomatic and<br>II. have no requirement for steroids 6 weeks prior to start of nivolumab-monotherapy treament. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases<br><br>**Drug related criteria:**<br>13. Medication that is known to interfere with any of the agents applied in the trial.<br>14. Has known hypersensitivity to nivolumab or ipilimumab or docetaxel or any of the constituents of the products.<br>15. Any other efficacious cancer treatment except protocol specified treatment at study start.<br>**Safety criteria:**<br>16. Patient has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. [Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.]<br>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 β-HCG) at screening.<br>**Methodological criteria:** |

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| | 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 targeting T-cell co-stimulation or checkpoint pathways)<br>19. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lifes of previously used trial medication, whichever is longer<br>20. Previous treatment in the present study (does not include screening failure). [Criterion is not applicable during re-assessment of eligibility for randomization]<br>**Regulatory and ethical criteria:**<br>21. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |
| Investigational agents | • nivolumab<br>• ipilimumab<br>• docetaxel |
| Treatment schedule | 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$^2$ Q3W) or nivolumab+ipilimumab combination (NIVO 3mg/kg Q2W + IPI 1mg/kg Q6W) until PD or death.<br>Randomization will be performed centrally.<br>The stratification parameters are:<br>• PD-L1 expression:<br>< 1% vs ≥ 1%<br>• time point of PD during nivolumab monotherapy:<br>≤2 months vs > 2 months<br>• HPV status (p16 IHC; mandatory for subjects with oropharynx carcinoma):<br>positive vs negative<br><br>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.<br><br>Tumor assessment:<br>Nivolumab monotherapy cohort:<br>• from 1st dose of NIVO monotherapy until 12 weeks of treatment: Q4W<br>• from weeks 13 until 6 months of NIVO monotherapy: Q6W<br>• from 7$^{th}$ month until PD or end of study treatment: Q12W<br>Randomized cohorts:<br>• Q8W for the first 6 months and Q12W thereafter.<br><br>Treatment will continue until<br>a) progressive disease or death or a maximum of 12 months measured from randomization<br>b) intolerable toxicity<br>c) withdrawal of consent.<br>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 |
| Primary endpoint | • objective response rate in all randomized patients |

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| Secondary endpoints | • 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))<br>• PFS (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))<br>• BOR, DOR<br>• QoL (EORTC QLQC30; HN35; EQ-5D)<br>• AEs/SAEs |
| Translational research: Exploratory objectives and endpoints | Tumor tissue analysis:<br>All listed analysis are to be performed on pre-treatment tumor samples and in tissue matrial from re-biopsies taken at disease progression under - nivolumab monotherapy OR after 6 months of nivolumab monotherapy:<br><br>• PD-L1<br>• IFN – gamma signature (nano-string technology)<br>• mutational load of the tumor<br>• genetic alterations in the JAK signal transduction pathway |
| Rationale<br>Hypothesis | 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).<br>However, most patients will relapse and require subsequent palliative chemotherapy. Platin combined with fluorouracil and cetuximab is the GOLD standard in 1st 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).<br>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.<br><br>**Research hypothesis:**<br>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. |
| Safety data | • AEs, SAEs and treatment emergent adverse events according to CTC 4.03<br>• Frequency of clinically significant abnormal laboratory parameters |
| Sample size estimation and | N=280 patients enrolled to receive NIVO monotherapy<br>N=154 patients randomized after rapidly progressing disease. |

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| Statistical analysis considerations | Sample size calculation is based on the assumptions:<br>• that NIVO/IPI improves ORR to 25% in the randomized population compared to 10% with docetaxel treatment;<br>• 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)<br>• approx. 30-35% drop-out before the possibility of randomization due to toxicity, withdrawal of consent or loss-to-follow-up<br><br>Calculation for the randomized part:<br>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.<br>Total sample size of the trial is N= 154/0.85/0.65 = 280<br><br>Analysis strategies:<br>The primary objective will be measured by the primary endpoint of ORR (based on investigator assessments) among all randomized subjects.<br>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.<br>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. |
| Study plan / time lines | First Patient In (FPI): Q3/2018<br>Last Patient In (LPI): after approx. 24 month<br>Last Patient Last treatment (LPLT): after max. 42 month<br>End of follow-up period after LPI: after approx. 48 month<br>Study report: after approx. 57 month<br>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-assoziierte Studie**

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

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| Art der Studie | Randomisierte, explorative Phase-II-Studie |
| Leiter der klinischen Prüfung | Institut für Klinisch-Onkologische Forschung (IKF)<br>Ärztl. Direktor: Prof. Dr. Salah-Eddin Al-Batran<br>Krankenhaus Nordwest GmbH<br>UCT - Universitäres Centrum für Tumorerkrankungen Frankfurt<br>Steinbacher Hohl 2-26 60488 Frankfurt<br>E-Mail: albatran@aio-portal.de |
| Zentrale Studienkoordination | IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwes<br>Dr. Caroline Schönherr<br>Steinbacher Hohl 2-26 60488 Frankfurt<br>Tel: 069 7601 4094, FAX: 069 7601 3655<br>E-Mail: schoenherr.caroline@ikf-khnw.de www.ikf-nordwest.de |
| Ziele der Studie | Primär<br>Anstieg des Serum Hämoglobins um 2g/dl oder Normalisierung (12g/dl) des Serum Hämoglobins<br>Sekundärparameter<br>• Fatigue erhoben mittels EORTC-QLQ-FA13<br>• Erfassung der Lebensqualität mittels des EORTC-C30 Fragebogens<br>• Handkraftmessung mittels Hydraulic Hand Dynamometer<br>• Anzahl der allogenen Bluttransfusionen insgesamt und Anzahl der Transfusionen pro Patient<br>• Zeit bis zum Anstieg oder Normalisierung des Hämoglobins<br>• Untersuchungen zur Genese der beobachteten Anämie (Eisenmangelanämie bei chronischen Erkrankungen vs. Absoluter Eisenmangel in Abgrenzung zur Anämie bei chronischen Erkrankungen)<br>• Anzahl, Dosis und Dauer der Therapien mit rekombinantem Erythropoetin (r-HuEPO)<br>• 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).<br>• Einfluss des Ernährungsstatus auf die Eisenmangelanämie und den Therapieerfolg<br>• Verträglichkeit und Toxizität<br>• Abbruchrate aufgrund von Toxizität oder Patientenwunsch<br>• Gesamtüberleben (OS, gemessen ab Datum des Studieneinschlusses) |

<table>
<tr><td>Studiendesign</td><td>Patienten mit metastasiertem CRC unter palliativer Chemotherapie und diagnostizierter Eisenmangelanämie - nach Protokollvorgaben - werden nach Randomisation in einem der folgenden Arme behandelt:<br>Arm A: Parenterale Eisensubstitution mit Eisencarboxymaltose (Ferinject)<br>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.<br>Tab.1: Dosierungsschema für die parenterale Eisensubstitution mit Eisencarboxymaltose (Ferinject)<br><br><table><tr><td>Hb (g/dl)</td><td>Körpergewicht 35 -69 kg</td><td>Körpergewicht ≧70 kg</td></tr><tr><td><10</td><td>1500 mg</td><td>2000 mg</td></tr><tr><td>≥10</td><td>1000 mg</td><td>1500 mg</td></tr></table>Arm B: Per orale Eisensubstitution mit Eisen(II)-glycin-sulfat-Komplex (Ferro sanol Duodenal Kapseln)<br>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.<br>Zusätzlich erfolgt in beiden Gruppen - Arm A und Arm B - eine orale Folsäure- und Vitamin B12-Substitution. Die Folsäure-Substitution beträgt 400 µg pro Tag und die Vitamin B12-Substitution beträgt 10 µg pro Tag. Beide Vitamine werden in vorgeschriebener Dosis einmal täglich über den gesamten Studienzeitraum eingenommen.<br>Die Diagnostik der Eisenmangelanämie erfolgt über das Serum Hämoglobin (≤ 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 < 20 % und einem Serum Ferritin < 30 ng/ml. Ein Defizit an funktionell verfügbarem Eisen liegt vor bei einer Transferrin-Sättigung < 20 % und einem Serum Ferritin > 30 bis maximal 800 ng/ml.<br>Das Monitoring der Laborparameter (Eisen, Transferrin, Ferritin, Transferrinsättigung, Differentialblutbild (numerisches Blutbild, inkl. hypochromer Erythrozyten), Retikulozyten Hb-Wert, MCV, MCH, sTfR (löslicher Transferrin-Rezeptor), CRP, Hepcidin) erfolgt 4-wöchentlich über das Zentrallabor. Steigt die Transferrin-Sättigung > 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).<br>Zusätzlich wird der Einfluss der Tumorerkrankung auf den Eisenstoffwechsel erfasst. Hierzu wird Hepcidin, 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.</td></tr>
<tr><td>Rationale</td><td>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 Eisenfreisetzung 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</td></tr>
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| | möglichst gering zu halten. Daten zeigen, dass eine Eisensubstitution den Abfall des Serum Hämoglobins verhindern kann und somit den Einsatz von r-HuEPO und Bluttransfusion reduziert.<br><br>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.<br>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. |
| Therapieschemata | Arm A: Parenterale Eisensubstitution mit Eisencarboxymaltose (Ferinject)<br>Eisencarboxymaltose 10 ml in maximal100 ml NaCl 0.9% (500 mg Eisen), 20 ml in maximal 250 ml NaCl 0.9% (1000 mg Eisen).<br>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.<br>Therapiedauer in der Studie: 12 Wochen.<br>Anschließend entscheidet der behandelnde Arzt über die weitergehende antianämische Behandlung.<br>Arm B: Eisensubstitution per oral mit Eisen(II)-glycin-sulfat-Komplex (Ferro sanol Duodenal Kapseln).<br>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.<br>Therapiedauer in der Studie: 12 Wochen<br>Anschließend entscheidet der behandelnde Arzt über die weitergehende antianämische Behandlung. |
| Einschlusskriterien | 1. Metastasiertes oder inoperables kolorektales Karzinom. Patienten, für die keine kurative Therapie möglich ist.<br>2. Laufende palliative Chemotherapie. Potentiell resektable Patienten, die eine Konversionstherapie erhalten, können nicht in die Studie eingeschlossen werden.<br>3. Eisenmangelanämie: Hb-Wert: ≤ 10.5 g/dl und Transferrinsättigung (TSAT) < 20% und/oder Serum Ferritin < 30 ng/ml<br>4. Männliche und weibliche Patienten im Alter $\geq$ 18 Jahren; mündig<br>5. ECOG ≤ 2<br>6. Schriftliche Einverständniserklärung des Patienten<br>7. Lebenserwartung des Patienten > 6 Monate<br>8. Körpergewicht ≥ 40 kg |
| Ausschlusskriterien | 1. Eisensubstitution oral oder i.v. bzw. Bluttransfusion in den letzten 4 Wochen<br>2. Alter <18 Jahre oder Körpergewicht < 40 kg<br>3. Resorptionsstörung bei Kurzdarmsyndrom oder nach Magenentfernung<br>4. Therapie mit rekombinantem Erythropoetin (r-HuEPO) in den letzten 4 Wochen<br>5. Chronische Diarrhö<br>6. Chronisch entzündliche Darmerkrankungen<br>7. Ferritin > 800 ng/ml am Studienstart<br>8. Bekannte Überempfindlichkeit gegen Eisencarboxymaltose und Eisen(II)-glycin-sulfat-Komplex oder Vorliegen von Kontraindikationen gegen Eisencarboxymaltose und Eisen(II)-glycin-sulfat-Komplex |

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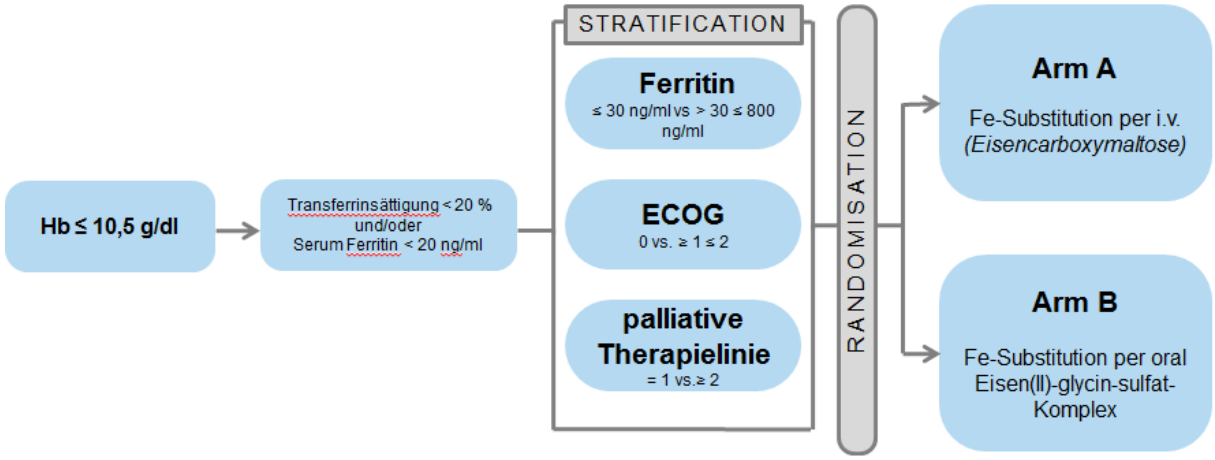
| | 9. Bekannter Vitamin B12 oder Folsäure Mangel<br>10. Notwendigkeit der parenteralen Ernährung<br>11. Teilnahme an einer anderen interventionellen Studie<br>12. Schwangerschaft oder Stillzeit |
| Fallzahl<br><br>Dauer der Studie | 64 Patienten<br><br>Individuelle Beobachtungszeit pro Patient 12 Wochen ab Einschluss (Therapiebeginn) bzgl. des primären Endpunktes. Weitere Beobachtung bzgl. des Überlebens z.B. telefonisch bis zu 2 Jahre.<br>Dauer der Studie insgesamt ca. 18 Monate plus bis zu 2 Jahren Nachbeobachtungszeit |
|  | |
| | Initiierung des 1. Zentrums erfolgte am 30. März 2015.<br>Rekrutierung: bis voraussichtlich 31. Dezember 2018.<br>Teilnehmende Prüfzentren: 19<br>Weitere Prüfzentren erwünscht: ja<br>Rekrutierungsstand per 10/2018: **60** |

**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**

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| Studiennummer/-Code: | AIO-LQ-0113/ass - QoLiTrap-Trial |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2013 – Sep 2019 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Art der Studie | Prospektive, nicht-interventionelle Studie |
| Studienleitung | Arbeitsgruppe Lebensqualität der AIO<br>Prof. Dr. R. Hofheinz<br>Tages Therapie Zentrum (TTZ) am<br>Interdisziplinären Tumorzentrum (ITM)<br>III. Medizinische Klinik<br>Universitätsklinikum Mannheim<br>Theodor-Kutzer-Ufer 1-3, 68167 Mannheim<br>Tel: 0621/383-2855; FAX 0621/383-3833<br>E-Mail: ralf.hofheinz@umm.de |
| Sponsor | Sanofi-Aventis Deutschland GmbH<br>Klinische Forschung, Burkhard Linße<br>Potsdamer Str. 8, 10785 Berlin<br>Tel: 030/2575-2821 |
| Studienziele | <u>Primäres Studienziel:</u><br>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.<br><br>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.<br><br><u>Sekundäre Studienziele:</u><br>• Auswirkung der Therapie auf andere Dimensionen/Skalen der Lebensqualität<br>• Auswirkungen der Toxizitäten auf die Lebensqualität<br>• Auswirkungen vorbestehender Symptome auf die Lebensqualität<br>• Prädiktive Faktoren für die Verbesserung der Lebensqualität<br>• Vergleich der Lebensqualität von Respondern und Non-Respondern<br>• Ermittlung unerwünschter Arzneimittelwirkungen/Ereignisse<br>• Vergleich der Lebensqualität in den Subgruppen RAS –WT und RAS- mt |
| Zielparameter | Lebensqualität |
| Patientenzahl | Geplant: 1500 Patienten (D 1340, A 75, CH 85)<br>Bereits eingeschlossen: 1172 (D 1037; A 58, CH 77) |
| Studienstart | 24.09.2013 |
| Studienende | LPI = Last patient in: September 2019<br>LPLV = Last patient last visit: 31. März 2020 |

| | LPO März 2020 |
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| Weitere teilnehmende Zentren erwünscht? | ja |
| Einschlusskriterien | Patienten mit metastasiertem kolorektalem Karzinom, die für eine Behandlung mit Aflibercept in Frage kommen |
| Therapieschema | 4 mg Aflibercept/ kg zusätzlich zur Chemotherapie |
| Evaluierung der Lebensqualität | 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).<br>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.<br>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. |
| Fallzahlbegründung | Basierend auf vorangegangen 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.<br>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 Aflibercept 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.<br>Die statistische Genauigkeit der Schätzungen für die Erfolgsraten werden mit Hilfe von 95% Konfidenzintervallen dargestellt.<br>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 enthalten.

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.

| Patientenzahl | Erfolgsrate 65%<br>95% Konfidenzintervall<br>(Blyth-Still-Casella) | Erfolgsrate 50%<br>95% Konfidenzintervall<br>(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% |

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)

# 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-assoziierte Studie**

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

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| Art der Studie | Phase-III, multizentrisch, prospektiv, randomisiert | |
| Sponsor's Responsible Person | Universitätsklinikum Ulm (AöR), Albert-Einstein-Allee 29, D-89081 Ulm<br>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<br>Studienzentrale<br>Prittwitzstr. 43<br>D-89075 Ulm<br>Germany | Physician: Dr. F. Schochter, Dr. S. Albrecht, Dr. A. Schramm, A.Polasik, Prof. Dr. J. Huber<br>Studycoordinators: Evelyn Jäckel, Heike Karl & Jessica D'Andrea<br>Tel: +49 (0) 731 500 58520/-58521<br>FAX: +49 (0) 731 500 58526<br>E-Mail: studienzentrale.ufk@uniklinik-ulm.de |
| Patientenzahl | Geplant: 120 Patientinnen<br>randomisiert: 96 (Stand Okt. 2018) | |
| 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.<br>Evaluation der Toxizität bei Patientinnen mit ossären Metastasen, welche Denosumab in Kombination mit verschiedenen Studienmedikationen erhalten. | |
| Studienziele | Primäres Zielkriterium:<br>▪ 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)<br><br>Sekundäre Zielkriterien:<br>▪ Progressionsfreies Überleben (PFS)<br>▪ Allgemeine Ansprechrate: Komplettremission (CR), Teilremission (PR)<br>▪ Klinische Erfolgsrate<br>▪ Gesamtüberleben<br>▪ Dynamik der zirkulierenden Tumorzellen<br>▪ Evaluation der Lebensqualität (EORTC QLQ-C30 und EORTC QLQ-BR23 Fragebögen)<br>▪ Toxizitätsanalyse von Lapatinib: Sicherheit und Verträglichkeit | |

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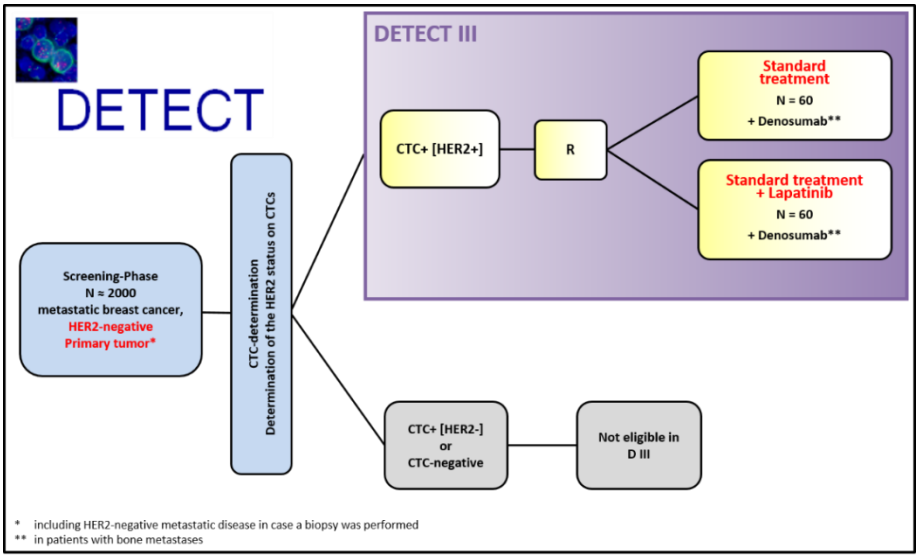
| | ▪ Compliance<br>▪ Schmerzanalyse: Messung anhand einer Numerischen Rating-Skala (NRS) |
| Studiendesign |  |
| Einschlusskriterien | 1. Schriftliche Einverständnis zur Studienteilnahme<br>2. Metastasiertes Mammakarzinom, das einer Operation oder der Strahlentherapie allein nicht zugänglich ist. Histopathologische Sicherung des primären Mammakarzinoms oder einer metastatischen Läsion des Mammakarzinoms und Bestimmung des Östrogen- und Progesteronrezeptorstatus<br>3. Bestimmung des HER2-Status des primären Mammakarzinoms und/oder einer metastatischen Läsion. HER2-Negativität aller untersuchten Gewebeproben, d.h. Immunhistochemie 0-1+ <u>oder</u> 2+ und Fluoreszenz in situ Hybridisierung (FISH) negativ <u>oder</u> nur FISH negativ.<br>4. Nachweis HER2-positiver zirkulierender Tumorzellen (CTC) (HER2-Status ermittelt über IHC oder FISH)<br>• Mindestens eine CTC/7.5 ml Blut (CellSearch® Circulating Tumor Cell Kit) und<br>• Mindestens eine HER2-positive CTC<br>5. Indikation zur Standard-Chemo- oder endokrinen Therapie, deren Kombination mit Lapatinib zugelassen ist (Tyverb® 250 mg Tabletten) oder in klinischen Studien evaluiert wird<br>6. Tumorevaluation innerhalb von 6 Wochen vor Studienrandomisierung<br>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]<br>8. Alter ≥ 18 Jahre<br>9. ECOG <u>≤</u> 2<br>10. Adäquate Knochenmarksreserve und Organfunktion<br>• Absolute Neutrophile ≥ 1500/µL,<br>• Thrombozyten ≥ 100000/µL,<br>• Hämoglobin ≥ 9g/dL,<br>• ALT (SGPT) ≤ 3.0 × ULN,<br>• AST (SGOT) ≤ 3.0 × ULN,<br>• Bilirubin (gesamt) ≤ 2 × ULN und ≤ 35% direkt<br>• Kreatinin ≤ 2.0 mg/dl oder 177µmol/L,<br>**<u>Cave:</u>** 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.<br>11. Echokardiographischer Nachweis einer ausreichenden linksventrikulären Ejektionsfraktion innerhalb des Referenzbereichs der jeweiligen Institution<br>12. Bei gebärfähigen Patientinnen gilt: |

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| | • Negativer Schwangerschaftstest (minimale Sensitivität 25 IU/L oder äquivalente Einheiten des HCG) innerhalb von 7 Tagen vor Randomisierung<br>• 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. |
| Ausschlusskriterien | 1. Anamnestisch bekannte Überempfindlichkeit gegenüber Lapatinib oder chemisch verwandten Substanzen<br>2. Mehr als 3 palliative Chemotherapie-Linien (dabei ist eine Chemotherapie-Linie definiert als jede neue Chemotherapie und jede Modifikation eines bestehenden Chemotherapieregimes)<br>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<br>4. Persistierende, therapeutisch relevante Nebenwirkungen einer vorangegangenen antineoplastischen Therapie während des Randomisierungszeitraums > Grad 1 (NCI CTCAE)<br>5. Anti-retrovirale Therapie aufgrund einer HIV-Infektion<br>6. Aktuelle Leber- oder Gallenwegserkrankung (mit Ausnahme von Patientinnen mit Gilberts-Syndrom, mit asymptomatischen Gallensteinen, Lebermetastasen oder stabiler chronischer Lebererkrankung)<br>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<br>8. Zweitkarzinom innerhalb der letzten 3 Jahre (außer in-situ-Karzinom der Cervix uteri oder Basaliom der Haut)<br>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))<br>10. Manifeste kardiale Vorerkrankung, definiert als:<br>• instabile Angina pectoris in der Vorgeschichte,<br>• therapiebedürftige oder klinisch relevante Arrhythmien in der Vorgeschichte (ausgenommen asymptomatisches Vorhofflimmern, welches einer Antikoagulation bedarf),<br>• Z. n. Myokardinfarkt innerhalb der letzten 6 Monate vor Studieneintritt,<br>• symptomatische Herzinsuffizienz,<br>• Ejektionsfraktion < 50% oder unterhalb des oberen Referenzbereichs der jeweiligen Institution<br>• jede andere kardiale Begleiterkrankung, die nach Ansicht des behandelnden Arztes zu einer unverhältnismäßigen Gefährdung der Patientin bei Studienteilnahme führen würde<br>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<br>12. Lebenserwartung < 3 Monate<br>13. Männliche Patienten<br>14. Schwangerschaft oder Stillzeit<br>15. HER2-positiver Primärtumor oder HER2-positive Gewebeprobe einer metastatischen Läsion<br>16. Jede vorangegangene Behandlung mit anti-HER2-gerichteter Therapie |
| 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

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

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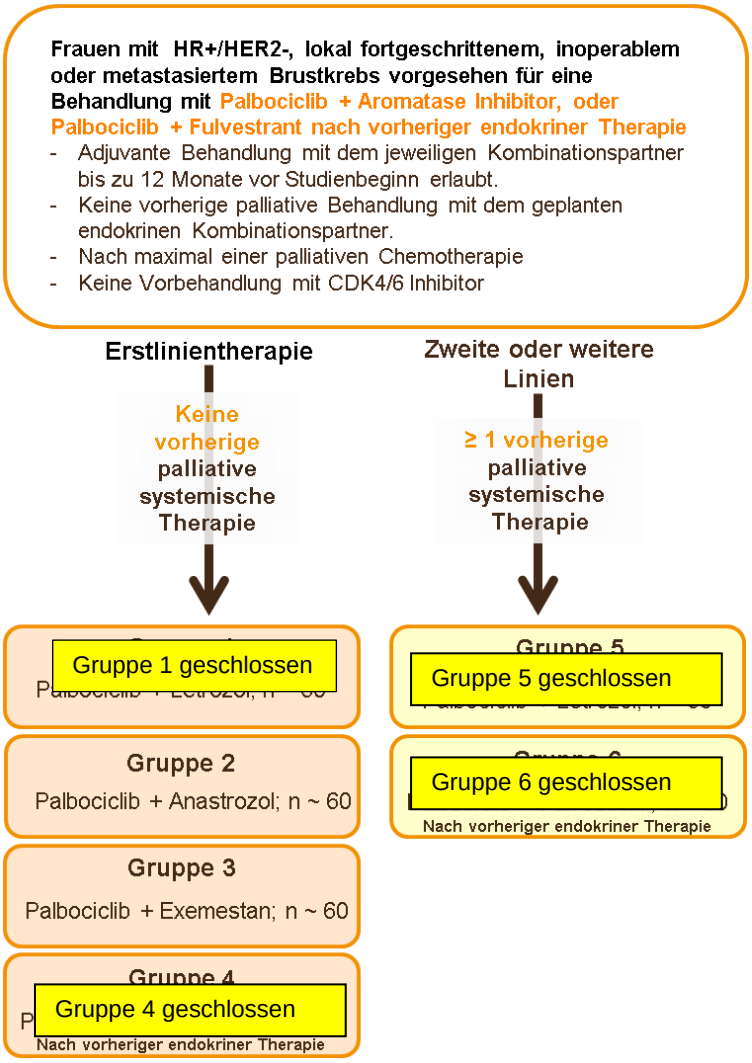
| LKP Deutschland | Dr. med. Manfred Welslau |
| Sponsor | iOMEDICO AG |
| Studienpopulation | Patientinnen mit histologisch gesichertem lokal fortgeschrittenem oder metastasiertem hormonrezeptor-positivem, HER2/neu negativem Brustkrebs, die für eine Kombinationstherapie mit Palbociclib und einem Aromataseinhibitor oder Fulvestrant (Fulvestrant nach vorheriger endokriner Therapie) geeignet sind. |
| Anzahl Patientinnen | 360 Patientinnen |
| Anzahl Zentren | 85 Zentren in Deutschland |
| Studiendesign | 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.<br>Insgesamt werden 360 Patientinnen in die Studie aufgenommen. Ziel der Studie ist es, 60 (58-62) Patientinnen je Rekrutierungsgruppe (siehe Abbildung) einzuschließen.<br>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 (*end of treatment*, EOT) definiert.<br>Nach EOT folgt für die Patientin die Follow-up (FU) Phase. Diese beinhaltet:<br>• die Palbociclib Sicherheits-FU Visite 30 Tage (+7 Tage) nach EOT,<br>• die FU-Phase bis zur Krankheitsprogression mit fortgeführten Erhebungen (nur für die Patienten, die bei EOT keine Progression zeigten) und<br>• die FU-Phase für Überleben bis zum Ende der Studie (*end of study*, EOS)<br>EOS ist definiert als letzte Visite der letzten eingeschlossenen Patientin (*last patient last visit*, LPLV). |

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| Zweck und Rationale | Brustkrebs ist die häufigste bösartige Krebserkrankung bei Frauen in der westlichen Welt und die Hauptursache von Krebstod bei Frauen weltweit (WHO 2014). Hormonrezeptor-positiver (HR+)/humaner epidermaler Wachstumsfaktor-Rezeptor 2-negativer (HER2-) Brustkrebs ist der häufigste molekulare Subtyp und macht ungefähr drei Viertel aller Brusttumore aus.<br>Endokrine Therapie ist eine Standardbehandlung für HR+ Brustkrebs und beinhaltet die Behandlung mit dem nicht-steroidalen Aromatase-Inhibitor Letrozol für postmenopausale Frauen.<br>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.<br>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.<br>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 (*progression-free survival*, PFS) in einem klinisch relevanten Ausmaß von 20,2 auf 10,2 Monate (HR 0,51). Die |

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| | Gesamtansprechrate (*overall response rate*, ORR) betrug 48% im Vergleich zu 41%. Die klinische Benefitrate (*clinical benefit rate*, CBR) war mit 84% im Vergleich zu 70% ebenfalls verbessert [1].<br>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.<br>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% ein komplette Response, 43% eine partielle Response und 15% eine stabile Erkrankung.<br>Die Kombination von Palbociclib und Exemestan im Vergleich zu Capecitabin wird zur Zeit in einer offenen, randomisierten Phase III Studie (PEARL; n=348) geprüft.<br>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].<br>Auf Grundlage dieser Ergebnisse wurde Palbociclib (Ibrance®) in Europa für die Behandlung von HR+/HER2- metastasiertem Brustkrebs nach endokriner Therapie für folgende Kombinationen zugelassen:<br>• In Kombination mit einem Aromataseinhibitor, oder<br>• In Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten.<br>Bei prä- oder perimenopausalen Frauen ist die endokrine Therapie mit einem luteinisierenden Hormon Releasing-Hormon (LHRH) zu kombinieren.<br>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]. |
| Primärer Zielparameter | Der primäre Zielparameter dieser Studie ist die Beurteilung der Effektivität über den klinischen Benefit nach 24 Wochen (*Clinical Benefit Rate*, CBR).<br>CBR ist nach RECIST 1.1 definiert als komplette Remission (*complete response*, CR), partielle Remission (*partial response*, PR) oder stabile Erkrankung (*stable disease*, SD). |
| Sekundäre Zielparameter | Beurteilung der Sicherheit und Verträglichkeit durch Erfassung von<br>• 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 (*progressive disease,* PD) bzw. bis zum Beginn der nächsten Krebstherapie, falls diese früher erfolgt.<br>• jeglichen Laborwertabweichungen bis EOT<br>• Häufigkeit und Dauer von Krankenhausaufenthalten bis zur Progression oder bis zum Beginn der nächsten Krebstherapie, falls diese früher erfolgt.<br>Beurteilung der Behandlungswirksamkeit durch Bestimmung von<br>• Progressionsfreies Überleben (PFS)<br>• Gesamtüberleben (OS)<br>• CBR nach 48 Wochen<br>• PFS-Rate nach einer 48-wöchigen (für alle Patientinnen) und nach einer 2-jährigen Behandlung (nur für Erstlinienpatientinnen)<br>• OS-Rate nach 48 Wochen (für alle Patientinnen) und danach jährlich bis Studienende (*end of study, EOS*) (nur für Erstlinienpatientinnen).<br>Beurteilung der Adhärenz über die Erfassung der<br>• Behandlungsdauer<br>• Gründe für einen Behandlungsabbruch |

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| | • Dosisanpassungen (Häufigkeit, Grund)<br>• Patiententagebuch bis EOT<br>Beurteilung der gesundheitsbezogenen Lebensqualität (*quality of life*, QoL), Fatigue, Angst und Depression<br>• Die gesundheitsbezogene QoL wird mit Hilfe des FACT-B-Fragebogens (*Functional Assessment of Cancer Therapy - Breast)* erfasst, alle 12 Wochen bis zur PD (oder bis zum Beginn der folgenden Krebstherapie, falls diese früher erfolgt)<br>• Fatigue wird mit dem BFI-Fragebogen (*Brief Fatigue Inventory*) erfasst, alle 12 Wochen bis zur PD (oder bis zum Beginn der folgenden Krebstherapie, falls diese früher erfolgt)<br>• Depression und Angst werden mit dem HADS-D-Fragebogen (*Hospital Anxiety and Depression Scale*) erfasst, alle 12 Wochen bis zur PD (oder bis zum Beginn der folgenden Krebstherapie, falls diese früher erfolgt)<br>Vergleich der QoL mit „Real-life“ Patientinnen, die eine Erstlinien-Chemotherapie im Rahmen der nicht-interventionellen MaLife Studie bekommen:<br>• 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<br>Ärztliche Beurteilung des allgemeinen Gesundheitszustands der Patientin sowie von Veränderungen im Gesundheitszustand im Vergleich zur vorangegangenen Visite<br>• 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)<br>Untersuchung, ob organspezifische Symptome als Indikatoren für PD dienen können<br>• 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. |
| Tertiäre Zielparameter | Etablierung einer dezentralen, virtuellen Biobank für die zukünftige Erfassung und zentrale Analyse von prädiktiven Biomarkern des CDK4/6-Signalwegs. |
| Haupt-Einschlusskriterien | 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<br>2. Frauen mit bestätigter Diagnose von fortgeschrittenem Adenokarzinom der Brust, als lokal fortgeschritten, inoperabel oder metastasiert definiert<br>3. Hormonrezeptor-positive (HR+) Erkrankung, definiert als Östrogenrezeptor-positiv (ER+) und/oder Progesteronrezeptor-positiv (PgR+)<br>4. Humaner epidermaler Wachstumsfaktor-Rezeptor 2-negative (HER2-) Erkrankung (HER2 neg/+ oder Her2++ mit CISH/FISH neg.)<br>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.<br>6. Alter ≥ 18 Jahre<br>7. Messbare Läsionen nach RECIST (*Response Evaluation Criterion in Solid Tumors*) oder nur Knochenmetastasen (bone-only)<br>8. Geeignet für eine Kombinationstherapie mit Palbociclib und |

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| | -Letrozol in der Erst und Folgelinien oder<br>-Anastrozol in der Erstlinie oder<br>-Exemestan in der Erstlinie oder<br>-Fulvestrant in der Erst- und Folgelinie (nach endokriner Therapie)<br>9. ECOG Status 0-2<br>10. Ausreichende Organ- und Knochenmarksfunktion<br>11. Auflösung aller akuten toxischen Effekte von früheren Therapien, inklusive Radiotherapie, Grad ≤1 (ausgenommen Toxizitäten, die nicht als Sicherheitsrisiko für die Patientin eingestuft werden), sowie Erholung nach chirurgischen Eingriffen<br>Deutschkenntnisse (fließend in Wort und Schrift) |
| Haupt-Ausschlusskriterien | 1. Vorherige Behandlung mit einem CDK4/6-Inhibitor<br>2. Vorherige adjuvante Therapie mit dem geplanten Kombinationspartner, wenn die letzte Einnahme <12 Monate vor Einschluss in die Studie stattfand<br>3. Vorherige palliative Therapie mit dem geplanten Kombinationspartner<br>4. Mehr als eine vorherige palliative Chemotherapie<br>5. Bekannte Hypersensitivität auf Letrozol, Anastrozol, Exemestan oder Fulvestrant oder einem seiner Trägerstoffe<br>6. Verzehr von Nahrungsmitteln oder gegenwärtige Einnahme von Substanzen, welche als starke Inhibitoren oder Auslöser von CYP3A4 bekannt sind<br>7. Gegenwärtige Einnahme von Substanzen, die Johanniskraut beinhalten<br>8. Teilnahme an anderen interventionellen Studien innerhalb der letzten 2 Wochen vor Beginn der Behandlung im Rahmen der vorliegenden Studie<br>9. QTc > 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<br>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<br>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<br>12. Diagnose jeglicher sekundären malignen Erkrankung innerhalb der letzten 3 Jahre vor Einschluss, ausgenommen eines angemessen behandeltem Basalzell- oder Plattenepithelkarzinom, oder Carcinoma *in situ* des Gebärmutterhalses<br>Bereits bekannte, nicht bestrahlte ZNS-Metastasen |
| Voraussichtlicher Zeitplan | Geplante Studiendauer: ca. 6 Jahre<br>FPI: Sep 2016<br>LPI: Dez 2018<br>LPO: Dez 2022<br>Ende Follow-up: Dez 2022<br>Daten prim. Zielparameter: Juli 2019 |
| Studien- und Referenztherapie | 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).<br>Die Kombinationspartner werden gemäß Produktinformationen verabreicht:<br>• Letrozol oral 2,5 mg 1 x täglich, kontinuierlich |

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| | • Anastrozol oral 1mg 1 x täglich, kontinuierlich<br>• Exemestan oral 25mg 1 x täglich, kontinuierlich<br>• Fulvestrant intramuskulär: 1. Zyklus: 500mg 1x Tag 1 und Tag 15; jeder weitere Zyklus: Tag 1<br>Bei prä- oder perimenopausalen Frauen ist die endokrine Therapie mit einem luteinisierenden Hormon Releasing-Hormon (LHRH) zu kombinieren. |
| Datenanalyse | 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.<br>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.<br>Die Darstellung sämtlicher Listings und Tabellen erfolgt bezogen auf die jeweilige Rekrutierungssgruppe (Erstlinien-/Folgelinientherapie).<br>Patientinnenbefragungen (*Patient-reported outcomes*, 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.<br>Deskriptive Statistik wird für die Beurteilung von Messzeitpunkten und Veränderungen im Lauf der Zeit in den Rekrutierungsgruppen Erstlinie/spätere Therapielinien durchgeführt.<br>Korrelationen zwischen CBR und QoL (FACT-B) sowie zwischen der ärztlichen Beurteilung und QoL werden ermittelt.<br>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.<br>Mögliche Indikatoren für PD werden durch Korrelation zwischen der Häufigkeit organspezifischer AEs und der PD-Häufigkeit in dem jeweiligen Organsystem zu bestimmten Zeitpunkten ermittelt. |

*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

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| Studiennummer/-Code: | AIO-MAM-0117/ass - RIBBIT (*IOM-050371 CLEE011ADE04T)* |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2018 – 2020 |
| Weitere Zentren: | Interessierte Zentren wenden sich bitte an den Sponsor |
| Letzte Aktualisierung | Oktober 2018 |
| Anzahl der initiierten Sites | 28 |
| Anzahl eingeschlossener Patienten | 5 |

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| Leiter der klinischen Prüfung | *Prof. Dr. Thomas Decker*<br>*Elisabethenstraße 19*<br>*88212 Ravensburg* |
| Sponsor | *iOMEDICO* |
| Studiendesign | 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.<br><br>160 Patientinnen werden eingeschlossen und 1:1 randomisiert (stratifiziert nach dem Vorhandensein von Lungen- und/oder Lebermetastasen) um<br>Arm A: eine Kombination aus Ribociclib mit AI; ODER<br>Arm B: Paclitaxel mit/ohne Bevacizumab<br>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 steroidalen AI kombiniert wird, wenn ein nicht-steroidaler AI in der Adjuvanz gegeben wurde und andersherum.<br>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.<br>Die endokrine Therapie mit dem AI im Ribociclib + AI Arm kann nach Absetzen von Ribociclib fortgesetzt werden. Der Abbruch von Ribociclib und AI (oder AI, |

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| | 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.<br>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. |
| Indikation | Diese Studie schließt erwachsene weibliche, postmenopausale Patientinnen mit HR-positivem, HER2-negativem Brustkrebs mit viszeralen Metastasen ein, die keine vorangegangene Therapie in der fortgeschrittenen Situation erhalten haben. |
| Prüfpräparat und Vergleichstherapie | *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).*<br>*Arm A: Ribociclib (600 mg/day) plus AI (entweder Letrozol (2.5 mg/Tag) ODER Anastrozol (1 mg/Tag) ODER Exemestan (25 mg/Tag))*<br>*Arm B: Paclitaxel (90 mg/m$^2$) ± Bevacizumab (10 mg/kg)* |
| *Anzahl von Patienten und Studienzentren* | *160 Patientinnen in 30 Zentren (niedergelassene Onkologen und Gynäkologen, onkologische Ambulanzen und Kliniken)* |
| Studienrationale | 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.<br><br>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.<br><br>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 viszeraler Metastasierung (Fietz et al. 2017). Die am häufigsten eingesetzte |

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| | Chemotherapie war Paclitaxel, welches eine der wirksamsten Substanzen bei Brustkrebs darstellt.<br>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-positive, PgR-positive: 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.<br><br>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. |
| Zielparameter | **Primäres Studienziel:**<br>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.<br><br>**Sekundäre Studienziele:**<br>Vergleich der beiden Studienarme hinsichtlich der folgenden Wirksamkeitsparameter: Ansprechraten (ORR), klinische Benefitrate (CBR), Zeit bis zum Ansprechen (TTR) und Gesamtüberleben (OS).<br>Bestimmung der Sicherheit und Verträglichkeit der beiden Behandlungsarme hinsichtlich der (S)UEs, ECOG Performance Status, Routinelaboruntersuchungen und Elektrokardiogramm.<br>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<br><br>**Exploratives Studienziel:**<br>Vergleich beider Therapiearme hinsichtlich des sPFS. |
| Studienendpunkte | **Primärer Endpunkt**:<br>• 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.<br><br>**Sekundäre Endpunkte:**<br>*Wirksamkeit:*<br><br>• ORR (komplettes oder partielles Ansprechen) erfasst durch den lokalen Untersucher mittels RECIST v1.1.<br>• CBR (komplettes oder partielles Ansprechen oder stabile Erkrankung für mindestens 24 Wochen) erfasst durch den lokalen Untersucher mittels RECIST v1.1. |

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| | • TTR (Zeit von der Randomisierung bis zum ersten Ansprechen (komplett oder partiell)) erfasst durch den lokalen Untersucher mittels RECIST v1.1.<br>• Gesamtüberleben definiert als Zeit von der Randomisierung bis zum Tod jeglicher Ursache.<br><br>*Sicherheit und Verträglichkeit:*<br><br>• (Schwerwiegende) Unerwünschte Ereignisse ((S)UE): Häufigkeit und Schweregrad gemäß CTCAE v4.03 bis 30 Tage nach Ende der Therapie<br>• Zeit bis zur Verschlechterung des ECOG Performance Status um mindestens einen Punkt<br>• Routinelaboruntersuchungen bis zum Therapieende<br>• Elektrokardiogramm (EKG) bis zum Therapieende<br><br>*Vom Patienten berichtete Lebensqualität:*<br><br>• Zeit bis zur Abnahme des Wertes der Skala „globaler Gesundheitsstatus“ des EORTC QLQ-C30 Fragebogens um mindestens 10 Punkte<br>• Veränderung im Vergleich zur Baseline der Skala „globaler Gesundheitsstatus“ und aller funktionellen und Symptom –Skalen des EORTC QLQ-C30<br>• 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<br>• Belastung durch Nebenwirkungen der Therapie zu allen Fragebogenzeitpunkten (Einzelfrage)<br>• Zeitliche Belastung durch die Therapie zu allen Fragebogenzeitpunkten (vier Einzelfragen)<br><br>***Explorativer Endpunkt**:*<br>• 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 |
| *Haupt-Einschlusskriterien* | • Alter ≥ 18 Jahre.<br>• Postmenopausale Frauen.<br>• Frauen mit vor Ort bestätigter Diagnose eines metastasierten Adenokarzinom der Brust ohne vorangegangene systemische antineoplatische Therapie in der palliativen Situation.<br>• Hormonrezeptor (HR)-positive Erkrankung, definiert als Östrogenrezeptor (ER)-positiv und / oder Progesteronrezeptor (PgR)-positiv.<br>• Human epidermal growth factor receptor 2 (HER2)-negative Erkrankung, definiert als IHC-Status HER2 negativ/+ oder IHC HER2++ bei CISH/FISH negativem Befund.<br>• Vorhandensein von viszeralen Metastasen (zusätzlich können weitere nicht-viszerale Metastasen vorhanden sein).<br>• Vorliegen von Zielläsionen und / oder nicht-Zielläsionen gemäß RECIST v1.1.<br>• Patienten müssen gemäß der entsprechenden Fachinformationen für eine palliative Therapie mit Ribociclib + AI und Paclitaxel +/- Bevacizumab qualifizieren.<br>• Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.<br>• Ausreichende Organ- und Knochenmarksfunktion innerhalb 7 Tage vor Randomisierung.<br>• Standard 12-Kanal EKG Werte: QTcF Intervall im Screening < 450 msec; durchschnittlicher Ruhepuls von 50-90 bpm<br>• Unterschriebene, schriftliche Einwilligung nach erfolgter Aufklärung vor Beginn von protokollspezifischen Maßnahmen. |
| *Haupt-Ausschlusskriterien* | • Jegliche vorangegangene Palliativtherapie.<br>• Vorangegangene Therapie mit irgendeinem CDK4/6 Inhibitor. |

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| | • Vorangegangene adjuvante Therapie mit einem AI, wenn die letzte Einnahme weniger als 12 Monate vor Studieneinschluss zurückliegt.<br>• Vorangegangene adjuvante oder neoadjuvante Therapie mit einem Taxan, wenn die letzte Verabreichung innerhalb von 12 Monaten vor Studieneinschluss war.<br>• Die Patientin erhält gleichzeitig eine andere anti-tumorale Therapie<br>• 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.<br>• 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).<br>• Bekannte Überempfindlichkeit gegen Ribociclib, AI, Paclitaxel, Bevacizumab oder irgendeinen ihrer Inhaltsstoffe.<br>• 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 > 150 oder < 90 mmHg oder diastolischer Blutdruck von > 100 mmHg).<br>• Die Patientin hatte eine arterielle Thrombose, die weniger als 12 Monate zurückliegt.<br>• Die Patientin hat eine Proteinurie (≥ 2+ auf dem Protein Messstäbchen)<br>• Die Patientin hat eine angeborene Blutungsneigung, eine erworbene Gerinnungsstörung oder nimmt die volle Dosis Anti-Koagulanzien ein<br>• 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.<br>• 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.<br>• Patientin erhält gleichzeitig Warfarin oder ein anderes von Kumarin abgeleitetes Anti-Koagulanz in therapeutischer, prophylaktischer oder anderer Indikation. Eine Therapie mit Heparin, niedermolekularem Heparin oder Fondaparinx ist erlaubt.<br>• Die Patientin erhält gleichzeitig oder innerhalb von 2 Wochen vor Begin der Studienmedikation systemische Kortikosteroide oder andere chronische Immunsuppressiva.<br>• 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).<br>• Patientin mit bekannter Anamnese einer HIV Infektion (Testung ist nicht vorgeschrieben).<br>• 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.).<br>• Vorangegangene Teilnahme an einer klinischen Prüfung innerhalb von 30 Tagen oder 5 Halbwertszeiten des Prüfpräparats vor Randomisierung, je nach dem was länger ist. |
| *Erfassung der Wirksamkeit* | • 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. |

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| | • Ganzkörper-Knochen-Scan zu Baseline und bei klinischer Indikation.<br>• Überlebensstatus alle 6 Monate unabhängig von Therapieabbruchgrund bis zum Tod oder, fall dies früher eintritt, dem Studienende |
| *Erfassung der Sicherheit* | • Kontinuierliche Erfassung und Einstufung aller UEs einschließlich der SUEs bis 30 Tage nach Therapieabbruch<br>• ECOG Performance Status zu Baseline und anschließend alle 12 Wochen bis zur Tumorprogression.<br>• Überwachung von Routinelaborparametern zu Baseline und jedem nachfolgenden Zyklus bis Therapieabbruch.<br>• 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. |
| *Erfassung der Lebensqualität* | *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.*<br>*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.* |
| *Data Analysis* | Zwei Interims- und eine finale Analyse werden durchgeführt.<br>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).<br>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).<br>Die finale Analyse wird nach dem Ende der Studie durchgeführt und liefert Daten zu allen Endpunkten.<br><br>Analyse Populationen:<br>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.<br>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.<br>Die Sicherheitspopulation (SAF) besteht aus allen Patienten, die Studienmedikation erhalten haben. Die Analyse wird stratifiziert nach der tatsächlich erhaltenen Therapie. Diese Population stellt die Analysepopulation für alle Sicherheitsanalysen dar.<br>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.<br>Subgruppen: |

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| | Taxan-haltige Vortherapie<br>Die finale Analyse der Wirksamkeit und der Patientencharakteristika wird pro Studienarm stratifiziert nach vorangegangener Taxantherapie (ja/nein)<br>Lungen- oder Lebermetastasen<br>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)<br>Paclitaxel +/- Bevacizumab<br>Die finale Analyse der Wirksamkeit, Sicherheit und Patientencharakteristika im Paclitaxel +/- Bevacizumab-Arm wird stratifiziert nach Therapie mit Bevacizumab (ja/nein).<br>Analyses:<br>Primäre Wirksamkeitsanalyse:<br>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 wurder.<br>Sekundäre Wirksamkeitsanalysen:<br>Absolute und relative Häufigkeiten der Gesamtansprechrate (ORR, komplettes oder partielles Ansprechen) nach 3 Monaten Therapie und gesamt werden für jeden Arm bestimmt.<br>Absolute und relative Häufigkeiten der CBR (komplettes oder partielles Ansprechen oder stabile Erkrankung für mindestens 24 Wochen) werden für jeden Arm bestimmt.<br>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<br>mit der maximalen Beobachtungszeit (LPLV) für Patienten mit Krankheitsprogression oder die verstorben sind<br>mit dem Datum der letzten Tumorevaluation für Patienten, die zum Ende der Studie leben und deren Erkrankung nicht progredient ist.<br>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.<br>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 Quartilen 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.<br>Explorative Wirksamkeitsanalyse: |

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| | sPFS wird mittels Kaplan-Meier Methode berechnet. Das sPFS ist definiert als Zeitraum von der Randomisierung bis zur symptomatischen Verschlechterung (Auftreten neuer oder Verschlechterung bestehender Symptome) oder Tod (vor Beginn der nächsten Therapie), ja nach dem, was zuerst eintritt. Falls vor Beginn der nachfolgenden Therapie oder am Ende der individuellen Beobachtung (je nach dem, 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.<br><br>Sicherheitsanalyse:<br><br>Patienten- und Fall-bezogene Häufigkeiten und Anteile in jedem Therapiearm werden hinsichtlich des Auftretens der folgenden Ereignisse berechnet<br><br>UEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab<br><br>SUEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab<br><br>UEs, die zum Abbruch von Ribociclib, AI, Paclitaxel, Bevacizumab führen<br><br>gesamt sowie nach CTCAE Schweregrad.<br><br>Auftretenshäufigkeit von UE (MedDRA-Preferred Term nach Systemorganklasse) in jeder Therapiegruppe wird berechnet für<br><br>UEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab<br><br>SUEs mit Kausalzusammenhang zu Ribociclib, AI, Paclitaxel, Bevacizumab<br><br>UEs, die zum Abbruch von Ribociclib, AI, Paclitaxel, Bevacizumab führen<br><br>gesamt sowie nach CTCAE Schweregrad<br><br>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 von Ereignissen und Rate zu 12 Monaten (mit 95%-Konfidenzintervall) werden für beide Therapiearme angegeben.<br><br>Ergebnisse aus Routinelaboruntersuchungen werden auf Patienten-Ebene in Listings dargestellt.<br><br>QoL Analysen:<br><br>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.<br><br>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.<br><br>Die Fläche unter der Kurve in den Skalenwerten des EORTC QLQ-C30 werden mittels deskriptiver Statistik für die Behandlungsgruppen zu den nachfolgenden Zeitpunkten dargestellt:<br>Baseline bis 24 Wochen nach Therapiebeginn<br>Baseline bis 1 Jahr nach Therapiebeginn<br>Baseline bis 2 Jahre nach Therapiebeginn |

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| | Baseline bis 3 Jahre nach Therapiebeginn<br>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 Regressionsmodels unter Berücksichtigung der Baseline Charakteristika ersetzt.<br>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.<br>Die Belastung durch Nebenwirkungen (Einzelfrage) wird pro Arm und Zeitpunkt mit Häufigkeiten und Anteil dargestellt<br>Die zeitliche Belastung durch die Therapie (vier Einzelfragen) wird pro Behandlungsarm und Fragebogenzeitpunkt mit Häufigkeiten und Anteil dargestellt. |
| *Geplante Studiendauer* | *Einschluss des ersten Patienten* *Q2/2018*<br>*Einschluss des letzten Patienten* *Q4/2020*<br>*Letzte Visite des letzten Patienten* *Q4/2024*<br>*Finale Analyse / Studienbericht* *Q4/2025* |
| Schlüsselworte | *Metastasierter Brustkrebs; viszerale Metastasen; HR+; HER2-; ER+; PgR+; CDK4/6 Inhibitor; Ribociclib; Aromataseinhibitor; Erstlinie; PFS; Lebensqualität* Zeitliche Belastung durch die Therapie (einzelner Punkt) |

## *Mammakarzinom, First-Line*

### AIO-MAM-0218/ass: Treatment and Outcome of Patients with Advanced breast cancer: cLinical research platform for real world data (OPAL)

**AIO-assoziiierte Studie**

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| Studiennummer/-Code: | AIO-MAM-0218/ass - OPAL |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2017 – 2021 |
| Weitere Zentren: | erwünscht |
| Letzte Aktualisierung | 17.10.2018 |

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| STUDY TYPE | National, observational, open, prospective, longitudinal, multicenter cohort study |
| PRINCIPAL INVESTIGATOR | Steeringboard: Prof. Dr. med. Thomas Decker, Prof. Dr. med. Elmar Stickeler, Prof. Dr. med. Achim Wöckel, PD Dr. med. Marc Thill, Dr. med. Anja Welt, Dr. med. Mark-Oliver Zahn |
| SPONSOR / Trial Office | iOMEDICO, Hanferstr. 28, 79108 Freiburg, Germany |
| CONDITION | Advanced breast cancer (ABC) |
| DESIGN | National, observational, open, prospective, longitudinal, multicenter cohort study |

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| INDICATION | Advanced breast cancer |
| OBJECTIVE(S) | To describe treatment reality (systemic treatments and sequential treatments) applied in German routine practice.<br>To assess effectiveness of systemic treatment with cytotoxic, endocrine and signaling pathway inhibitors by various outcome parameters such as response rate, progression free survival, overall survival. |
| INTERVENTION(S) | Non-interventional |
| OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH | Patients will be asked to give additional informed consent agreeing that their tumor samples taken during routine treatment can be used for further scientific testing. For the decentralized biobank, pathological material will remain with the local pathologist. Future research is possible. |
| BACKROUND/RATIONALE | The OPAL clinical research platform will continue the data collection from the Tumor Registry Breast Cancer, started in 2007, and provide data on treatment reality from all health care sectors in Germany. It will show if and how the choice of treatment changes over time and assess the effective-ness of different treatments for advanced breast cancer in routine care. Associated modules will set up a decentralized, biobank for future translational research and investigate patient-reported outcomes (PRO) in clinical routine. |
| KEY EXCLUSION CRITERIA | • Patients with prior systemic therapy for ABC<br>• Patient who do not receive any systemic therapy for ABC |
| KEY INCLUSION CRITERIA | • Female and male patients with advanced breast cancer (synchrone or metachrone metastasized or locally advanced, inoperable)<br>• Patients at the start of their initial first-line systemic treatment for ABC, which can be cytotoxic, endocrine or targeting a specific signaling pathway, what ever is given first<br>• Written informed consent<br>  • Patients participating in the PRO module: signing of informed consent form and completion of baseline questionnaire before start of initial systemic treatment<br>  • Patients not participating in the PRO module: within six weeks after start of systemic first-line for ABC |
| OUTCOME(S) | Response rate, progression free survival, overall survival |
| STATISTICAL ANALYSIS | Descriptive |
| SAMPLE SIZE | 2000 patients<br>(1000 Hormonereceptor-positive, Her2-negative, 500 Her2-positive, 500 triple-negative) |
| TRIAL DURATION | 9 years |
| PARTICIPATING CENTERS | Study sites from Germany |
| NUMBER of PATIENTS | 2000 patients |
| CURRENT NUMBER of PATIENTS | 120 |

*Fortgeschrittenes Mammakarzinom, First-Line*

**AIO-MAM-0118/ass: Phase III Studie zum Vergleich einer Erstlinientherapie mit Trastuzumab-Biosimilar (Kanjinti®) plus Pertuzumab plus Vinorelbin gegenüber Trastuzumab-Biosimilar (Kanjinti®) plus Pertuzumab plus Docetaxel im HER2-positiven fortgeschrittenen Brustkrebs (ATTILA)**

| **AIO-assoziierte Studie** | |
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| Studiennummer/-Code: | AIO-MAM-0118/ass - ATTILA |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum: | 2018 – 2021 |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | 01.06.2018 |

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| STUDY TYPE | Randomisierte, offene, zweiarmige interventionelle Phase III Studie in Deutschland |
| PRINCIPAL INVESTIGATOR | Dr. Anja Welt<br>Universitätsklinikum Essen, Innere Klinik (Tumorforschung)<br>Hufelandstr. 55, 45122 Essen |
| SPONSOR / TRIAL OFFICE | iOMEDICO AG<br>Hanferstr. 28<br>79108 Freiburg |
| CONDITION | Her2+ fortgeschrittener Brustkrebs |
| DESIGN | Dies ist eine randomisierte, offene, zweiarmige Phase III Studie in Deutschland zur Untersuchung ob eine Vinorelbin-basierte Dreifachkombination eine weniger toxische Therapieoption als eine Docetaxel-basierte Dreifachkombination für die Behandlung des HER2-positiven fortgeschrittenen Mammakarzinoms darstellt. Untersucht wird dies an Patientinnen, die noch keine systemische palliative Therapie für den metastasierten Tumor erhalten haben.<br>Insgesamt werden 264 Patientinnen in einem 1:1 Verhältnis, stratifiziert nach Vorhandensein von viszeralen Metastasen (ja/nein) und HR-Status (positiv/negativ), randomisiert, um eine Dreifachkombination aus Kanjinti® (trastuzumab) plus Pertuzumab plus Vinorelbin oder aus Kanjinti® (trastuzumab) plus Pertuzumab plus Docetaxel zu erhalten. Die Therapie wird bis zur Krankheitsprogression, nicht vertretbarer Toxizität oder dem Tod fortgesetzt. Für den Fall, dass Docetaxel beziehungsweise Vinorelbin beendet werden müssen, kann die Therapie mit Kanjinti® (trastuzumab) und Pertuzumab fortgeführt werden; ebenso kann die Therapie mit Kanjinti® (trastuzumab) und Vinorelbin beziehungsweise Docetaxel fortgesetzt werden, wenn Pertuzumab abgesetzt werden muss. Gleichermaßen kann die Therapie mit Vinorelbin beziehungsweise Docetaxel fortgeführt werden, wenn die anti-HER2 Antikörper Kanjinti® (trastuzumab) und Pertuzumab beendet werden müssen. Eine endokrine Erhaltungstherapie ist nicht erlaubt. Tumorevaluationen müssen bis zur Tumorprogression (oder dem Tod) oder dem Beginn der Nächstlinientherapie, je nach dem was zuerst eintritt, durchgeführt werden, auch wenn die Therapie aus anderen Gründen vor der Tumorprogression beendet wird.<br>Der primäre Endpunkt ist die patientenberichtete Lebensqualität gemessen als Fläche unter der Kurve (area under the curve, AUC) des Functional |

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| | assessment of Cancer Therapy – Breast (FACT-B) Fragbogens im Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) nach 18 Wochen (unabhängig von der Therapiesituation zu diesem Zeitpunkt). Patienten werden zu Beginn vor dem Start der Therapie, anschließend alle 3 Wochen über einen Zeitraum von 24 Wochen und danach alle 3 Monate für einen Zeitraum von bis zu 36 Monaten oder bis LPO (20 Monate nach LPI) befragt, je nachdem was zuerst eintritt.<br>Zusätzlich wird das Überleben der Patienten nachbeobachtet bis 79 Todesfälle in jedem Arm erreicht sind. Während dieser Follow-up Phase für das Überleben werden keine weiteren Daten erfasst. |
| INDICATION | Erwachsene Frauen mit fortgeschrittenem (lokal fortgeschrittenem und inoperablen oder metastasiertem) HER2-positivem Adenokarzinom der Brust. |
| OBJECTIVE(S) | Das primäre Ziel dieser Studie ist der Vergleich der patientenberichteten Lebensqualität der beiden Behandlungsarme.<br>Sekundäre Ziele sind:<br>• Die Beurteilung und der Vergleich von Wirksamkeitsparametern in den beiden Behandlungsarmen<br>• Die Erfassung und der Vergleich des Sicherheitsprofils der beiden Arme und der Vergleich der Sicherheit der Dreifachkombination mit historischen Kontrollen, die Trastuzumab verwendeten<br>• Die Beurteilung und der Vergleich der patientenberichteten gesundheitsbezogenen QoL<br>Das explorative Studienziel ist der Vergleich der beiden Arme hinsichtlich Gesundheitsökonomie-relevanter Parameter. |
| INTERVENTION(S) | IMP: Kanjinti® (trastuzumab), Pertuzumab, Vinorelbin, Docetaxel<br><br>Die Studientherapie wird in dreiwöchentlichen Zyklen verabreicht.<br>Arm 1: Kanjinti® (trastuzumab) plus Pertuzumab plus Vinorelbin<br>Kanjinti® (trastuzumab): Initialdosis 8 mg/kg an Tag 1 von Zyklus 1, gefolgt von 6 mg/kg an Tag 1 der nachfolgenden Zyklen.<br>Pertuzumab: Initialdosis 840 mg an Tag 1 von Zyklus 1, gefolgt von 420 mg an Tag 1 der nachfolgenden Zyklen.<br>Vinorelbin: 25 mg/m$^2$ an den Tagen 1 und 8 von Zyklus 1, welche in den nachfolgenden Zyklen, falls toleriert, auf 30-35 mg/m$^2$ erhöht werden kann, gegeben an den Tagen 1 und 8 der nachfolgenden Zyklen.<br>Arm 2: Kanjinti® (trastuzumab) plus Pertuzumab plus Docetaxel<br>Kanjinti® (trastuzumab): Initialdosis 8 mg/kg an Tag 1 von Zyklus 1, gefolgt von 6 mg/kg an Tag 1 der nachfolgenden Zyklen.<br>Pertuzumab: Initialdosis 840 mg an Tag 1 von Zyklus 1, gefolgt von 420 mg an Tag 1 der nachfolgenden Zyklen.<br>Docetaxel: 75 mg/m$^2$ an Tag 1 von Zyklus 1 und Tag 1 aller nachfolgenden Zyklen. Falls vertretbar, kann die Dosis auf 100 mg/m$^2$ erhöht werden. |
| BACKROUND/RATIONALE | Die Dreifachkombination aus Docetaxel plus Trastuzumab plus Pertuzumab wird basierend auf Daten der CLEOPATRA Phase III Studie als Erstlinientherapie des HER2-positiven metastasierten Mammakarzinoms empfohlen. Die zweifache Blockade von HER2 in Kombination mit Docetaxel lieferte einen beträchtlichen Vorteil bezüglich PFS und OS im Vergleich zur Kombinationstherapie aus Trastuzumab und Docetaxel (Baselga et al. 2012; Swain et al. 2015).<br>Die sehr wirksamen Taxan-basierten Therapien gehen mit schweren Nebenwirkungen und Langzeittoxizitäten einschließlich peripherer Neuropathien, Überempfindlichkeitsreaktionen, Haarausfall, |

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| | Abgeschlagenheit und febriler Neutropenien einher (Lin and Winer 2011). Es wurde gezeigt, dass Taxan- (und Athrazyklin-) freie Erstlinientherapieoptionen bei geringerer Toxizität nicht mit einem geringeren Gesamtüberleben bei Patienten mit metastasiertem Brustkrebs einhergehen (Marschner et al. 2013). Während diese Registerdaten alle Brustkrebssubtypen umfassen, wurden ähnliche Ergebnisse, nämlich dass es keinen Unterschied im Gesamtüberleben zwischen Taxan-haltigen und Taxan-freien Erstlinientherapien gibt, sowohl für die Gruppe der HR-positiven, HER2-negativen als auch der HER2-positiven Brustkrebspatientinnen in randomisierten kontrollierten Studien berichtet.<br><br>Die Kombination von Vinorelbin plus Trastuzumab zeigte in den TRAVIOTA und HERNATA Studien eine gleiche Wirksamkeit wie die Kombination aus einem Taxan, entweder Paclitaxel oder Docetaxel, mit Trastuzumab (Andersson et al. 2011; Burstein et al. 2007). In der erstgenannten Studie betrugen die Ansprechraten 51% und 40% für den Vinorelbin plus Trastuzumab-Arm beziehungsweise den Taxan-Arm (Paclitaxel oder Docetaxel) (Burstein et al. 2007). Die HERNATA Studie verglich Vinorelbin mit Docetaxel, beide kombiniert mit Trastuzumab, als Erstlinientherapie in insgesamt 283 Patienten mit HER2-positivem, metastasierten Brustkrebs. Die mediane Zeit bis zur Progression (time to progression, TTP) für Vinorelbin beziehungsweise Docetaxel betrug 15,3 Monate beziehungsweise 12,4 Monate, ohne signifikanten Unterschied (P= 0,67) (Andersson et al. 2011). Bei gleicher Wirksamkeit, traten unter der Kombination aus Vinorelbin signifikant weniger unerwünschte Ereignisse auf und entsprechend weniger Patienten beendeten die Therapie aufgrund von Toxizität (P<0,001). Behandlungsbedingte Nebenwirkungen von Grad 3 bis 4 wurden häufiger für Docetaxel berichtet. Darunter febrile Neutropenie (36,0% vs. 10,1%), Leukopenie (40,3% vs. 21,0%), Infektionen (25,1% vs. 13,0%), Fieber (4,3% vs. 0%), Neuropathie (30,9% vs. 3,6%), Nagelveränderungen (7,9% vs. 0,7%) und Ödeme (6,5% vs. 0%) (Andersson et al. 2011).<br><br>Die Dreifachkombination aus Vinorelbin plus Trastuzumab plus Pertuzumab als Erstlinientherapie des fortgeschrittenen Mammakarzinoms wurde in der multizentrischen Phase II Studie VELVET untersucht (Andersson et al. 2017; Perez et al. 2016). Die Dreifachkombination aus sequentiell verabreichtem Pertuzumab gefolgt von Trastuzumab gefolgt von Vinorelbin war wirksam und erreichte eine Ansprechrate von 74,2% bei allen Patienten und von 84% bei Patienten mit messbarer Erkrankung sowie ein medianes PFS von 14,3 Monaten (Perez et al. 2016).<br><br>In einer randomisierten, doppel-blinden, multizentrischen Phase III Studie an 725 Patientinnen mit Brustkrebs im Frühstadium zeigte das Trastuzumab Biosimilar Kanjinti® gleiche Wirksamkeit und Sicherheit wie das Referenzprodukt (Herceptin®) (von Minckwitz et al. 2017). Die Wirksamkeit mit dem primären Endpunkt komplette Remission, sowie auch die unerwünschten Ereignisse und die Immunogenität waren in den Behandlungsgruppen vergleichbar. Somit stellt das Trastuzumab Biosimilar eine ähnlich wirksame, verträgliche und weniger kostenintensive Therapieoption für den HER2-positiven Brustkrebs dar und kann austauschbar mit dem kommerziellen Referenzprodukt als Monotherapie oder in Kombination mit Chemotherapie eingesetzt werden.<br><br>Zusammengefasst stellen die Kombinationen aus den HER2-spezifischen Antikörpern Trastuzumab und Pertuzumab mit Docetaxel oder Vinorelbin zwei wirksame Therapieoptionen dar. Die ATTILA Studie wird zum ersten Mal einen direkten head-to-head Vergleich einer Taxan-haltigen gegen eine Taxan-freie Dreifachkombination mit HER2-gerichteten Substanzen liefern, um zu untersuchen, ob Vinorelbin plus Trastuzumab-Biosimilar plus Pertuzumab besser verträglich ist. Hierzu wird die Lebensqualität (QoL) verglichen. Außerdem werden Wirksamkeit wie auch gesundheitsökonomische Faktoren sowie Sicherheit und Verträglichkeit analysiert. |

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| KEY EXCLUSION CRITERIA | • Vorangegangene systemische Therapie in palliativer Intention (Chemotherapie, Hormontherapie und / oder biologische Therapie)<br>• Bestehende periphere sensorische oder Motorneuropathie Grad 2 oder höher (NCI CTCAE v5.0).<br>• Hinweis auf Metastasen im Zentralnervensystem. CT oder MRT des Gehirns sind nur dann vorgeschrieben, wenn es klinische Hinweise auf Hirnmetastasen gibt.<br>• Vorliegen einer unkontrollierten Hypertonie (systolisch > 150 mmHg und / oder diastolisch > 100 mmHg) oder klinisch bedeutsame kardiovaskuläre Erkrankung.<br>• Vorgeschichte einer LVEF < 50% während oder nach einer vorangegangenen (neo)adjuvanten Therapie mit Trastuzumab.<br>• Bestehende schwerwiegende, unkontrollierte systemische Erkrankung (z.B. kardiovaskulär, pulmonal, metabolisch; Wundheilungsstörung, Ulzera oder Knochenbrüche).<br>• Größere Operation innerhalb von 28 Tagen vor Beginn der Studienmedikation oder Erwartung, dass eine größere Operation innerhalb der Studienbehandlung notwendig wird.<br>• Bekannte Infektion mit HIV, HBV oder HCV (Test ist nicht vorgeschrieben).<br>• Luftnot im Ruhezustand als Komplikation der fortgeschrittenen Erkrankung oder anderer Erkrankungen, welche eine kontinuierliche Sauerstofftherapie erfordert.<br>• Bekannte Überempfindlichkeit gegenüber irgendeiner Studienmedikation oder den Trägerstoffen der rekombinanten humanen oder humanisierten Antikörper.<br>• Teilnahme an einer klinischen Prüfung innerhalb von 30 Tagen vor Randomisierung.<br>• Schwangere oder stillende Frauen. |
| KEY INCLUSION CRITERIA | • Unterschriebene und datierte schriftliche Einwilligung vor Beginn von protokollspezifischen Vorgängen.<br>• Histologisch oder zytologisch gesichertes Adenokarzinom der Brust. Lokal fortgeschrittene und inoperable oder metastasierte Erkrankung.<br>• HER2-positive Erkrankung, definiert als IHC HER2+++ oder CISH/FISH positiver Status.<br>• Weibliche Patientin über 18 Jahre.<br>• Im Fall einer adjuvanten Behandlung: krankheitsfreies Intervall von mindestens 12 Monaten nach Beendigung der adjuvanten Therapie (ausgenommen hormonelle Therapie).<br>• Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.<br>• Linksventrikuläre Auswurffraktion (LVEF) ≥ 50%.<br>• Für gebärfähige Frauen, definiert als physiologisch im Stande schwanger zu werden:<br>  ○ Negativer Schwangerschaftstest.<br>  ○ Einwilligung zur effektiven Kontrazeption während der Studientherapie und für 6 Monate nach der letzten Dosis der Studienbehandlung<br>• Lebenserwartung von mindestens 12 Wochen<br>• Ausreichende Organ- und Knochenmarksfunktion |
| OUTCOME(S) | Das primäre Ziel dieser Studie ist der Vergleich der patientenberichteten Lebensqualität der beiden Behandlungsarme.<br>Sekundäre Ziele sind: |

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| | • Die Beurteilung und der Vergleich von Wirksamkeitsparametern in den beiden Behandlungsarmen<br>• Die Erfassung und der Vergleich des Sicherheitsprofils der beiden Arme und der Vergleich der Sicherheit der Dreifachkombination mit historischen Kontrollen, die Trastuzumab verwendeten<br>• Die Beurteilung und der Vergleich der patientenberichteten gesundheitsbezogenen QoL<br>Das explorative Studienziel ist der Vergleich der beiden Arme hinsichtlich Gesundheitsökonomie-relevanter Parameter. |
| STATISTICAL ANALYSIS | Primärer Endpunkt<br>- Die AUC des FACT-B TOI-PFB wird mit Hilfe von Trapezen bestimmt. Hierfür werden die Werte des FACT-B TOI-PFB zu den verschiedenen Zeitpunkten (gemessen in Tagen seit Randomisierung) mittels gerader Linien verbunden. Die Fläche unter dieser Kurve ist die primäre Variable. Das Ergebnis wird stratifiziert nach Studienarm und mittels deskriptiver Statistiken (Mittelwert, Standardabweichung, Median, 25. und 75. Perzentil, Minimum und Maximum) dargestellt.<br>Der Mittelwertunterschied der AUC der beiden Arme wird mit einem zweiseitigen t-Test für zwei Stichproben gleicher Varianz getestet.<br>Sekundäre Endpunkte – Lebensqualität<br>- Absolute und relative Häufigkeiten der Anzahl Patienten, die zum jeweiligen Fragebogen-Zeitpunkt noch Therapie erhalten haben, sowie die Anzahl (von der Patientin) zurückgesendeter Fragebögen werden für jeden Fragebogen-Zeitpunkt dargestellt.<br>- Für jeden Zeitpunkt werden alle Fragebögen-Scores, sowie deren Veränderung zur Baseline mittels deskriptiver Statistiken (Mittelwert, Standardabweichung, Median, 25. und 75. Perzentil, Minimum und Maximum) dargestellt.<br>- Die AUC des FACT-B TOI-PFB, gemessen von Baseline bis 12, 18, 24 und 36 Monate nach Randomisierung (unabhängig von der jeweiligen Krankheits- und Behandlungssituation), wird mit Hilfe eines Trapez-Ansatzes bestimmt. Die AUC wird für alle Patienten, für die der FACT-B TOI-PFB für alle Zeitpunkte bis 12, 18, 24 und 36 Monate bestimmbar ist, berechnet. Die Ergebnisse werden mit deskriptiven Statistiken dargestellt (Mittelwert, Standardabweichung, Median, 25. und 75. Perzentil, Minimum und Maximum).<br>- Die Zeit bis zur Verschlechterung des FACT-B TOI-PFB um fünf Punkte wird mit der Kaplan-Meier Methode analysiert. Daten von Patienten ohne eine Verschlechterung um mindestens fünf Punkte verglichen zur Baseline werden mit dem Datum des letzten ausgefüllten Fragebogens zensiert. Für die Zeit bis zur Verschlechterung um fünf Punkte werden die Anzahl Ereignisse sowie alle Quartile zusammen mit 95% Konfidenzgrenzen angegeben. Eine Kaplan-Meier Grafik wird erstellt.<br>- Die Zeit bis zur Verschlechterung der FACT-B breast cancer subscale (BCS) um zwei Punkte wird mit der Kaplan-Meier Methode analysiert. Daten von Patienten ohne eine Verschlechterung um mindestens zwei Punkte verglichen zur Baseline werden mit dem Datum des letzten ausgefüllten Fragebogens zensiert. Für die Zeit bis zur Verschlechterung um zwei Punkte werden die Anzahl Ereignisse sowie alle Quartile zusammen mit 95% Konfidenzgrenzen angegeben. Eine Kaplan-Meier Grafik wird erstellt.<br>Sekundäre Endpunkte - Wirksamkeit<br>- Das progressionsfreie Überleben, definiert als die Zeit von Randomisierung bis zum Datum der Krankheitsprogression oder zum Tod, je nach dem, was zuerst eintritt, wird mit der Kaplan-Meier Methode analysiert. Für Patientinnen, die bei Datenbankschluss am Leben sind und keine Krankheitsprogression erfahren haben, werden die Daten mit dem Datum des letzten Kontaktes zensiert. Falls vor der Krankheitsprogression eine Folgetherapie begonnen wurde, so werden die Daten mit Beginn dieser Folgetherapie zensiert. Für das progressionsfreie Überleben werden die Anzahl Ereignisse, Quartile |

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| | zusammen mit 95% Konfidenzgrenzen, sowie 12- und 24-Monatsraten mit 95% Konfidenzintervallen angegeben. Eine Kaplan-Meier Grafik wird erstellt.<br>- Das Gesamtüberleben ist definiert als die Zeit von Randomisierung bis zum Tod. Es wird mittels Kaplan-Meier Methode analysiert. Für Patienten, die zum Zeitpunkt des Datenbankschnittes / -schlusses am Leben sind, werden die Daten zum Zeitpunkt des letzten Kontaktes zensiert. Für das Gesamtüberleben werden die Anzahl Ereignisse, alle Quartile mit 95% Konfidenzgrenzen, sowie 12-, 24-, 36-, 48- und 60-Monatsraten mit 95% Konfidenzgrenzen angegeben. Eine Kaplan-Meier Grafik wird erstellt.<br>- Die Gesamtansprechrate ist definiert als der Anteil Patienten, für die eine komplette oder partielle Remission als bestes Ansprechen erreicht wurde. Absolute und relative Häufigkeiten der Gesamtansprechrate werden zusammen mit 95% Konfidenzgrenzen präsentiert.<br>- Die Rate des klinischen Nutzens (clinical benefit rate) ist definiert als der Anteil Patienten, für die eine komplette oder partielle Remission oder eine über mindestens 24 Wochen stabile Erkrankung erreicht werden konnte. Absolute und relative Häufigkeiten mit 95% Konfidenzgrenzen werden für die Rate des klinischen Nutzens dargestellt.<br>- Die Zeit bis zum Therapieversagen (time to treatment failure) ist definiert als Zeit von Randomisierung bis zum Absetzen aller Studienmedikamente. Das Datum des Absetzens ist dabei das früheste Datum aus den folgenden:<br>o Ende des letzten Zyklus ( = 20 Tage nach der ersten Gabe einer Studienmedikation im letzten Zyklus)<br>o Krankheitsprogression nach der letzten Gabe einer Studienmedikation<br>o Tod<br>o Beginn einer Folgetherapie.<br>Die Zeit bis zum Therapieversagen wird mit der Kaplan-Meier Methode bestimmt. Falls eine Therapie bei Datenbankschluss noch nicht beendet ist, so werden die Daten des betroffenen Patienten zum Zeitpunkt der letzten Gabe einer Studienmedikation zensiert. Für die Zeit bis zum Therapieversagen werden die Anzahl Ereignisse, sowie Quartile mit 95% Konfidenzgrenzen angegeben. Eine Kaplan-Meier Grafik wird erstellt.<br>Sekundäre Endpunkte - Sicherheit<br>- Übersichtstabellen für Unerwünschte Ereignisse müssen nur diejenigen Ereignisse enthalten, die während der Behandlungsphase neu aufgetreten sind oder sich während dieser Phase verschlechtert haben (treatment-emergent adverse events, TEAE). Trotzdem werden alle Daten zur Sicherheit (inklusive der Daten aus der Prä- und der Post-Behandlungsphase) gelistet und die während der Prä- und Post-Behandlungsphase erhobenen Daten werden gekennzeichnet. Alle Unerwünschten Ereignisse werden nach MedDRA v20 oder höher kodiert. Die Inzididenz von TEAE (neu aufgetreten oder verschlechtert seit Baseline) wird nach MedDRA Systemorganklasse und Bevorzugtem Term, nach Schweregrad (basiert auf CTCAE Graden), schwerwiegend (ja/nein), Zusammenhang zur Studienmedikation getrennt nach Behandlungsarm zusammengefasst. Des Weiteren wird die Inzidenz von TEAE, die zum Abbruch der Studienbehandlung führen, mit MedDRA Systemorganklasse und Bevorzugtem Term, gesamt und stratifiziert nach Schweregrad (CTCAE Grad) für jeden Behandlungsarm dargestellt. Fallbasierte absolute und relative Häufigkeiten werden für jede vorkommende MedDRA Systemorganklasse und jeden Bevorzugten Term insgesamt und stratifiziert nach Schweregrad (basiert auf CTCAE Graden), stratifiziert nach schwerwiegend (ja/nein) und nach Zusammenhang zur Studienmedikation für jeden Behandlungsarm angegeben.<br>- Als schwerwiegendes Unerwünschtes Ereignis dokumentierte Todesfälle und nicht-tödliche schwerwiegende Unerwünschte Ereignisse werden pro Patient gelistet und pro Behandlungsarm tabellarisch dargestellt.<br>- Sicherheits-Laborwerte der klinischen Routine werden pro Patient gelistet. |

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| | - Für die LVEF wird der Wert alle 3 Monate unter Behandlung, alle 6 Monate für die anschließenden 24 Monate, die Veränderung zur Baseline zu jedem Messzeitpunkt und der schlechteste Wert unter Behandlung mit deskriptiven Statistiken dargestellt. Die LVEF wird zusätzlich für jeden Messzeitpunkt gruppiert (≥55%, 45-54%, 30-44%, <30%) ausgewertet (absolute und relative Häufigkeiten). Eine Kreuztabelle wird die gruppierte LVEF bei Baseline dem gruppierten schlechtesten Wert unter Behandlung gegenüberstellen.<br>Explorative Endpunkte – Gesundheitsökonomie-relevante Parameter<br>- Die Behandlungskosten werden durch die Multiplikation des Medikamentenpreises mit der verabreichten Gesamtdosis ermittelt. Deskriptive Statistiken (Mittelwert, Standardabweichung, Median, 25. und 75. Perzentil, Minimum und Maximum) werden die Kosten pro Substanz und die Gesamt-Arzneimittelkosten pro Behandlungsarm darstellen.<br>- Die Anzahl Krankenhausaufenthalte (stationär) sowie die Gründe dafür werden patienten-basiert präsentiert (absolute und relative Häufigkeiten). Des Weiteren wird die Gesamtdauer an Krankenhausaufenthalten pro Patient (gesamt und gruppiert nach Grund des Aufenthalts) angegeben (Mittelwert, Standardabweichung, Median, 25. und 75. Perzentil, Minimum und Maximum).<br>- Die Inzidenz febriler Infektionen sowie die Anzahl febriler Infektionen pro Patient werden in Häufigkeitstabellen dargestellt. Die Gesamtdauer febriler Infekte pro Patient wird mittels deskriptiver Statistiken zusammengefasst (Mittelwert, Standardabweichung, Median, 25. und 75. Perzentil, Minimum und Maximum).<br>- Beschäftigungsstatus (Arbeitsunfähigkeit): die absolute und relative Häufigkeit der Anzahl Patienten mit kurzzeitiger oder dauerhafter Arbeitsunfähigkeit wird präsentiert. Die Gesamtzahl Tage, an denen der Patient arbeitsunfähig war (falls nicht dauerhaft arbeitsunfähig) wird angegeben (Mittelwert, Standardabweichung, Median, 25. und 75. Perzentil, Minimum und Maximum).<br><br>Subgruppenanalysen (für die primäre Variable und sekundäre Wirksamkeitsparameter)<br>- Alter ( <65 / ≥65 Jahre)<br>- Hormonrezeptorstatus (positiv / negativ)<br>- Art der Metastasierung (viszeral / ausschließlich nicht-viszeral / keine Metastasierung).<br><br>Interimsanalyse<br>Eine Interimsanalyse wird 6 Monate nach der Rekrutierung von 50 Patienten (insgesamt) durchgeführt. Es werden Daten dieser ersten 50 Patienten analysiert. Die Interimsanalyse hat ihren Fokus auf den Daten zur Sicherheit (Unerwünschte Ereignisse). Es werden Häufigkeiten der aufgetretenen Unerwünschten Ereignissen präsentiert (insbesondere Herzerkrankungen und LVEF Dysfunktion). Zusätzlich werden demographische Baseline-Daten in der Interimsanalyse enthalten sein.<br><br>Abschlussanalyse<br>Die Abschlussanalyse wird nach der letzten Visite des letzten Patienten (last patient last visit) durchgeführt. In der Abschlussanalyse werden die finalen Daten für alle Endpunkt, bis auf das Gesamtüberleben, präsentiert. Für das Gesamtüberleben werden vorläufige Daten berechnet.<br><br>Analyse zum Gesamtüberleben<br>Nach Ende der Studie (end of study) wird die finale Analyse zum Gesamtüberleben durchgeführt. |
| SAMPLE SIZE | Patienten: 264 - geplant<br>Studienzentren: 40 |

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| TRIAL DURATION | Rekrutierungsdauer: 36 Monate<br>Ende der Therapie (EOT) / "/last patient out (LPO)": 20 Monate nach Einschluss des letzten Patienten<br>Letzte Visite des letzten Patienten (Last patient last visit ;LPLV): Ende des Sicherheits-Follow-up (EOT + 30 Tage)<br><br>Datenbankauszug: 6 Monate nach Rekrutierung von 50 Patienten<br>Interimsanalyse: 2 Monate nach Datenbankauszug<br><br>Datenbankauszug für die finale Analyse (Gesamtüberleben: vorläufige Daten): 22 Monate nach Einschluss des letzten Patienten<br>Finale Analyse (Gesamtüberleben: vorläufige Analyse): 4 Monate nach Datenbankauszug<br>Klinischer Abschlussbericht: 4 Monate nach finaler Analyse<br><br>Ende der Studie (EOS): Follow-up des Überlebens bis 79 Todesfälle in jedem Arm eingetreten sind)<br>Überlebensanalyse: 2 Monate nach Ende der Studie<br>Addendum zum klinischen Abschlussbericht (finale Analyse des Gesamtüberlebens): nach der Überlebensanalyse |

# 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-assoziierte Studie**

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

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| APPLICANT/ COORDINATING INVESTIGATOR | Univ.-Prof. Dr. Matthias M. Weber, Unit of Endocrinology, I. Med. Department<br>Langenbeckstraße 1, 55131 Mainz<br>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.<br>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<br>Typical or Atypical Carcinoid of the lung with a Ki67 < 20%<br>Prior therapy with any antibody/drug targeting T-cell co-regulatory proteins<br>Major surgery within 4 weeks of first dose of study medication.<br>TACE, TAE, SIRT or PRRT within 3 months of starting study treatment<br>Patients pretreated with Interferon as last treatment line prior to study entry<br>Concurrent anticancer treatment within 28 days before the start of trial treatment<br>active infection requiring systemic therapy including, HIV/AIDS, HBV or HCV<br>Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent<br>Pregnancy or lactation<br>Vaccination within 4 weeks of the first dose of avelumab and while on trial<br>Abnormal kidney function (eGRF < 60 ml/min) |
| KEY INCLUSION CRITERIA | male or female patient ≥ 18 years<br>Histologically proven neuroendocrine neoplasia NEC G3 (WHO 2010) |

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| | One block or 20 slides (4 microns) of archival tumor tissue to perform central pathological review and biomarker assessment<br>No curative option available<br>Progressive disease within 9 months after prior first line chemotherapy (platinum based chemotherapy or STZ/TEM/DTIC based chemotherapy in NET G3)<br>Presence of measurable disease as per RECIST1.1 criteria<br>ECOG Performance Status 0 – 2<br>Written informed consent |
| 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 | 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. |
| 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-assozzierte Studie**

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| Studiennummer/-Code: | AIO-NET-0117/ass – RamuNET-Trial |
| Status: | Genehmigung erfolgt – Initiierung der ersten Zentren in Q4 2018 geplant |
| Rekrutierungszeitraum: | 12 Monate |
| Weitere Zentren: | Wenden Sie sich ggfs. an Prof. Michl |
| Letzte Aktualisierung | November 2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. med. Patrick Michl<br>Universitätsklinikum Halle<br>Universitätsklinik für Innere Medizin I<br>Ernst-Grube-Straße 40<br>06120 Halle (Saale)<br>Phone: +49 (0) 345 - 557 2661 |

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| | Fax: +49 (0) 345 - 557 2253<br>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 dacarbacine 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$^2$ d1 every 4 weeks iv) plus ramucirumab (8mg/kg d1 + d15 iv) |
| KEY EXCLUSION CRITERIA | • Pregnancy (positive urin or blood pregnancy test) or lactation.<br>• Secondary malignancy in patient's history with the exception of: disease-free period > 5 years before randomization or non-melanoma skin cancer or curatively treated cervical carcinoma in situ or other noninvasive in situ neoplasm.<br>• Allergy against dacarbazine or ramucirumab<br>• Current enrolment or participation within the last 4 weeks in a clinical drug trial<br>• 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.<br>• 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.<br>• Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management<br>• 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<br>• Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy.<br>• 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<br>• Uncontrolled severe physical or mental disorders such as: neurological or psychiatric disorders including seisure, advanced dementia, psychosis, active uncontrolled infections or sepsis, HIV, replicative hepatitis B or C infection<br>• History of gastrointestinal perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.<br>• 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.<br>• Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy. |
| KEY INCLUSION CRITERIA | • Histologically confirmed unresectable metastatic G1-G2 differentiated PNET excluding neuroendocrine carcinomas (NEC). Both non-functional and functional NET can be included.<br>• Age: 18-75 years<br>• Measurable disease (RECIST 1.1)<br>• 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. |

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| | • If the tumor biopsy is older than 6 months in progressive disease a rebiopsy is mandatory<br>• ECOG 0-1<br>• Life expectancy > 12 weeks<br>• Adequate renal function (serum creatinine ≤1.5 x ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (if serum creatinine is >1.5 x ULN, a 24-hour urine collection to calculate creatinine clearance must be performed). Urinary protein is ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol).<br>• Adequate hepatic function (total bilirubin ≤1.5 mg/dL (25.65 µmol/L), and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN; or 5.0 x ULN in the setting of liver metastases)<br>• Adequate bone marrow function (absolute neutrophil count >1,500/mm$^3$, platelets >100,000/mm$^3$, hemoglobin>9 g/dL)<br>• Adequate coagulation function (INR ≤1.5 and PTT ≤ 5 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.<br>• Pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices)<br>• The patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods, Pearl Index <1). Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of protocol therapy.<br>• Written informed consent |
| OUTCOME(S) | Primary endpoint<br>• Disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria<br>Secondary endpoints<br>• Objective tumor response (ORR)<br>• progression-free survival (PFS)<br>• overall survival (OS)<br>• toxicity<br>• biochemical response (tumor marker chromogranin A; in cases of functional NET: gastrin, insulin etc.)<br>• QoL (EORTC QLQ-C30 questionnaire)<br>• translational research for predictive biomarkers (e.g. circulating VEGF, ANGPT1/2 and IL8 levels, immunohistochemical VEGFR2 expression) |
| STUDY TYPE | Prospective single-arm multi-center phase IIa trial |
| STATISTICAL ANALYSIS | This trial is planned as a pilot study to evaluate the efficacy of combination treatment of ramucirumab and dacarbazine.<br>Primary endpoint is the disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria<br>The sample size calculation follows an exact binomial single-stage design (A'Hern 2001)<br>$H_0$: p<=$p_0$=60% versus $H_1$: p>=$p_1$=80%, alpha=0.05, beta=0.1<br>The design requires 45 subjects recruited to decide whether the disease control rate, *p*, is less than or equal to *p0* = 60% or greater than or equal to *p1* = 80%.<br>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). |
| SAMPLE SIZE | To be allocated to trial: 46 |
| TRIAL DURATION | Recruitment period: 12 months<br>Treatment per patient: until disease progression or intolerable toxicity<br>Follow-up per patient: 24 months after begin of treatment.<br>First patient in to last patient out (months): 36<br>Duration of the entire trial (months): 42 months<br>Intended start date: 1st quarter 2018 |

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| | Expected end of the study: 3rd quarter 2021 |
| PARTICIPATING CENTERS | - UK Halle<br>- UKE Hamburg<br>- Zentralklinik Bad Berka<br>- Charité<br>- UKGM Standort Marburg<br>- UK Ulm<br>- UK Göttingen |

*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 177Lu-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).**
**177Lu-edotreotide vs. everolimus in GEP-NET (COMPETE-Trial)**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | AIO-NET-0417/ass – COMPETE-Trial |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 24 Monate |
| Weitere Zentren: | leider nicht möglich |
| Letzte Aktualisierung | April 2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | ITM Solucin GmbH/<br>Prof. Dr. Richard Baum<br>Zentralklinik Bad Berka GmbH |
| CONDITION | Well-differentiated neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET), with positive SSTR expression |
| OBJECTIVE(S) | **Primary objective**<br>To demonstrate the efficacy of PRRT with 177Lu-edotreotide to prolong median progression-free survival (mPFS) in patients with inoperable, progressive, SSTR+ GEP-NET, compared to everolimus<br>**Secondary objectives**<br>1. To assess overall survival (OS) during study period, defined as the date from randomisation until death<br>2. To determine objective response rates (ORR), defined as the proportion of patients achieving partial (PR) or complete response (CR) as best outcome<br>3. To determine disease control rates (DCR), defined as the proportion of patients achieving stable disease (SD), PR or CR as best outcome<br>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<br>5. To determine functional response rates (FRR), considering Cg-A and specific hormones (where increased at baseline)<br>6. To assess the safety and tolerability of 177Lu-edotreotide in GEP-NET patients<br>7. To determine the health-related quality of life (HRQL) in GEP-NET patients during and after therapy (EORTC QLQ-C30 questionnaire)<br>8. To evaluate symptomatic tumour response (EORTC GI.NET21 |

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| | questionnaire)<br>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<br>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<br><br>**Tertiary objectives (in 177Lu-edotreotide patients)**<br>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<br>2. To evaluate the value of pre-therapeutic SSTR imaging (SRI) to predict tumour response (globally/at lesion level)<br>3. To evaluate the relationship between PRRT radiation dose (in Gy) |
| INTERVENTION(S) | - Slow intravenous infusion/injection (IV) of $^{177}$Lu-edotreotide, an octreotide-derived somatostatin analogue containing the chelator DOTA, radiolabelled with n.c.a. lutetium-177, a radio-lanthanide, emitting β- and γ-radiation<br>- A maximum of four cycles of 7.5 ± 0.7 GBq $^{177}$Lu-edotreotide |
| KEY EXCLUSION CRITERIA | A patient will be excluded from participation in the trial if one or more of the following criteria are met:<br>1. Known hypersensitivity to edotreotide or everolimus<br>2. Known hypersensitivity to DOTA, lutetium-177, or any excipient of edotreotide or everolimus or any other Rapamycin derivative<br>3. Known hypersensitivity to lysine, arginine, or any excipient of the nephroprotective amino acid solution<br>4. Prior exposure to any peptide receptor radionuclide therapy (PRRT), including $^{177}$Lu-edotreotide, $^{90}$Y-edotreotide or other SSTR-targeting agents (e.g. $^{177}$Lu-octreotate or high-dose $^{111}$In-pentetreotide)<br>5. Prior therapy with mTor inhibitors<br>6. Prior EFR (extended field radiation) to GEP-NET lesions or radioembolisation therapy (e.g. $^{90}$Y microspheres, $^{131}$I-lipiodol) with administration to the liver<br>7. Therapy with an investigational compound and/or medical device within 30 days or 5 half-life periods (whichever is longer) prior to randomisation<br>8. Subjects who have received a live vaccine up to 4 weeks prior to first dose<br>9. Current therapy with any prohibited medication<br>10. Ongoing toxicity grade 2 according to CTCAE version 4.03 from previous standard or investigational therapies<br>11. Indication for surgical lesion removal with curative potential<br>12. Planned (for the period of study participation): chemotherapy, immunotherapy, radiation therapy, chemo-embolisation, bland embolisation, radio-embolisation, treatment with cyclosporine-A<br>13. Neuroendocrine tumours, not meeting the inclusion criteria:<br>• With known non-GEP-NET origin (e.g. pulmonary or gonadal primaries)<br>• Functional GE-NET<br>• NET with unknown primaries (CUP), manifesting as liver metastases<br>• Poorly differentiated neuroendocrine carcinomas(G3)<br>• NET for which no histological specimen for secondary histological analysis can be obtained<br>14. Total hepatic tumour burden > 70%<br>15. Brain metastases<br>16. Secondary malignoma within previous 5 years (except basalioma)<br>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<br>18. Renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments, as follows:<br>• Renal |

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| | ○ Serum potassium > 5.0 mmol/L<br>○ Renal obstruction<br>○ Known nephropathy from any cause<br>• Hepatic<br>○ Total bilirubin >1.5 x ULN<br>○ AST or ALT > 2.5 x ULN<br>○ Alkaline phosphatase > 5 x ULN<br>○ Albumin < 3 g/dL, unless prothrombin time is within normal range<br>○ Known cirrhosis or other distinctly restricted liver function<br>• Cardiovascular<br>○ New York Heart Association classification III & IV<br>○ Uncontrolled hypertension<br>• Haematopoietic<br>○ Platelets ≤ 80 * $10^9$/L<br>○ Absolute neutrophil count (ANC) < 1 x $10^9$ cells/L<br>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 $^{177}$Lu) after the last treatment cycle.<br>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.). |
| KEY INCLUSION CRITERIA | All patients must meet all of the following criteria:<br>1. Written informed consent<br>2. Male or female ≥ 18 years of age<br>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 < 20%), unresectable or metastatic<br>4. Availability of existing biopsy specimen from primary tumour or metastasis or, if unavailable, willingness to undergo current biopsy for secondary central analysis<br>5. Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥ 1 cm in longest diameter, and ≥ 2 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<br>6. Somatostatin receptor positive ($SSTR^+$) disease, as evidenced by SSTR imaging (SRI) within 4 months prior to randomisation, by:<br>• $^{68}$Ga-based SSTR PET imaging (e.g. using $^{68}$Ga-edotreotide or $^{68}$Ga-DOTATATE), or<br>• $^{111}$In-pentetreotide SSTR SPECT/planar imaging, or<br>• $^{99m}$Tc-octreotide SSTR SPECT/planar imaging<br>All target lesions and ≥ 90% of non-target lesions need to be positive for SSTR, demonstrated by adequate tracer uptake, being defined as being “clearly differentiable from background”<br>7. Radiological disease progression, defined as:<br>• Progressive disease per RECIST 1.1. criteria, eviden-ced by consecutive morphological imaging (CT or MRI) with ≥ 90 days interval during the 12 months prior to randomisation<br>8. Karnofsky performance status (KPS) scale ≥ 70<br>9. Life expectancy of at least 6 months<br>10. Glomerular filtration rate (GFR, MDRD) ≥ 60 mL/min/1.73 $m^2$<br>11. For patients included in France only, verification and confirmation of their affiliation with a social security |

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| OUTCOME(S) | To demonstrate the efficacy of PRRT with 177Lu-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 177Lu-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 | **Primary Variable:**<br>**Progression-free survival**<br>Median progression-free survival (mPFS)<br><br>**Secondary variables:**<br>**Efficacy**<br>a) Percentage patients progression-free at 2 years (% 2y-PFS)<br>b) Objective response rate (ORR), % patients achieving PR and CR<br>c) Disease control rate (DCR), % patients achieving PR, CR and SD<br>d) Median duration of disease control (mDDC)<br>e) Median overall survival (mOS)<br>f) Percentage overall survival at 2 years (% 2y-OS)<br>g) Percentage patients experiencing functional tumour response (CgA, specific hormones), classified as functional SD, PR, CR<br>h) Median duration of functional response<br>i) Percentage of patients experiencing symptomatic tumour response (EORTC GI.NET21 questionnaire), classified as symptomatic SD, PR, CR<br>j) Median duration of symptomatic response<br>**Safety and tolerability**<br>a) Calculated GFR, percentage depart from baseline value<br>b) Measured TER, percentage depart from baseline value<br>c) Renal volume ($V_{kidney}$), percentage depart from baseline value<br>d) General safety parameters:<br>Frequency of occurrence and severity of abnormal findings in safety investigations (physical examination, vital signs,<br>12-lead ECG, clinical laboratory, adverse events, concomitant medication)<br>**Health-related quality of life (HRQL)**<br>a) Maximum HRQL improvement (EORTC QLQ-C30 questionnaire) total scores, relative to baseline<br>b) Median duration of maximum HRQL improvement<br>**Tumour dosimetry measures**<br>Cumulative absorbed dose (Gy) from $^{177}$Lu-edotreotide to target tumour lesions, estimated from $^{177}$Lu-edotreotide dosimetry after first dose.<br><br>Stratified randomisation will be used to control for primary tumour origin (GE-NET vs. P-NET) and for prior medical therapy (1$^{st}$ line vs. 2$^{nd}$ line, as well as types of previous therapies).<br>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-variates primary tumour origin, prior medical treatment, tumour grade and baseline KPS, will be compared using exploratory statistics.<br>All other secondary variables will be analysed descriptively by treatment group. |
| SAMPLE SIZE | In total, 300 GEP-NET patients will be randomised in 2:1 fashion to receive either<br>• PRRT with $^{177}$Lu-edotreotide consisting of a maximum of four cycles (7.5 ± 0.7 GBq $^{177}$Lu-edotreotide each), administered as IV infusion at 3-monthly intervals for 9 months, or until diagnosis of progression (200 patients), or<br>• 10 mg everolimus (Afinitor®) daily, administered orally as a tablet until diagnosis of progression (100 patients) |

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| TRIAL DURATION | Study duration per patient will be 24 months. Collection of survival data and information on further antineoplastic treatments will be continued after EOS.<br>• Screening period: 90 days (day -90 to day -1)<br>• Study period:<br>- Treatment period IMP: Four single doses administered on days 0, 90, 180 and 270, unless diagnosis of progression or EOS<br>- Treatment period RP: Daily oral administration from day 0 until diagnosis of progression or EOS.<br>- Follow-up period: day 0 – month 24 (or until diagnosis of progression, whichever is earlier).<br>• Post-study period follow-up:<br>- $^{177}$Lu-edotreotide therapy for patients (having progressed under everolimus therapy): Administration and follow-up as for study patients, until secondary progression.<br>- All patients: collection of overall survival (OS) data. |
| 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)**

| **AIO-Studie** | |
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| Studiennummer/-Code: | AIO-NET-0112 - EVINEC |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2015 – 2018 |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | Oktober 2018 |

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| Study Type | Phase-II<br>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<br>Friedrich Alexander Universität Erlangen, Medizinische Klinik 1<br>Endokrinologie, Ulmenweg 18, 91054 Erlangen<br>Tel: 09131- 85 45007, FAX: 09131-85 34005<br>E-Mail: marianne.pavel@uk-erlangen.de |
| Sponsor/ Study coordinator | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>Tel: +49 30 814534431; FAX: +49 30 322932926<br>E-Mail: info@aio-studien-ggmbh.de |
| Study Objectives | Primary objective:<br>• 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. |

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| | 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).<br>Safety and tolerability of Everolimus can be inferred if type, frequencies and seriousness of observed AEs are comparable to those determined in previous everolimus trials in NET (Radiant-1, 2 and 3).<br><br><u>Secondary objectives:</u><br>• To estimate progression free survival (PFS)<br>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.)<br>• To estimate Objective Response Rate (ORR)<br>Objective response rate defined as the rate of best overall response (CR+PR), determined by RECIST V 1.1.<br>• To estimate Disease control rate (DCR)<br>Disease control rate defined as the rate of best overall response and stable disease (CR+PR+SD), determined by RECIST V 1.1.<br>• To estimate Duration of Response (DR) and Time to Progression (TTP)<br>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.<br>• To estimate Overall Survival (OS)<br>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.<br>• To evaluate Quality of Life<br>Quality of life (HRQoL) will be evaluated using the EORTC QLQ-C30.<br>• To explore blood levels of tumor markers (chromogranin A & B, neuronspecific enolase, progastrin releasing peptide) as correlative tumor markers for clinical outcome in NET patients<br>Percentage of patients showing normalization or a decrease of chromogranin A & B, neuronspecific enolase, progastrin releasing peptide.<br>• To explore expression of mTOR pathway components in tumor tissue (archive) in correlation to tumor response |
| Number of patients | **Enrolled: 39**<br>A total of 40 patients will be enrolled.<br>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 ≥ 7.2 % 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).<br>A drop-out rate of 30 % will be assumed. |
| Anticipated start date | Q2 2015 |
| Study Centers | Number of sites total: approx. 10 |
| Duration of study | 1.5 years |
| More centers? | No |
| Key inclusion criteria | 1. Signed written informed consent<br>2. Male or female ≥ 18 years of age |

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| | 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<br>4. Treatment during first-line therapy with platin-based chemotherapy<br>5. Measurable disease according to RECIST 1.1<br>6. ECOG status 0 - 2 (Karnofsky Performance status ≥ 80 %)<br>7. Women of child-bearing potential must have a negative pregnancy test<br>8. Laboratory requirements:<br>• Hematology<br>- Absolute neutrophil count ≥ 1.5 x $10^9$/L<br>- Platelet count ≥ 100 x $10^9$/L<br>- Leukocyte count $\geq$ 3.0 x $10^9$/L<br>- Hemoglobin ≥ 9 g/dL or 5.59 mmol/L<br>• Hepatic Function<br>- Total bilirubin ≤ 1.5 time the upper limit normal (ULN)<br>- AST ≤ 3 x ULN in absence of liver metastases, or ≤ 5 x ULN in presence of liver metastases<br>- ALT ≤ 3 x ULN in absence of liver metastases, or ≤ 5 x ULN in presence of liver metastases<br>• Renal Function<br>- Creatinine clearance ≥ 50 mL/min according to Cockroft-Gault formula<br>• Metabolic Function<br>- Magnesium ≥ lower limit of normal<br>- Calcium ≥ lower limit of normal<br>- Others:<br>o CRP (PCT if CRP is elevated to exclude infection),<br>o negative Urinary screening test for leukocytes and nitrite (U - stix) to exclude urinary tract infection |
| Key exlusion criteria | 1. Known or suspected allergy or hypersensitivity reaction to any of the components of study treatment or their exipients.<br>2. Previous therapy with mTOR inhibitor<br>3. Radiotherapy:<br>• Concurrent radiotherapy involving target lesions used for this study.<br>• Concurrent palliative radiation (but radiation for non-target lesions is allowed if other target lesions are available outside the involved field)<br>• previous pre-operative or post-operative radiotherapy within 3 months before study treatment<br>4. History of other malignant tumours within the last 5 years, except basal cell carcinoma or curatively excised cervical carcinoma in situ<br>5. Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids<br>6. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) $\leq$ 1 year before enrolment<br>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<br>8. Known active HBV, HCV or HIV infection<br>9. Serious concomitant disease or medical condition that in the judgment of the investigator renders the patient at high risk from treatment complication<br>10. Any systemic disease requiring oral intake of corticosteroids (except for replacement therapy of corticosteroids – hydrocortisone in case of adrenal or pituitary insufficiency<br>11. Hearing loss $\geq$ Grade 3 (CTCAE v4.03)<br>12. Patient pregnant or breast feeding, or planning to become pregnant within 8 weeks after the end of treatment |

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| | 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.<br>14. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 28 days prior to treatment start<br>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).<br>16. Known drug abuse/alcohol abuse<br>17. Peripheral polyneuropathy $\geq$ Grade 2 (CTCAE v4.03)<br>18. Active chronic inflammatory bowel disease<br>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<br>20. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities. (AMG § 40, Abs. 1 No. 4)<br>21. Affected persons who might be dependent on the sponsor or the investigator |
| Investigational drug | Name/Substance: **Everolimus**<br>Formulation: 10 mg/day<br>Administration route: oral (tablet) |
| Scheme of therapy | 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.<br>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.<br>If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose. |
| Study rationale | 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.<br>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.<br>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 ≥ 2, (data in review).<br>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 |

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| | 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 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 | 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.<br>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.<br>Descriptive statistics will be used for the analysis of the following:<br>• Quality of Life Data (HRQoL)<br>• Demographic Data<br>For laboratory parameters, the distribution over time (mean values) as well as changes from baseline will be calculated and reported with descriptive statistics.<br>Percentage of patients showing normalization or a decrease of chromogranin A & B, neuronspecific enolase, progastrin releasing peptide will be evaluated by measures of descriptive statistics.<br>The details of the statistical analysis will be defined in a Statistical Analysis Plan, which will be prepared before database closure. |

*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-assoziierte Studie**

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

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| Art der Studie<br>Study Type | Phase-II<br>Randomized phase III open label and *cross-over* 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)<br>Prof. Ramon Salazar, Barcelona, Spain (international Study Lead) |

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| Kontaktadresse/<br>Kontaktperson: | Prof. Dr. Marianne Pavel<br>Charité Universitätsmedizin Berlin, Campus Virchow Klinikum (CVK)<br>Medical Department, Division of Hepatology and Gastroenterology<br>Augustenburger Platz 1, 13353 Berlin, Germany<br>Tel: +49 30 450 553022, FAX: +49 30 450 553977<br>E-Mail: marianne.pavel@charite.de |
| Studienziele/<br>Objectives | Primary<br>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.<br><br>Secondary<br>• 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.<br>• 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.<br>• 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.<br>• 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.<br>• 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. |
| Patientenzahl<br>Number of patients | Geplant: 180 Patienten<br>Bereits eingeschlossen: 108 (Stand Okt. 2017) |
| Rekrutierungzeitraum | 04/2014 - 12/2018 |
| Weitere teilnehmende Zentren erwünscht? | Approximately 50 centres planned |
| Haupt-Einschlusskriterien /<br>Key inclusion criteria | • Adult patients ≥ 18 years old.<br>• Histologically proven diagnosis of unresectable or metastatic, advanced pancreatic NET.<br>• Documented confirmation of pancreatic NET G1 or G2 as per ENETS classification system:<br>• G1: <2 mitoses per 2 mm2 and/or Ki-67 index ≤ 2%<br>• G2: 2–20 mitoses per 2 mm2 and/or Ki-67 index >2% and ≤ 20%<br>• 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.<br>• 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.<br>• 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. |

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| | • ECOG Performance status score 0 - 2.<br>• Life expectancy > 12 months.<br>• Presence of measurable disease as per RECIST criteria 1.0, documented by a Triphasic Computed Tomography (CT) scan or multiphase MRI radiological assessment.<br>• 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.<br>• Adequate bone marrow function, documented by ANC > 1.5 x $10^9$/L, platelets > 100 x $10^9$/L, haemoglobin > 9 g/dL.<br>• 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).<br>• Adequate renal function documented by: serum creatinine < 1.5 x ULN.<br>• Fasting serum cholesterol < 300 mg/dL or < 7.75 mmol/L and fasting triglycerides < 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.<br>• 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.<br>• Written Informed Consent obtained according to local regulations. |
| Haupt-Ausschlusskriterien<br>/<br>Key exlusion criteria | • Patients with poorly differentiated pancreatic neuroendocrine tumor; this is, pNET G3 as per ENETS classification system:<br>• G3: 21 or more mitoses per 2 mm2 and/or Ki-67 index >20%<br>• Previous treatment with chemotherapy and/or mTOR inhibitors (sirolimus, temsirolimus, everolimus, deforolimus) or tirosyne kinase inhibitors (sunitinib, sorafenib, axitinib, pazopanib, regerafenib).<br>• Immune therapy or radiation therapy within 4 weeks prior to the patient entering the study.<br>- 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.<br>• Previous treatment with Peptide-Receptor Radionuclide Therapy (PRRT) within the last 6 months and/or without progression following PRRT.<br>• Uncontrolled diabetes mellitus defined as: fasting serum glucose > 1.5 x ULN.<br>• Patients with any severe and/or uncontrolled medical conditions such as:<br>• unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, serious uncontrolled cardiac arrhythmia,<br>• active or uncontrolled severe infection,<br>• 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.<br>• severely impaired lung function (spirometry and DLCO 50% or less of normal and O2 saturation 88% or less at rest on room air),<br>• active, bleeding diathesis<br>• 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).<br>• Patients on chronic treatment with corticosteroids or any other immunosuppressive agent.<br>• Patients known to be HIV seropositive.<br>• 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.<br>• Known intolerance or hypersensitivity to 5FU or STZ or its excipients.<br>• Participation in any other clinical trial or concomitant treatment with any other investigational drug. |

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| | • 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.<br>• 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.<br>• For administrative matters (insurance) patients ≥ 95 are not allowed. |
| Therapieschema<br>Scheme of therapy | **Everolimus**<br>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).<br><br>**STZ-5FU**<br>- STZ 0.5 g/m2 days 1–5 and 5-FU 400 mg/m2 days 1–5 every 6 weeks (*Moertel*)<br>or,<br>- 0.5 g/m2 STZ on days 1–5 and 400mg/m2 5-FU on days 1-3 and then, 1-day treatment with 1g/m2 STZ and 1 day treatment with 400mg/m2 5-FU every 3 weeks (*Uppsala*). |
| Tumorevaluierung<br>Criteria for evaluation | Rate of patients with second progression free survival at 84 weeks of treatment, assessed by local investigator using RECIST criteria 1.0.<br><br>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.<br><br>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. |
| Rationale | STZ 5-FU chemotherapy is the actual standard of care for advanced pNETS in the European Union (ENETS guidelines; Neuroendocrinology 2012).<br>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.<br>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. |

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

**AIO-NET-0216/ass: 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-assoziierte Studie**

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| 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 |

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| Sponsor Name, | IPSEN Pharma<br>Ipsen Contact:<br>• Ali Majdi, Senior Director Global Medical Affairs, abdelali.majdi@ipsen.com<br>• Catherine Viollet, Global Project Manager, catherine.viollet @ipsen.com |
| Zentren in Deutschland | • Charite, Berlin<br>Principal Investigator: Marianne Pavel<br>• Nationales Centrum für Tumorerkrankungen, Heidelberg<br>Principal Investigator: Leonidas Apostolidis |
| Study Objectives | Primary<br>• 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.<br><br>Secondary<br>• To evaluate the clinical and biological safety profile.<br>• To evaluate time to progression.<br>• To evaluate PFS rate every 12 weeks.<br>• To evaluate overall survival at Week 48 and at the end of the study period in each cohort.<br>• To evaluate the objective response rate (ORR) as per RECIST v1.0 every 12 weeks.<br>• 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.<br>• To evaluate the best overall response as per RECIST v1.0.<br>• To evaluate the duration of stable disease (SD) as per RECIST v1.0.<br>• To evaluate the effect on symptoms (diarrhoea, flushing).<br>• To evaluate quality of life.<br>• To evaluate the changes in tumour biomarkers<br>• To evaluate the pharmacokinetic (PK) profile |
| Study Timelines | Study Start Date: November 2015<br>Estimated Study Completion Date: October 2019 |
| Study Design | This is a phase II, multicentre, prospective, open label, noncomparative, exploratory study.<br>(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 criteria specified below: |

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| | Inclusion Criteria:<br>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) ≤20%.<br>2) Positive somatostatin receptors type 2<br>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<br>Exclusion Criteria:<br>1) Grade 3 or rapidly progressive (within 12 weeks) NET<br>2) Any NET other than pancreatic and midgut<br>3) Previous treatment with any antitumour agent for NET other than lanreotide Autogel® 120 mg every 28 days<br>4) Gallbladder lithiasis at Screening echography or history of cholelithiasis with no cholecystectomy since then. |
| 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-assoziierte Studie**

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| 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 | Okt. 2018 |

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| Verantwortlicher Studienleiter nach AMG | Prof. Dr. Lothar Bergmann<br>Universitätsklinikum Frankfurt<br>Medizinische Klinik II<br>Theodor-Stern-Kai 7<br>60590 Frankfurt |
| Studienziele | **Primäres Studienziel:** OS Rate nach 12 Monate<br><br>**Sekundäre Studienziele:**<br><br>OS Rate nach 6 und 12 Monaten<br>Dauer der Response (DOR)<br>Progressionsfreie Überleben (PFS)<br>Mediane Gesamtüberleben (mOS)<br>Ojektive Responserate (ORR)<br>Sicherheit und Tolerabilität der Therapien |
| Patientenzahl | Geplant: 306, Rekrutierend<br>Teilnehmende Zentren: Deutschland, Frankreich, Belgien, Holland, UK u.a. |
| Haupt-Einschlusskriterien | **Inclusion:**<br>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.<br>b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.<br>2. Target Population<br>a) Histological confirmation of non-clear RCC with at least 50% non-clear cell component according to actual WHO classification36<br>b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC<br>c) Karnofsky > 70% (See Appendix 2, 14.2)<br>d) Measurable disease |
| Haupt-Ausschlusskriterien | Exclusion Criteria:<br>a) Any active brain metastases requiring systemic corticosteroids. Baseline imaging of the brain by MRI is required in patients with clinical signs of potential CNS involvement within 28 days prior to randomization. |

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| | a) Tumors with a clear-cell component of > 50%<br>Medical History and Concurrent Diseases<br>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.<br>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.<br>d) Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 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.<br>e) Any condition requiring systemic treatment with corticosteroids (> 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 > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.<br>f) Uncontrolled adrenal insufficiency.<br>g) Ongoing symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation, or prolongation of the Fridericia corrected QT (QTcF) interval defined as > 450 msec for males and > 470 msec for females, where $QTcF = QT / 3\sqrt{RR}$<br>h) Poorly controlled hypertension (defined as systolic blood pressure (SBP) of $\geq$ 150 mmHg or diastolic blood pressure (DBP) of $\geq$ 90<br>i) mmHg), despite antihypertensive therapy.<br>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.<br>k) History of cerebrovascular accident including transient ischemic attack within the past 12 months.<br>l) History of deep vein thrombosis (DVT) unless adequately treated with low molecular weight heparin<br>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.<br>n) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months.<br>o) Serious, non-healing wound or ulcer.<br>p) Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 30 days.<br>q) Any requirement for anti-coagulation, except for low molecular weight heparin.<br>r) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or |

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| | squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.<br>s) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).<br>t) Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.<br>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.<br>v) Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug.<br>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.<br>x) Receiving concomitant CYP3A4 inducers or strong CYP3A4 inhibitors (See Appendix 4, **Fehler! Verweisquelle konnte nicht gefunden werden.**).<br>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).<br>z) Hypersensitivity to sunitinib or any of the excipients<br>aa) Patients who were vaccinated with a live vaccine 2 weeks prior to the start of the CT |
| Tumorevaluierung<br>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 | 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. |

**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**-assoziierte Studie

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| Studiennummer/-Code: | AIO-NZK-0115/ass - PREPARE |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2017 - 2020 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Study Type | Open-label, randomized, observational phase III study |
| Coordinating investigator (LKP) | Prof. Dr. med. Viktor Grünwald<br>Medizinische Hochschule Hannover<br>Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation<br>Carl-Neuberg-Straße 1, 30625 Hannover<br>Telefon: +49 511 532 2301, E-Mail: gruenwald.viktor@mh-hannover.de |
| Sponsor: | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431, info@aio-studien-ggmbh.de |
| Objectives | Primary objective:<br><br>To determine the impact of a 24 weeks concomitant coaching on patient reported outcomes of patients receiving standard treatment for mRCC with sunitinib.<br>Secondary objectives:<br><br>Assessment of the impact of a 24 weeks concomitant coaching on additional QoL measures, patient compliance, efficacy and safety.<br>Exploratory objectives:<br><br>Assessment of inflammatory markers in tumor samples and serum. |
| Endpoints | Primary endpoint:<br><br>QoL assessment during sunitinib treatment:<br>Rate of responders to concomitant coaching assessed by the FKSI-15 questionnaire<br><br>Secondary endpoints:<br><br>• ORR according to RECIST 1.1 criteria<br>• OS<br>• PFS<br>• Duration of treatment<br>• Dose density of sunitinib<br>• Rate of hospitalization irrespective of TEAEs<br>• Treatment beyond progression<br>• Further cancer treatment and time to first subsequent therapy (TFST)<br>• 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)<br>• Treatment Emergent Adverse Events according to CTC 4.03: |

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| | • Frequency/incidence, severity, percentage reduction, time-to-event of ADRs, SAEs and specific TEAEs (e.g. hand-foot syndrome, diarrhea, stomatitis, fatigue, hypertension)<br>• Reduction of grade 3/4 ADRs<br>• Health related Quality of Life (FACT-G, EQ-5D)<br>• Time to improvement or deterioration measured by HRQoL<br>• Assessment of comorbidities by Charlson Comorbidity Index (CCI) and social status |
| Number of patients | N=430 total Currently recruited: 32 |
| Start date | Q1/2017 |
| More centres? | Target number: 100 / Yes (currently 24 sites participating) |
| Key inclusion criteria | **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.<br>**2.** Age ≥ 18 years at time of study entry.<br>**3.** Advanced or metastatic renal cell carcinoma, not amendable to surgery with curative intent, rendering the patient eligible for TKI treatment with sunitinib.<br>**4.** Intended first-line treatment with sunitinib.<br>**5.** Documented progressive disease within 6 months prior to study inclusion.<br>**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.<br>**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.<br>**8.** Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥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.<br>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. |
| Key exlusion criteria | **1.** Any other anti-cancer treatment aside of sunitinib for mRCC (except palliative radiotherapy).<br>**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].<br>**3.** CNS metastases, unless local therapy has been for at least 3 month and patient does not require the use of steroids.<br>**4.** Chronic liver disease with Child-Pugh B or C score<br>**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).<br>**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.<br>**7.** Participation in another clinical study with an investigational product during the last 30 days before inclusion.<br>**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. |

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| | **9.** Previous enrollment or randomization in the present study (does not include screening failure).<br>**10.** Involvement in the planning and/or conduct of the study (applies to both Pfizer staff and/or staff of sponsor and study site).<br>**11.** Patient who might be affiliated or otherwise dependent on the sponsor, site or the investigator.<br>**12.** Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities [§ 40 Abs. 1 S. 3 Nr. 4 AMG].<br>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]. |
| Scheme of therapy | Cancer treatment<br>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.<br><br>Concomitant coaching [primary intervention]:<br>The corner stones of the pro-active coaching are as follows:<br>• Patient education<br>○ Information on nature and severity of treatment emergent AEs<br>○ Information about remedies for TEAEs<br>○ Propagation and explanation of tests and treatment decisions<br>○ Patient instruction on self-care and preventive measures<br><br>• Preemptive AE treatment strategies<br>○ Proactive assessment of treatment emergent AEs with emphasis on predefined ADRs of special interest (fatigue, diarrhea, stomatitis, skin toxicities, hypertension)<br>• Supervision of reported ADR severity, ADR mitigation strategies and cancer treatment modification by treating physician<br>• 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)<br>• Availability of coach for unscheduled contacts by phone (during normal business hours)<br><br>**PREPARE**<br>Advanced or metastatic renal cell carcinoma, not amendable to surgery with curative intent and scheduled systemic cancer therapy with sunitinib<br>R 1:1<br>**Arm A – N = 215 [intervention]**<br>• Cancer therapy according to SOC<br>• QoL assessments / primary endpoint FKSI-15<br>**Concomitant coaching (6 month)**<br>• Pro-active TEAE management<br>**Arm B – N = 215 [control observation]**<br>• Cancer therapy according to SOC<br>• QoL assessments / primary endpoint FKSI-15<br>• Re-active TEAE management (SOC) |
| Criteria for tumor evaluation | RECIST 1.1 |
| Rationale | 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 |

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| | 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.<br><br>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.<br><br>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. |

*Fortgeschrittenes Nierenzellkarzinom*

**AIO-NZK-0118/ass: Cabozantinib in adult patients with advanced renal cell carcinoma following prior systemic check point inhibition therapy: a retrospective, non-interventional study (CaboCHECK)**

| **AIO-assoziiert Studie** | |
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| Studiennummer/-Code: | AIO-NZK-0118/ass |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum: | Studienstart geplant Q4 2018 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | 25.10.2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. med. Viktor Grünwald<br>Medical School Hannover (MHH)<br>Dept. of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation<br>Carl-Neuberg-Str. 1<br>30625 Hannover |
| CONDITION | Advanced renal cell carcinoma (RCC) |
| OBJECTIVE(S) | Primary objective<br>- To evaluate the safety of cabozantinib tablets in patients with advanced renal cell carcinoma (RCC) after pre-treatment with nivolumab or nivolumab plus ipilimumab<br>Secondary objectives<br>- To describe the efficency of cabozantinib tablets patients with advanced renal cell carcinoma (RCC) after pre-treatment with nivolumab or nivolumab plus ipilimumab. |
| INTERVENTION(S) | Cabozantinib after pre-treatment with nivolumab or nivolumab plus ipilimumab |
| KEY EXCLUSION CRITERIA | 1. Patients who are unable to consent because they do not understand the nature, significance and implications of the observational trial<br>2. Involvement in the planning and / or conduct of the study (applies to both Ipsen staff and/or staff of sponsor and study site) |
| KEY INCLUSION CRITERIA | 1. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject<br>2. Patients with advanced or metastatic renal cell carcinoma, including all subtypes<br>3. Age ≥ 18 years |

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| | 4. Completion of treatment with nivolumab or nivolumab / ipilimumab combination therapy (any line of therapy) directly followed by cabozantinib treatment |
| OUTCOME(S) | Endpoints<br>• Incidence of serious adverse events at least possibly related to cabozantinib treatment during and up to 30 days after the end of cabozantinib treatment<br>• Secondary safety endpoints are the number of<br>dose reductions, dose interruptions and terminations of cabozantinib treatment due to adverse events.<br><br>Secondary effectiveness endpoints are objective response rate, clinical benefit rate, duration of response, duration of cabozantinib treatment, and time to next treatment. |
| STUDY TYPE | Retrospective non-interventional study |
| STATISTICAL ANALYSIS | The sample size has been set to 200 patients, treated with cabozantinib between June 2015 and today, based on feasibility considerations. This sample size will be sufficient to detect an adverse effect occurring with a true frequency of 2.3% at least once with a probability of 99%. On the other hand, the power to detect an adverse effect with a true incidence rate of 1% would be >80%. This implies that the proposed retrospective analysis will be able to provide important safety information, and a valuable addition to the global cabozantinib safety data base.<br>Appropriate descriptive methods will be applied for all data analyses. If appropriate and unless otherwise specified, 2-sided 95% confidence interval (CIs) will be displayed and if p-values are presented, they will be for exploratory purposes only.<br>Descriptive statistics will include number of available data, number of missing data and the following:<br>- Mean, standard deviation (SD), minimum, interquartile range (0.25, 0.75), median, maximum when appropriate for continuous variables;<br>- Frequency count and percentage for categorical nominal variables;<br>- Both the above for categorical ordinal variables.<br>- Missing data will not be replaced. |
| SAMPLE SIZE | N=200 |
| TRIAL DURATION | 18 months |
| PARTICIPATING CENTERS | 25 sites planned |

# 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-assoziierte Studie**

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| Studiennummer/-Code: | AIO-STO-0315/ass - RAMSES – FLOT7 |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2016 - 2019 |
| Weitere Zentren: | Nicht benötigt |
| Letzte Aktualisierung | 19.10.2018 |

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| Study type | Multicenter, randomized, open label phase II/III study |
| Investigational and control drugs | Ramucirumab<br>FLOT (backbone therapy) |
| Sponsor | IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest<br>Steinbacher Hohl 2-26<br>60488 Frankfurt am MainContact: Prof. Dr. Salah-Eddin Al-Batran,<br>Dr. Claudia Pauligk, Ulli Simone Bankstahl, Dr. Gerrit zur Hausen |
| Objectives | Phase II:<br>• To compare rate of pathological complete or subtotal responses (pCR/SR) in patients treated with ramucirumab plus FLOT versus patients treated with FLOT alone.<br>• To determine R0 resection rates, progression-free survival (PFS), overall survival (OS)<br>Phase III:<br>• To compare OS in both trial arms<br>• To determine R0 resection rates, pathological response rates, PFS and OS rates at 3 and 5 years and PFS.<br>Safety Objectives (phase II and III)<br>• 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 ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities<br>• To evaluate the perioperative morbidity and mortality of the regimens described above |
| Study design | 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.<br>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.<br>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.<br>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).<br>Arm A (FLOT) |

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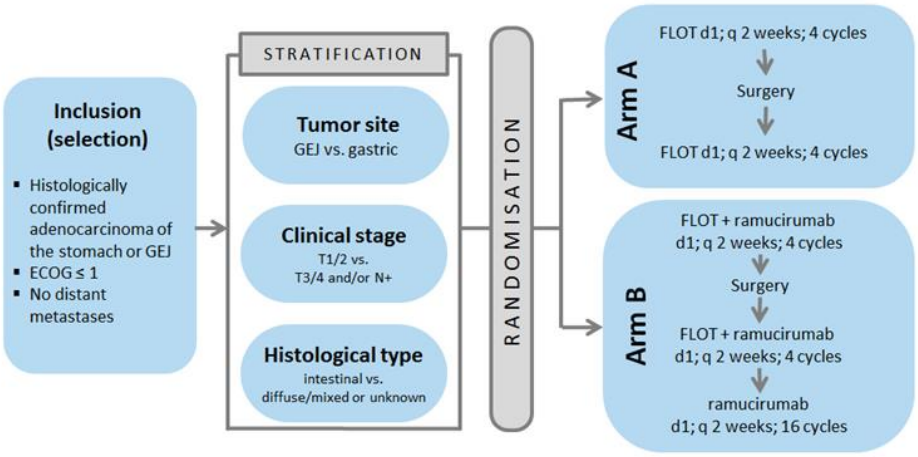
| | Patients randomized to Arm A will receive 4 pre-operative cycles (8 weeks) of biweekly FLOT (Docetaxel 50 mg/m² in 250 ml NaCl 0.9%, iv over 1 h; Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2h; Leucovorin 200 mg/m² in 250 ml NaCl 0.9%, iv over 30 min; 5-FU 2600 mg/m², iv over 24 h, q2wk) of the preoperative 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.<br>Arm B (FLOT/ramucirumab)<br>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.<br>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.<br>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.<br><br>  <br>Figure 2: Study Flow Chart.<br><br>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).<br>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 |

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| | 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 | **FLOT**<br>· Docetaxel 50 mg/m², iv over 1 h, d1<br>· Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2h, d1<br>· Leucovorin 200 mg/m² in 250 ml NaCl 0,9%, iv over 1 h, d1<br>· 5-FU 2600 mg/m², iv over 24 h, d1<br>(= 1 cycle)<br>Start of next cycle on day 15 (d15)<br><br>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. |
| Inclusion criteria | 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:<br>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)<br>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<br>2. No preceding cytotoxic or targeted therapy<br>3. No prior partial or complete tumor resection<br>4. Female and male patients ≥ 18 and ≤ 70 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.2<br>5. ECOG ≤ 1<br>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.<br>7. Laparoscopic exclusion of peritoneal carcinomatosis, if suspected clinically<br>8. Adequate haematological, hepatic and renal function parameters:<br>a. Leukocytes ≥ 3000/mm³, platelets ≥ 100,000/mm³, neutrophil count (ANC) ≥1000/µL, hemoglobin ≥9 g/dL (5.58 mmol/L),<br>b. Adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5, and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation |

[1] 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.

[2] There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.

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| | therapy). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to randomization.<br>c. Serum creatinine ≤ 1.5 x upper limit of normal<br>d. Urinary protein ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol).<br>e. Bilirubin ≤ 1.5 x upper limit of normal, AST and ALT ≤ 3.0 x upper limit of normal, alkaline phosphatase ≤ 6 x upper limit of normal<br>9. Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures |
| Exclusion criteria | 1. Known hypersensitivity against ramucirumab, 5-FU, leucovorin, oxaliplatin, or docetaxel<br>2. Other known contraindications against ramucirumab, 5-FU, leucovorin, oxaliplatin, or docetaxel<br>3. Patients with esophageal cancer and those with adenocarcinoma of GEJ type I and all patients who are planned to have transthoracic esophagectomy.<br>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<br>5. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina<br>6. Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.<br>7. Clinically significant valvular defect<br>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<br>9. Radiologically documented evidence of major blood vessel invasion or encasement by cancer.<br>10. Patients with involved retroperitoneal (e.g. para-aortal, paracaval or interaortocaval lymph nodes) or mesenterial lymph nodes (distant metastasis!)<br>11. Known brain metastases<br>12. Other severe internal disease or acute infection<br>13. Peripheral polyneuropathy ≥ NCI Grade II<br>14. Chronic inflammatory bowel disease<br>15. Grade 3-4 GI bleeding within 3 months prior to enrollment.<br>16. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment.<br>17. The patient has undergone major surgery within 28 days prior to enrollment.<br>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.<br>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.<br>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.<br>21. On-treatment participation in another clinical study in the period 30 days prior to inclusion and during the study<br>22. Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.<br>23. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) |

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| | 24. Any other concurrent antineoplastic treatment including irradiation<br>25. Current chronic alcohol, nicotine or drug abuse or history of chronic alcohol abuse during last 12 months. Nicotine abuse is defined as ≥ 25 pack-years (Willigendael et al., 2004). |
| Sample size | Phase II portion: n = 180 (90 per Arm)<br>Phase III portion: n = 758 patients (379 per Arm) |
| Duration of the study (planned) | 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<br>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<br>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. |
| Teilnehmende Zentren | Germany: 51<br>Italy: 13 |
| Anzahl eingeschl. Pat. | Germany: 155 (Stand 19.10.2018; recruitment paused; remaining patients to be recruited in Italy)<br>Italy: 0 |

**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**

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| Studiennummer/-Code: | AIO-STO-0215 - RENAISSANCE / FLOT5 |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2016 - 2020 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | 22.10.2018 |

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| Trial type | Prospective, randomized, multicentre, open label, phase III trial |
| Coordinating investigators | Prof. Dr. med. Salah-Eddin Al-Batran (LKP)<br>Institut für Klinisch-Onkologische Forschung (IKF)<br>Krankenhaus Nordwest<br>UCT – Universitäres Centrum für Tumorerkrankungen Frankfurt<br>Steinbacher Hohl 2-26, 60488 Frankfurt<br>Tel. 069/7601-4420, Fax 069/7601-3655, albatran.salah@khnw.de<br><br>Prof. Dr. med. Stefan P. Mönig<br>Hôpitaux Universitaires de Genève, Service de Chirurgie viscéral<br>stefan.moenig@hcuge.ch |
| 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 |

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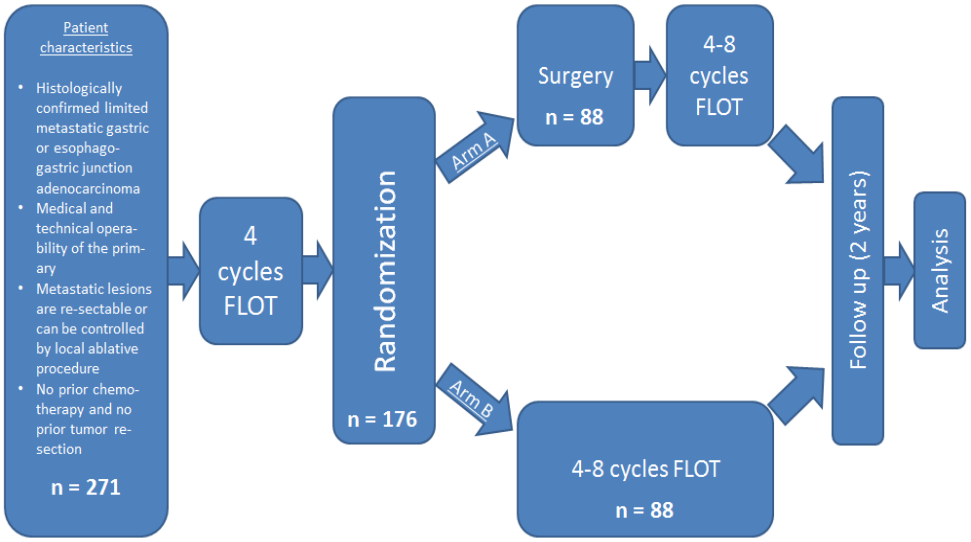
| | with synchronously limited metastatic esophagogastric adenocarcinoma. The primary endpoint is overall survival. |
| Intervention(s) | Experimental intervention/index test:<br>Arm A: Four cycles of FLOT (Docetaxel 50 mg/m², iv over 2 h, d1; Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2h, d1; Leucovorin 200 mg/m² in 250 ml NaCl 0,9%, iv over 1 h, d1; 5-FU 2600 mg/m², 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.<br>Control intervention/reference test:<br>Arm B: Patients will receive 8 to 12 cycles of FLOT for palliation (current standard).<br>Follow-up per patient:<br>Survival status will be assessed every 3 months for up to 5 years after randomization.<br>Duration of intervention per patient:<br>Basically, a total treatment of 8-12 cycles FLOT (16 to 24 weeks) will be administered.<br>Experimental and/or control off-label or on-label in Germany:<br>not applicable |
| Key inclusion and exclusion criteria | Key inclusion criteria:<br>- Histologically confirmed limited metastatic gastric or esophagogastric junction adenocarcinoma.<br>- Medical and technical operability of the primary (central evaluation).<br>- 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.<br>- No prior chemotherapy and no prior tumor resection.<br>Key exclusion criteria:<br>- Medical inoperability.<br>- Inability to understand the study and/or comply with the protocol procedures.<br>- Extensive metastatic status or cM0.<br>- Secondary malignancy < 3 years ago. |
| Outcome(s) | Primary efficacy endpoint: Overall survival (OS)<br>Key secondary endpoint(s): 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<br>Assessment of safety: 30 days and 90 days mortality/morbidity, toxic effects are graded using CTC adverse events criteria ver. 4.0 |
| Sample size | 176 (88 per Arm) |
| Trial duration | First patient in to last patient out (months): 72<br>Duration of the entire trial (months): 72<br>Recruitment period (months): 48 |
| Anzahl eingeschl. Pat. | 92 (Stand 22.10.2018) |

**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-assoziierte Studie**

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| Studiennummer/-Code: | AIO-STO-0115/ass - PETRARCA-Trial |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2016 - 2018 |
| Weitere Zentren: | Nicht benötigt |
| Letzte Aktualisierung | 19.10.2018 |

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| Investigational and control drugs | Pertuzumab (Perjeta)<br>Herceptin<br>FLOT (backbone therapy) |
| Study type | Randomized, open, phase II/III |
| Coordinating Investigator (LKP according to AMG) | Prof. Dr. Ralf-Dieter Hofheinz<br>TagesTherapieZentrum am Interdisziplinären Tumorzentrum<br>Universitätsmedizin Mannheim der Universität Heidelberg<br>Theodor-Kutzer Ufer 1-3, Haus 9,<br>68167 Mannheim<br>e-mail: ralf.hofheinz@umm.de |
| Sponsor | IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest<br>Steinbacher Hohl 2-26<br>60488 Frankfurt/Main Contact: Prof. Salah-E. Al-Batran, Dr. Claudia Pauligk, Ulli S. Bankstahl, Dr. Gerrit zur Hausen |

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| Objectives / Endpoints (efficacy, safety) | Phase II:<br>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.<br>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)*<br>*Only in case the study does not continue into phase III<br><br>Phase III:<br>To compare median DFS in both trial arms<br>To determine R0 resection rates, pathological response rates, DFS and OS rates at 3 and 5 years and median OS.<br>To analyze the predictive effect of molecular alterations (exploratory)<br><br>Safety Objectives (phase II and III)<br>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 $\geq$ 3 adverse events, and Grade $\geq$ 3 laboratory toxicities<br>To evaluate the perioperative morbidity and mortality of the regimens described above<br><br>Primary efficacy endpoint (phase II)<br>• Rate of pathological complete response<br><br>Secondary efficacy endpoints (phase II)<br>• R0 resection rate<br>• Median disease-free survival (DFS)*<br>• Median overall survival (OS)*<br>• PK Analysis (in selected centers)<br>• Subgroup analyses: pathological response according to HER-2 status HER-2 IHC 3+ vs. other cases<br>• Subgroup analyses: DFS and OS according to HER-2 status HER-2 IHC 3+ vs. other cases*<br>* Only in case the study does not continue into phase III<br>Primary efficacy endpoint (phase III)<br>• Median DFS<br>Secondary efficacy endpoints (phase III)<br>• R0 resection rate<br>• Pathological response rates<br>• DFS rates at 3 and 5 years<br>• OS rates at 3 and 5 years<br>• Median OS<br>• Subgroup analyses: pathological response, DFS, and OS according to HER-2 status HER-2 IHC 3+ vs. other cases |
| Background / Rationale | 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.<br>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 |

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| | 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. |
| Study design | 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.<br>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.<br>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.<br>Patients will be stratified by age (18-69 vs. ≥ 70), 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).<br><u>Arm A (FLOT)</u><br>Patients randomized to Arm A will receive 4 pre-operative treatments of FLOT (Docetaxel 50 mg/m², iv over 1 h; Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2 h; Leucovorin 200 mg/m² in 250 ml NaCl 0.9 %, iv over 30 min; 5-FU 2600 mg/m², 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.<br><u>Arm B (FLOT/Herceptin/Perjeta)</u><br>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).<br><br>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.<br>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. |
| Population | Adult patients with HER2-positive, locally advanced EGA scheduled to receive perioperative chemotherapy. |
| Inclusion/exclusion criteria | Inclusion<br>• 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: |

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| | - Medical and technical operability<br>- Centralized detection of either an adenocarcinoma with HER-2 3+ (IHC) or HER-2 2+ (IHC) with amplification proven by FISH, SISH or CISH<br>• No preceding cytotoxic or targeted therapy<br>• No prior partial or complete tumor resection<br>• Exclusion of the infiltration of any adjacent organs or structures by CT or MRI<br>• Exclusion of distant metastasis by CT or MRI of thorax and abdomen, and bone scan (if osseous lesions are suspected due to clinical signs)<br>• Female and male patients ≥ 18 years. Patients in reproductive age must be willing to use adequate contraception during the study and for 7 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.<br>• ECOG ≤ 2<br>• Laparoscopic exclusion of peritoneal carcinomatosis, if suspected clinically<br>• Adequate haematological, hepatic and renal function parameters:<br>- Leukocytes ≥ 3.000/mm³, platelets ≥ 100.000/mm3<br>- Serum creatinine ≤ 1.5 x upper limit of normal, or GFR > 40 ml/min<br>- Bilirubin ≤ 1.5 x upper limit of normal, AST and ALT ≤ 3.5 x upper limit of normal, alkaline phosphatase ≤ 6 x upper limit of normal<br>• LVEF value ≥ 55 %, as assessed by echocardiography<br>• Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures<br><br>Exclusion<br>• Patients with involved retroperitoneal (e.g. para-aortal, paracaval or interaortocaval lymph nodes) or mesenterial lymph nodes (distant metastasis!)<br>• Known hypersensitivity against Herceptin, pertuzumab, 5-FU, leucovorin, oxaliplatin, or docetaxel<br>• Other known contraindications against Herceptin, pertuzumab, 5-FU, leucovorin, oxaliplatin, or docetaxel<br>• Documented history of congestive heart failure of any NYHA, myocardial infarction within the past 6 months before the first dose of study treatment<br>• Clinically significant valvular defect, history of poorly controlled arterial hypertension (systolic blood pressure > 180 mmHG or diastolic blood pressure > 100 mmHg) or uncontrollable high-risk cardiac arrhythmia (i.e tachycardia with a heart rate > 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)<br>• 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<br>• Known brain metastases<br>• Other severe internal disease or acute infection<br>• Peripheral polyneuropathy ≥ NCI Grade II<br>• Chronic inflammatory bowel disease<br>• Clinically significant active GI bleeding<br>• On-treatment participation in another clinical study in the period 30 days prior to inclusion and during the study<br>• Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment. |

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| | • Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)<br>• Any other concurrent antineoplastic treatment including irradiation |
| Dose, regimen, treatment cycle | Arm A (FLOT):<br><br>Pre-operative therapy:<br>Docetaxel 50 mg/m², iv over 2 h, d1, d15, d29, d43<br>Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2h, d1, d15, d29, d43<br>Leucovorin 200 mg/m² in 250 ml NaCl 0.9 %, iv over 1 h, d1, d15, d29, d43 *<br>5-FU 2600 mg/m², iv over 24 h, d1, d15, d29, d43<br><br>Surgery is recommended to be scheduled 4 weeks after d43.<br><br>Post-operative therapy (start 6 to 8 weeks after surgery):<br>Docetaxel 50 mg/m², iv over 2 h, d1, d15, d29, d43<br>Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2h, d1, d15, d29, d43<br>Leucovorin 200 mg/m² in 250 ml NaCl 0.9 %, iv over 1 h, d1, d15, d29, d43 *<br>5-FU 2600 mg/m², iv over 24 h, d1, d15, d29, d43<br><br>Arm B (FLOT/Herceptin/Perjeta)<br><br>Pre-operative therapy:<br>Herceptin 8/6 mg/kg 250 ml of 0.9 % NaCl, d1, d22, d43 **<br>Perjeta 840 mg in 250 ml NaCl 0.9 %, d1, d22, d43<br>Docetaxel 50 mg/m², iv over 1 h, d1, d15, d29, d43<br>Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2 h, d1, d15, d29, d43<br>Leucovorin 200 mg/m² in 250 ml NaCl 0.9 %, iv over 30 min, d1, d15, d29, d43 *<br>5-FU 2600 mg/m², iv over 24 h, d1, d15, d29, d43<br><br>Surgery is recommended to be scheduled 4 weeks after d43.<br><br>Post-operative therapy (start 6 to 8 weeks after surgery):<br>Herceptin 8/6 mg/kg in 250 ml NaCl 0.9 %, d1, d22, d43 **<br>Perjeta 840 mg in 250 ml NaCl 0.9 %, d1, d22, d43<br>Docetaxel 50 mg/m², iv over 1 h, d1, d15, d29, d43<br>Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2 h, d1, d15, d29, d43<br>Leucovorin 200 mg/m² in 250 ml NaCl 0,9 %, iv over 30 min, d1, d15, d29, d43 *<br>5-FU 2600 mg/m², iv over 24 h, d1, d15, d29, d43.<br>(*) 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.<br><br>9 additional doses of Herceptin and Perjeta follow after the end of post-operative FLOT. |
| Key dates | Recruitment duration: 1 year for phase II<br>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<br><br>Due to slow recruitment, the number of patients has been reduced from 100 to 80 patients in summer 2018.<br><br>Number of sites: 60<br>Location of sites: Germany |
| No. patients included | 81 (Stand 02.08.2018) |

**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**

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| Studiennummer/-Code: | AIO-STO-0317 - DANTE-Trial |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2018-2020 |
| Weitere Zentren: | nein |
| Letzte Aktualisierung | Oktober 2018 |

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| Study type | Multicenter, randomized, open label phase II study |
| Protocol Code | MO30039 / DANTE |
| Investigational and control drugs | Atezolizumab<br>FLOT (backbone therapy) |
| Objectives | Primary Efficacy Objective<br>• 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<br><br>Secondary Efficacy Objectives<br>• 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<br>• Pathological complete and subtotal regression (TRG1a/b by Becker). TRG1a/b is defined as < 10% residual tumor per tumor bed based on evaluation of the resected esophagogastric specimen in the primary by a central reference pathologist.<br>• TRG1a and TRG1a/b in the sampled regional lymph nodes.<br>• 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.<br>• Overall survival (OS) where OS is defined as the time from randomization to death from any cause<br>• 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..<br><br>Safety Objectives<br>• Incidence, frequency, severity, and timing of adverse events (AEs)<br>• Changes in vital signs, physical findings, and clinical laboratory results<br>• Perioperative morbidity and mortality |
| Study design | 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.<br>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 |

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| | esophagogastric tumor tissue following two and four cycles of neoadjuvant therapy.<br>Potential study participants will be assessed for eligibility during a 28-day screening period that includes central verification of clinical stage and 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.<br>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.<br><br>Arm A: Atezolizumab with FLOT:<br>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.<br><br>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.<br><br>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.<br>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.<br>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.<br>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). |

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| | 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 | **Arm A: Atezolizumab with FLOT**<br><br>Atezolizumab Day 1 q2w: 840 mg/m2 IV over 1 hour<br>combined with:<br>FLOT<br>docetaxel Day 1 q2w: 50 mg/m² IV over 2 hours<br>oxaliplatin Day 1 q2w: 85 mg/m² IV over 2 hours<br>leucovorin Day 1 q2wk: 200 mg/m² IV over 1 hour<br>5-FU Day 1 q2wk: 2600 mg/m² IV over 24 hours<br><br>pre-operative: four cycles; post-operative four cycles<br><br>Atezolizumab alone<br>(8 cycles following completion of post-operative atezolizumab/chemotherapy)<br>Atezolizumab<br>Day 1 q3w: 1,200 mg/m² IV over 1 hour<br><br>**Arm B: FLOT alone**<br><br>FLOT as described in Arm A.<br>pre-operative: four cycles; post-operative four cycles |
| Inclusion criteria | Patients must meet the following criteria to be eligible for the study:<br>• Have provided written informed consent<br>In the investigator's judgement, is willing and able to comply with the study protocol including the planned surgical treatment<br>• Female and male patients* ≥ 18 years of age<br>• 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:<br>• is not infiltrating any adjacent organs or structures by CT or MRI evaluation<br>• does not involve peritoneal carcinomatosis<br>• is considered medically and technically resectable<br>• Note: 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.<br>• No prior cytotoxic or targeted therapy<br>• No prior partial or complete esophagogastric tumor resection<br>• ECOG ≤ 1<br>• 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 |

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| | requires paraffin embedded biopsy samples. Patients are included in the trial upon available results only.<br>• Females of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <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 ≥12 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 < 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.<br>• Males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:<br>• 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.<br>• Adequate hematological, hepatic and renal function as indicated by the following parameters:<br>• Leukocytes ≥ 3.000/mm³, platelets ≥ 100.000/mm3 without transfusion, absolute neutrophil count (ANC) ≥ 1500/mm3 without granulocyte colony-stimulating factor support, Hemoglobin ≥ 90 g/L (9 g/dL) - Patients may be transfused to meet this criterion.<br>• Bilirubin ≤ 1.5 x upper limit of normal, aspartate transaminase and alanine transaminase ≤ 2.5 x upper limit of normal, alkaline phosphatase ≤ 2.5 x upper limit of normal<br>• Serum creatinine ≤ 1.5 x upper limit of normal, or glomerular filtration rate > 45 ml/min<br>• Serum albumin ≥ 25 g/L (2.5 g/dL)<br>• For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 x ULN; for patients receiving therapeutic anticoagulation: stable anticoagulant regimen<br>• * There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently. |
| Exclusion criteria | 26. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion protein; Known |

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| | hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation<br>27. Any known contraindication (including hypersensitivity) to docetaxel, 5-FU, leucovorin, or oxaliplatin.<br>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.<br>Note: 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:<br>• Rash must cover < 10% of body surface area<br>• Disease is well controlled at baseline and requires only low-potency topical corticosteroids<br>• 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<br>29. Prior allogeneic bone marrow transplantation or prior solid organ transplantation<br>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.<br>Note: History of radiation pneumonitis within the radiation field (fibrosis) is permitted.<br>31. Positive test for human immunodeficiency virus (HIV)<br>32. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C<br>Note: 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).<br>33. Active tuberculosis<br>34. Uncontrolled tumor-related pain; Patients requiring pain medication must be on a stable regimen at study entry<br>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<br>36. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibodies<br>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<br>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.<br>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.<br>40. Significant cardiovascular disease, such as cardiac disease (New York Heart Association Class II or greater), myocardial infarction or |

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| | cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina.<br>41. Clinically significant valvular defect<br>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<br>43. Known central nervous system metastases<br>44. Peripheral polyneuropathy ≥ NCI CTCAE grade 2<br>45. Serum albumin < 2.5 g/dL.<br>46. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)<br>47. Serious infection requiring oral or IV antibiotics within 14 days prior to study enrollment<br>48. Chronic inflammatory bowel disease<br>49. Clinically significant active gastrointestinal bleeding<br>50. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment<br>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<br>52. Participation in another interventional clinical study ≤ 30 days prior to study enrollment or planned participation in such a study at the same time as this study<br>53. Receipt of an investigational drug within 28 days prior to initiation of study drug<br>54. Pregnancy or breast feeding, or planning to become pregnant within 5 months after the end of treatment.<br>Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment. |
| Sample size | 295 patients will be randomized into the study at a 1:1 ratio. |
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*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)**

**AIO-Studie**

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| Studiennummer/-Code: | AIO-STO-0118 // RACE |
| Status: | in Vorbereitung<br>Förderantrag bei der Deutschen Krebshilfe wurde 2018 bewilligt. |
| Rekrutierungszeitraum: | Studienstart noch offen |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | 22.10.2018 |

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| STUDY TYPE | Multicenter randomized phase III |
| PRINCIPAL INVESTIGATOR | Prof. Dr. Ralf-Dieter Hofheinz<br>TagesTherapieZentrum am Interdisziplinären Tumorzentrum<br>Universitätsmedizin Mannheim der Universität Heidelberg<br>Theodor-Kutzer Ufer 1-3, Haus 9<br>68167 Mannheim |
| TRIAL OFFICE | IKF Klinische Krebsforschung GmbH<br>am Krankenhaus Nordwest<br>Steinbacher Hohl 2-26<br>60488 Frankfurt/Main |
| SPONSOR | Ruprecht-Karls Universität Heidelberg<br>Represented by the chancellor Angela Kalous<br>Seminarstraße 2<br>69117 Heidelberg |
| 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) | Arm A (control arm)<br>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)<br><br>Arm B (experimental arm)<br>Two cycles of neoadjuvant induction chemotherapy with FLOT (5-FU 2600 mg/m2 d1, leucovorin 200 mg/m2 d1, oxaliplatin 85 mg/m2 d1, docetaxel 50 mg/m2 d1) every two weeks (4 weeks of therapy) followed by radiochemo-therapy beginning at day 21 after day one of the last cycle of chemotherapy. Radiochemotherapy consists of oxaliplatin 45 mg/m2 weekly (d1, 8, 15, 22, 29) and continuous infusional 5-FU 225 mg/m2 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) |

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| OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH | na |
| BACKROUND/RATIONALE | 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.<br>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).<br>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 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.<br>In addition to addressing clinical questions, companion studies are foreseen:<br>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. |
| KEY EXCLUSION CRITERIA | • 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)<br>• Known hypersensitivity /contraindications against 5-FU, leucovorin, oxaliplatin or docetaxel<br>• Clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV<br>• Clinically significant valvular defect<br>• 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<br>• Other severe disease or acute infection<br>• Peripheral polyneuropathy > NCI Grade II according to CTCAE version 4.0<br>• Participation in another clinical trial in the period 30 days prior to inclusion and during the study<br>• Subject pregnant or breast feeding<br>• Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)<br>• Any other concurrent antineoplastic treatment including irradiation |

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| KEY INCLUSION CRITERIA | • 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<br>• Staging according to TNM classification assessed by endoscopic ultrasound, spiral computed tomography of the chest and abdomen<br>• Patients must be surgical candidates as determined by the treating surgeon<br>• ECOG performance status 0-1<br>• Age 18 years and above<br>• Adequate hematologic and liver and renal function<br>• Consent to biomarker analyses on tumor tissue and blood |
| OUTCOME(S) | Progression-free survival<br>Overall survival including survival rates after 1, 3 and 5 years<br>R0 resection rate<br>Number of harvested lymph notes<br>Site of tumor relapse.<br>Perioperative complication and mortality rate<br>Safety/toxicity as assessed by NCI CTC criteria<br>Quality of life (QoL) by using the EORTC QLQ- C30 and the esophagogastric module Oes24 |
| STATISTICAL ANALYSIS | Efficacy/test accuracy:<br>The primary aim is to compare PFS between both study groups.<br>Description of the primary efficacy/test accuracy analysis and population:<br>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.<br>Safety:<br>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.<br>Secondary endpoints:<br>Descriptive statistics; 95% confidence intervals for relevant quantities and effect sizes; analysis of overall survival as described for PFS;<br>stratified Chi-squared tests for comparison of categorical measures (response rate, R0 resection rate); linear regression for comparison of continuous outcomes (QoL scores) |
| 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 – palliativeTherapie, 1st-line*

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

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| **AIO**-Studie | 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 | Oktober 2018 |

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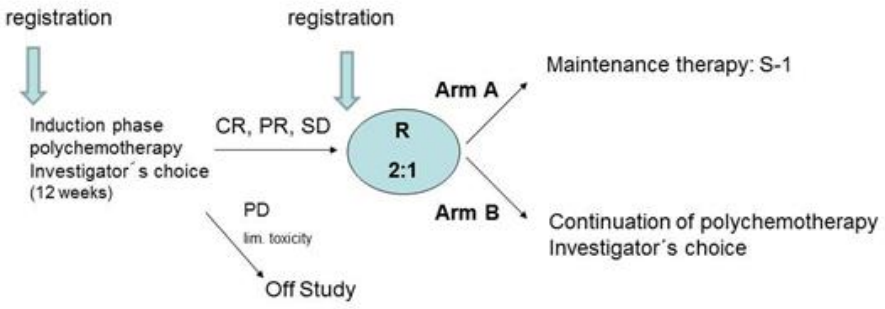
| Sponsor | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany<br>Tel:+49-30-814534435, FAX:+49-30-322932926 |
| Coordinating Investigator | Dr. Georg Martin Haag<br>NCT-Med. Onkologie, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany<br>Tel: +49-6221-564801, FAX: +49-6221-5633853<br>E-Mail: 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.<br>Eligible patients having completed the preplanned induction therapy without 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.<br>• 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.<br>• 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. |
|  | |
| Indication | Metastatic esophagogastric adenocarcinoma |
| Proposed countries / Total number of sites | Approximately 50 sites in 6 European countries (Austria, Belgium, France, Germany, Spain, Sweden) |
| Status | • 217 patients registered, 144 randomized<br>• 30 Study Sites initiated in Germany |

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| | • 20 Study Sites initiated in Austria, Sweden, Spain, Belgium, France |
| 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 | To compare S-1 de-escalation vs. continuation of chemotherapy after induction therapy with respect to<br>• Safety/toxicity<br>• Progression-free-survival<br>• Quality of life |
| Tertiary objectives | • Assessment of malnutrition<br>• Overall Survival of non-randomized patients<br>• Validation of biomarkers associated with the fluoropyrimidine pharmacodynamics and pharmacokinetics<br>• Exploration of new promising biomarkers for chemotherapy sensitivity / toxicity |
| Planned sample size | A total of 297 patients will be randomized |
| Inclusion Criteria | 1. Signed written informed consent incl. participation in translational research<br>2. Male or female patient 18 years or older<br>3. 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)<br>4. Adjuvant/neoadjuvant or perioperative chemotherapy or (chemo-)radiotherapy must have been finished at least 6 months before start of the induction therapy<br>5. For patients enrolled before induction therapy: No previous systemic treatment (i.e.chemotherapy) for metastatic disease<br>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<br>7. ECOG Performance Score 0-1 (Karnofsky Performance status >= 80%)<br>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)<br>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<br>10. Hematology and biochemistry laboratory results within the limits normally expected for the patient population, defined by the following:<br>• Absolute neutrophil count ≥ 1500/µl<br>• Platelet count ≥ 100000/µl<br>• Leukocyte count > 3000/µl<br>• Hemoglobin ≥ 9 g/dL or 5.59 mmol/l, previous transfusions (>3 days) of erythrocytes are allowed<br>• Total bilirubin ≤ 1.5 times the upper limit of normal (ULN), in patients with known Meulengracht syndrom ≤3 x ULN<br>• AST ≤ 3xULN in absence of liver metastases, or ≤5xULN in presence of liver metastases<br>• ALT ≤ 3xULN in absence of liver metastases, or ≤5xULN in presence of liver metastases<br>• Creatinine clearance ≥30 mL/min according to Cockcroft-Gault formula |

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| Exclusion Criteria | 1. Previous major sugery 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.<br>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<br>3. Known brain metastases<br>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.<br>5. For patients enrolled before the induction therapy: Previous systemic treatment (i.e. chemotherapy) for metastatic disease<br>6. Known active HBV, HCV infection or documented HIV infection<br>7. Serious concomitant disease or medical condition that by judgment of the Investigator renders the patient at high risk of treatment complications<br>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<br>9. Female patient pregnant or breast feeding<br>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 weeks after the end of treatment in such a manner that the risk of pregnancy is minimized.<br>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)<br>12. Chronic diarrhea or short bowel syndrome<br>13. Known hypersensitivity to S-1, other fluoropyrimidines or platinum compounds. Contraindication to receive S-1 or the polychemotherapy (induction & arm B) chosen for this patient as per current Summary of Product Characteristics. Known DPD decifiency<br>14. For patients enrolled before the induction therapy: Grade ≥ 2 peripheral neuropathy<br>15. Known drug abuse/alcohol abuse |
| Investigational Agent | S-1, an oral fluoropyrimidine (tegafur, gimeracil, oteracil)<br>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 | **Arm A: De-escalation therapy (S-1):**<br>S-1 30 mg/m² bid d1-14 q21d<br><br>**Arm B: Chemotherapy by Investigator's choice**<br>Continuation of polychemotherapy administered during induction therapy (i.e. Cisplatin/5-FU, FLO/mod. Folfox-6, Cisplatin/S-1, EOF/EOX, FLOT, XP) |
| Primary endpoint | • Overall survival defined as the time from randomization until death from any cause |

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| Secondary endpoints | • Adverse Events according to the CTCAE Criteria (Version 4.03)<br>• Progression-free-survival defined as the time from randomization until disease progression or death from any cause<br>• Quality of life according to the EORTC QLQ-C30 and QLQ-STO22 |
| Tertiary endpoints | • Nutritional status according to the NRS Nutritional Risk Screening questionnaire<br>• Overall survival of non-randomized patients<br>• Identification of molecularly defined subgroups with benefit from S-1 maintenance therapy |
| Randomization procedure | 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<br>• 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)<br>• Polychemotherapy (two-drug vs. three-drug combinations)<br>• Enrollment before vs. after the induction chemotherapy |
| 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 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. |
| Interim / partial analyses required | No confirmatory interim analyses with the aim to prematurely stop the trial are planned. |
| Translational analyses | 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.<br>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. |
| Study plan | First Patient In (FPI): Feb/2015<br>Last Patient In (LPI): Mar/2019<br>Last Patient Off Treatment: Sep/2019<br>Last Patient Last Visit (LPLV): Dec/2019 |

**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.**

**AIO-Studie**

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| Studiennummer/-Code: | AIO-STO-0217 - INTEGA-trial |
| Status: | Rekrutierung |
| Rekrutierungszeitraum | 2018 – 2020 |
| Weitere Zentren: | sind erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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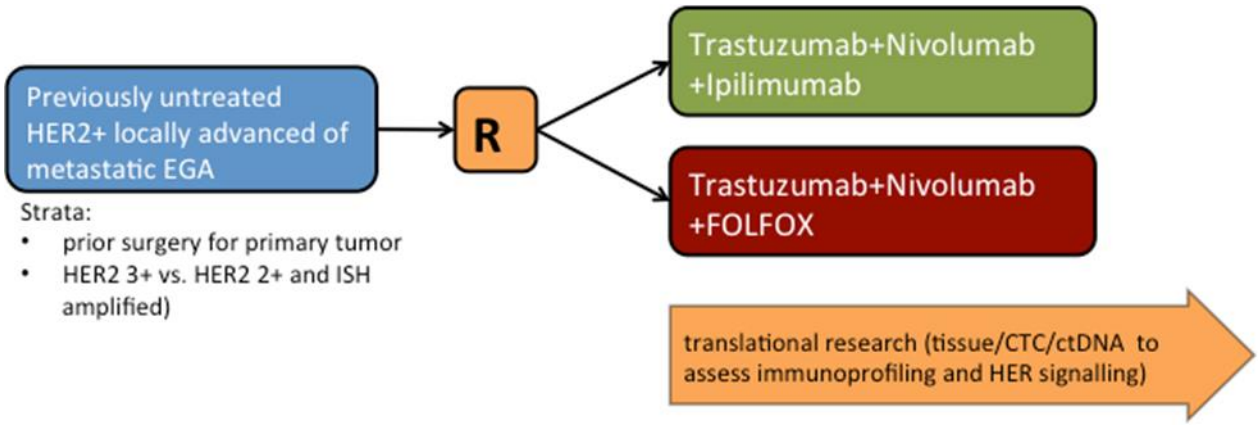
| **National Coordinating Investigator (LKP)** | PD Dr. Alexander Stein<br>Universitätsklinikum Hamburg-Eppendorf,<br>II. Medizinische Klinik und Poliklinik<br>(Onkologie, Hämatologie, KMT mit Sektion Pneumologie)<br>Hubertus Wald Tumorzentrum – UCCH<br>Martinistr. 52, Gebäude Ost 24<br>20246 Hamburg |
| **Sponsor** | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8<br>14057 Berlin |
| **Design** | Randomized, open labelled, multicenter phase II trial |
| **Indication** | Patients with previously untreated metastatic HER2 positive esophagogastric adenocarcinoma |
| **Recruitment status** | 97 patients planned, 24 patients enrolled |
| **Total number of sites** | 40 planned, 30 initiated |
| **Study Duration** | 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.<br>Expected total trial duration 4 years. |
| **Endpoints** | Primary endpoint:<br>• Overall Survival including milestone rate @ 12 months<br>Secondary endpoints:<br>• 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)<br>• Progression Free Survival (PFS) according to RECIST v1.1<br>• Response Rate (RR) according to RECIST v1.1<br>• Quality of life (EORTC QLQ-C30 and STO-22)<br>• Translational research (correlation of immune response signatures, changes in HER2 and PD-L1 and HER signaling status in tissue, CTC and ctDNA with efficacy<br>• central imaging review and determination of ORR and PFS according to modified RECIST) |
| **Trial Overview** | |

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| **Inclusion Criteria** | 1. 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.<br>2. 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))<br>3. Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease.<br>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.<br>5. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D).<br>6. ECOG performance status score of 0 or 1 (Appendix B).<br>7. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03 ):<br>a. WBC ≥ 2000/uL<br>b. Neutrophils ≥ 1500/µL<br>c. Platelets ≥ $100x10^3$/µL<br>d. Hemoglobin ≥ 9.0 g/dL<br>e. eGFR ≥ 30ml/min<br>f. AST ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present)<br>g. ALT ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present)<br>h. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)<br>8. Males and Females, ≥ 18 years of age<br>9. 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.<br>10. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.<br>11. 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.<br>12. 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- |

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| | 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.<br>13. 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. |
| **Exclusion Criteria** | 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 > 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)<br>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 < 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.<br>3. History of exposure to the following cumulative doses of anthracyclines (epirubicin > 720 mg/m$^2$, doxorubicin or liposomal doxorubicin > 360 mg/m$^2$, mitoxantrone > 120 mg/m$^2$ and idarubicin > 90 mg/m$^2$, other (other anthracycline greater than the equivalent of 360 mg/m$^2$ of doxorubicin). If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m$^2$ of doxorubicin<br>4. Baseline LVEF value < 55%, assessed by echocardiogram, multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) scan<br>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.<br>6. 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.<br>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.<br>8. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.<br>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. |

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| | 10. Significant acute or chronic infections including, among others:<br>a. Any positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)<br>b. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.<br>11. History of allergy or hypersensitivity to study drugs or any constituent of the products<br>12. History of allogeneic tissue/solid organ transplant<br>13. Participation in another clinical study with an investigational product during the last 30 days before inclusion<br>14. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |
| **Treatment, Dosage and Administration** | All eligible patients will be randomized, stratified for prior surgery of primary tumour and HER2 postivity status to<br><br>**Arm A**<br>**Week 1-12**<br>Trastuzumab 6mg/kg d1 every 3 weeks (loading dose 8mg/kg)<br>Nivolumab 1mg/kg i.v. d1 every 3 weeks<br>Ipilimumab 3mg/kg i.v. d1 every 3 weeks<br><br>**Week 13 till EOT**<br>Trastuzumab 4mg/kg d1 every 2 weeks<br>Nivolumab 240mg i.v. d1 every 2 weeks<br><br>**Arm B**<br>Trastuzumab 4mg/kg d1 every 2 weeks (loading dose 6mg/kg)<br>Nivolumab 240mg i.v. d1 every 2 weeks<br>mFOLFOX6 every 2 weeks<br>Oxaliplatin at a dose of 85 mg/m$^2$ IV over two hours (day 1)<br>5-FU 400 mg/m$^2$ IV bolus (day 1)<br>LV at a dose of 400 mg/m$^2$ iv over two hours (day 1)<br>5-FU at a dose of 2400 mg/m$^2$ IV over 46 hours (day 1-3)<br><br>**Duration of treatment**<br><br>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. |
| **Assessments** | **Baseline (within 4 weeks before treatment start)**<br><br>• Review of inclusion and exclusion criteria<br>• Medical and medication history, physical examination including height, weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), oxygen saturation, ECOG-performance status<br>• Laboratory Tests<br>• Blood draw for translational research<br>• Obtain paraffin-embedded tumor-tissue for translational research<br>• Echocardiography and ECG<br>• Quality of life assessment (EORTC QLQ-C30 and STO-22)<br>• Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan) |

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| | **During treatment (at start of treatment and every 2 or 3 weeks, +3/-2 days previous to any new cycle) (**safety-relevant assessments, including pregnancy test have to be completed before dosing)<br>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication<br>• Laboratory tests (hematology and chemistry panel), including<br>• Free T3/T4 and TSH (every 6 weeks)<br>• Pregnancy test for women of childbearing potential (every 4 weeks)<br>• Quality of life assessment (EORTC QLQ-C30 and STO-22) every 2 months (together with imaging)<br>• Blood draw for translational research (cycle 2,5 and end of treatment)<br>• Echocardiography every 3 months<br>**Additional assessments during treatment with nivolumab, ipilimumab and trastuzumab in arm A until week 13 on day 12 of every cycle (+/-3 days)**<br>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication<br>• Laboratory tests (hematology and chemistry panel)<br>**Final staging**<br>When any subject discontinues dosing of all study treatment, the following assessments should be made:<br>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication<br>• Laboratory tests (baseline panel), including free T4 and TSH and pregnancy test for women of childbearing potential<br>• Echocardiography and ECG<br>• Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan)<br>**30 and 100 days safety follow-up (±7 days)**<br>• Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication<br>• Laboratory tests (hematology and chemistry panel), including free T3/T4 and TSH and pregnancy test for women of childbearing potential<br>**Extended safety follow-up**<br>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.<br>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.<br>**Follow-up**<br>All subjects will be followed every 3 months ± 28 days for up to 4 years after start of recruitment.<br>In case of progressive disease after study treatment only:<br>• Survival, disease status, protracted toxicity, further treatment<br>In any other case additionally:<br>• Disease assessment, physical examination including weight, ECOG-performance status<br>**Tumor Response Assessment**<br>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, |

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| | pelvis and all other sites of disease). After treatment discontinuation for other than progressive disease imaging will be performed according to standard of care until progression or death. CT and/or MRI scans will be independently reviewed, thus blinded data will be collected.<br><br>**Safety**<br><br>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.<br><br>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.<br><br>Treatment related serious adverse events rate (SAE) will be determined.<br><br>**Quality of Life**<br><br>Quality of life will be assessed using the EORTC QLQ-C30 and STO-22 every 8 weeks together with tumor response assessment. |
| **Translational Research** | The following translational research is currently planned, but may be adapted taking into account new research data<br>• Tumor-infiltrating lymphocytes (TiL) repertoire determination from tumor<br>• Liquid biopsy next-generation sequencing (NGS) immunoprofiling (*TCRβ* & *IgH*) 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)<br>• 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.<br>• CTC will be evaluated for changes in HER2 and PD-L1 status<br>• ctDNA will be evaluated for HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA)<br>• Central imaging review and determination of ORR and PFS according to modified RECIST.<br>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. |
| **Statistical Considerations** | 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.<br><br>The TOGA trial has defined the standard 1st 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).<br><br>The INTEGA trial will evaluate two experimental regimen in 1st 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 |

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| | translates into a hazard ratio of 0.6 compared to the standard OSR@12 of 55% for chemotherapy and trastuzumab.<br>**Sample size estimation:**<br>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.<br>Randomization will be performed according to the following stratification criteria:<br>• Prior surgery of the primary tumour yes vs. no<br>• HER2 status IHC 3+ vs. IHC 2+ and ISH amplified |
| **Early Toxicity Analysis** | 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.<br>Safety Run-In Phase for the first 15 patients<br>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.<br>• 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. |

### 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)

**AIO**-Studie

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| Studiennummer/-Code: | AIO-STO-0417 - MOONLIGHT |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum | 2018 - 2020 |
| Weitere Zentren: | interessierte Zentren wenden sich bitte an das IKF in Frankfurt |
| Letzte Aktualisierung | Okt. 2018 |

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| Study type | Randomized, open labelled, multicenter phase II trial |
| Authors of the proposal | Prof Dr. Sylvie Lorenzen, Munich<br>Prof. Dr. Salah-Eddin Al-Batran, Frankfurt |
| Objectives / Endpoints (efficacy, safety) | Primary endpoint:<br>PFS based on the ITT population<br>Secondary endpoints:<br>Overall Response Rate (ORR) according to RECIST v1.1<br>Duration of response and disease stabilization<br>Overall survival (OS)<br>Safety (according to NCI-CTCAE V 4.03) and tolerability |

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| | Quality of life (EORTC QLQ-C30). The QoL analyses will include QoL mean values, QoL response and time to symptom deterioration (TTSD)<br>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 | 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) beeing 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).<br>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.<br>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.<br>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 an doubled response rate (55% vs 29%; p=0.0016) when pembrolizumab was added to a cisplatinum-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 .<br><br>References:<br>Cunningham et al 2008; N Engl J Med 2008; 358:36-46.<br>Yamada et al; Annals of Oncology 2015;26:141-148.<br>Al-Batran et al; J Clin Oncol 2008;26:1435<br>Le et al; ASCO GI 2016, abstract 6<br>Bang et al; ASCO 2015, abstract 4001 |

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| | Chung et al; ESMO 2015, Abstract No. 2364<br>Curran et al; PNAS 2010;107: 4275-80.<br>Janjigian et al; J Clin Oncol 34, 2016 (suppl; abstr 4010)<br>Kershaw et al; OncoImmunology 2013 2:e25962.<br>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 | **Inclusion Criteria:**<br>1. All subjects must have inoperable, advanced or metastatic GC or GEJ adenocarcinoma.<br>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.<br>3. Subject must be previously untreated with systemic treatment given as primary therapy for advanced or metastatic disease.<br>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.<br>5. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization.<br>6. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D).<br>7. ECOG performance status score of 0 or 1 (Appendix B).<br>8. Life expectancy > 12 weeks<br>9. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03 ):<br>a. WBC ≥ 2000/uL<br>b. Neutrophils ≥ 1500/µL<br>c. Platelets ≥ $100x10^3$/µL<br>d. Hemoglobin ≥ 9.0 g/dL<br>e. Serum creatinine ≤ 1.5 x ULN<br>f. AST ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present)<br>g. ALT ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present)<br>h. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)<br>10. Males and Females* ≥ 18 years of age<br>11. There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.<br>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.<br>13. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.<br>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.<br>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.<br>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 |

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| | 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.<br>**Exclusion Criteria:**<br>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)<br>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.<br>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.<br>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.<br>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.<br>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.<br>23. > Grade 1 peripheral neuropathy according to CTCAE version4.03<br>24. Known Dihydropyrimidine dehydrogenase (DPD) deficiency<br>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.<br>26. Ascites which cannot be controlled with appropriate interventions.<br>27. Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry; congestive heart failure NYHA grade 3 and 4<br>28. Significant acute or chronic infections including, among others:<br>a. Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)<br>b. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.<br>29. History of allergy or hypersensitivity to study drugs or any constituent of the products<br>30. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. |

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| | **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<br>Study treatment: FOLFOX + Nivolumab and Ipilimumab; FOLFOX |
| Investigational and Control Arm, Dose, regimen, treatment cycle | Randomisation 1 (experimental) :1 (control)<br>Each Cycle: either:<br>- Experimental Treatment: Arm A<br>FOLFOX (Oxaliplatin 85 mg/m², leucovorin 400 mg/m2 and fluorouracil 400 mg/m² administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle, every 2 weeks)<br>+<br>Nivolumab 240mg “Flatdose” i.v. d1 every 2 weeks<br>+<br>Ipilimumab 1mg/kg i.v. d1 every 6 weeks<br>Or<br>- Standard Treatment Arm B<br>FOLFOX (Oxaliplatin 85 mg/m², leucovorin 400 mg/m2 and fluorouracil 400 mg/m² administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle, every 2 weeks).<br><br>Duration of treatment<br>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.<br>1:1 Randomization will be performed according to the following stratification criteria:<br>• ECOG PS (0 vs 1)<br>• Tumor status (prior resection vs. no prior resection) |
| Key dates | FPFV: Q2 2018<br>Planned time for recruitment 2,0 years<br>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<br>Location of sites: Germany |

*Lokal fortgeschrittenes oder metastasiertes Adenokarzinom des Magens oder gastroösophagealen Übergangs – palliativeTherapie, 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)**

**AIO-Studie**

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| Studiennummer/-Code: | AIO-STO-0415 - RAMIRIS |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum | 2017 - |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | Oktober 2018 |

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| Study type | Randomized, multicenter phase II trial |
| Principal Investigator | Prof. Dr. med. Sylvie Lorenzen<br>Klinikum rechts der Isar der Technischen Universität München, Abteilung für Hämatologie und Onkologie, Ismaningerstr. 22, 81675 München<br>Tel. 089/41409848; Fax 089/4140-3654822 sylvielorenzen@gmx.de |
| Objectives / Endpoints (efficacy, safety) | Primary endpoint:<br>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<br><br>Secondary endpoints**:**<br>To compare treatment arms with respect to<br>• Progression-free survival<br>• Objective response rate (CR + PR)<br>• Tumor control rate (CR, PR, SD)<br>• Duration of disease stabilization<br>• Safety (according to NCI-CTCAE V 4.0) and tolerability<br>• Assessments of quality of life, anxiety/depression and satisfaction during treatment and follow-up (EORTC QLQ C30).<br><br>Exploratory endpoints **(optional):**<br>Translational research analysis in serum samples, e.g. :<br>• Chemokines and angiogenic factors in plasma (e.g. sCAIX, PGE2, Tryptase, PlGF, GM-CSF, G-CSF, S100A8, S100A9) |
| Background / Rationale | 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. |

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| | More and more patients get treated with taxanes in the perioperative or 1st line metastatic setting. For those patients the benefit of a combination of 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.<br>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.<br>In colorectal cancer FOLFIRI was tolerable together with ramucirumab (Tabernero et al., Lancet Oncol 2015).<br>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. |
| 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 | **Inclusion**<br>1. Signed written informed consent<br>2. Male or female* ≥ 18 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.<br>3. Histologically proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction<br>4. Metastatic or locally advanced disease, not amenable to potentially curative resection<br>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<br>6. Measurable or non-measurable but evaluable disease<br>7. ECOG performance status 0-1<br>8. Life expectancy > 12 weeks<br>9. Adequate hematological, hepatic and renal functions:<br>• Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L<br>• Platelets ≥ 100 x $10^9$/L<br>• Total bilirubin ≤ 1.5 times the upper normal limit (UNL)<br>• AST (SGOT) and ALT (SGPT) ≤ 2.5 x UNL in absence of liver metastases, or ≤ 5 xUNL in presence of liver metastases; AP ≤ 5 xUNL<br>• Creatinine ≤ 2 x UNL<br>10. Ability to comply with scheduled assessments and with management of toxicities<br>**Exclusion**<br>Patients with any of the following will not be eligible for participation:<br>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 |

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| | effectively treated. Patients curatively treated and disease-free for at least 5 years will be discussed with the sponsor before inclusion<br>2. Squamous gastric cancer<br>3. Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol<br>4. Previous therapy with paclitaxel or FOLFIRI<br>5. Current treatment with any anti-cancer therapy ≤ 2 weeks prior to study treatment start unless rapidly progressing disease is measured<br>6. Concurrent treatment with any other anti-cancer therapy<br>7. Previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study<br>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<br>9. Grade 3-4 GI bleeding within 3 months prior to enrollment<br>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<br>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.<br>12. Known brain or leptomeningeal metastases<br>13. Known allergic/ hypersensitivity reaction to any of the components of the treatment<br>14. Contraindications to the use of atropine<br>15. Other serious illness or medical conditions within the last 12 months prior to study drug administration<br>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<br>17. The patient has uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management<br>18. Active uncontrolled infection<br>19. Current history of chronic diarrhea<br>20. Active disseminated intravascular coagulation<br>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<br>22. Known Dihydropyrimidine dehydrogenase (DPD) deficiency<br>23. Prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.<br>24. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy |

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| | 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<br>26. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to treatment start<br>27. Known drug abuse/ alcohol abuse<br>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 $\leq$ 1. Note: Neuropathy due to prior chemotherapy is allowed if not > NCI Grade II according to CTCAE version 4.03<br>29. Subject pregnant or breast feeding, or planning to become pregnant within 3 months after the end of treatment<br>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<br>31. Patients known to have a HER 2 positive Cancer who have not been treated already with a HER 2 targeting agent.<br>32. Patients with a psychiatric illness or patients imprisoned or working in the institution of the treating physician. |
| Investigational and Control Arm, Dose, Regimen, treatment cycle | Randomisation 2:1<br>Each Cycle: either:<br>- Experimental Treatment: Arm A (FOLFIRI + Ramucirumab)<br>Ramucirumab 8 mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle<br>plus<br>FOLFIRI (Irinotecan 180 mg/m$^2$; i.v. bolus of 5-FU 400 mg/m$^2$, i.v. infusion of leucovorin* 400 mg/m$^2$, followed by a 46-hour continuous administration of 5-FU 2400 mg/m$^2$ on day 1 and 15 of a 28-day cycle)<br>or<br>- Standard Treatment: Arm B (Paclitaxel + Ramucirumab)<br>Ramucirumab 8mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle<br>plus<br>Paclitaxel 80 mg/m$^2$ on day 1, 8, 15<br>Each cycle will be repeated after 28 days (from day 1) until the patient experiences progress<br><br>(*) Note: Leucovorin can be replaced by sodium folinate that is given according to local guideline. |
| Statistical considerations | 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.<br>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).<br>The OS rate of FOLFIRI + ramucirumab after 6 months is chosen as primary efficacy endpoint.<br>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.<br>Design and assumptions: |

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| | • Explorative randomized phase II study with 2:1 randomization.<br>• Primary endpoint: OS rate after 6 months, based on an ITT population.<br>• 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.<br>• 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.<br>• Probability to accept the experimental therapy as promising (≥ 65% OS rate) with respect to efficacy, in spite of a true OS rate of ≤ 50%: 0.05 (type I error)<br>• Probability to reject the experimental therapy as not sufficiently efficient (≤ 50%), although the true OS rate is promising (≥ 65%): 0.2 (type II error, corresponding to a power of 80%). |
| 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.<br>Thus, a total number of about 67 + 34 = 101 evaluable patients is required.<br>Assuming a 10% drop out rate we are planning to include 111 pts |
| Key dates | FPFV: Q2 2017<br>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)<br>Location of sites: Germany<br>Participating sites: 13 |
| Anzahl eingeschl. Pat. | 76 (Stand 18.10.2018) |
| Weitere Zentren: | nein |

*Metastasiertes/fortgeschrittenes Magenkarzinom, Second-Line (2nd Line)*

**AIO-STO-0218: Avelumab + Paclitaxel/ Ramucirumab as second line treatment in gastro-esophageal adenocarcinoma: a phase II trial of the AIO (The RAP Trial)**

**AIO-Studie**

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| Studiennummer/-Code: | AIO-STO-0218 – RAP-Trial |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum: | Studienstart noch offen, geplant ab 4. Quartal 2018 |
| Weitere Zentren: | Ihre Anfragen richten Sie bitte an das Trial Office |
| Letzte Aktualisierung | 05.07.2018 |

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| STUDY TYPE | Clinical Trial according AMG, Phase II |
| PRINCIPAL INVESTIGATOR | PD Dr. med. Peter Thuss-Patience |
| TRIAL OFFICE | Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum (CC14) Med. Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie Augustenburger Platz 1, 13353 Berlin |
| SPONSOR | Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum (CC14) Med. Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie Augustenburger Platz 1, 13353 Berlin |
| CONDITION | Phase II – AIO Studie |
| DESIGN | Single-Arm, open label |
| INDICATION | Gastric-Cancer / Gastro-esophageal Cancer |
| OBJECTIVE(S) | The primary clinical objective is to determine the efficacy of a standard second-line regimen (paclitaxel + ramucirumab) with avelumab in patients with metastatic gastro-oesophageal cancer in terms of overall survival rate (OSR) at 6 months (according to RECIST v1.1).<br>The main secondary objective is to determine safety and tolerability, according to NCI CTC AE v5.0 and to the obtained data on vital signs, clinical parameters and feasibility of the regimen. Further secondary objectives are to determine the efficacy of the therapy in terms of objective response rate (acc. to RECIST v1.1) including the duration of response, overall survival (OS), OSR at 12 month, progression free survival (PFS) and progression free survival rate (PFSR) at 6 months and at 12 months.<br>For efficacy parameters (PFS and ORR) an exploratory analysis according to modified RECIST will be performed. |
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| INTERVENTION(S) | Avelumab + Ramucirumab/Paclitaxel |
| OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH | The primary translational objective is the determination of an efficacy predictive immune signature (diversification pattern and TiL clone expansion in peripheral blood) and the subgroup analyses of all primary and secondary endpoints in view of PD-L1 status. |
| BACKROUND/RATIONALE | Second-line chemotherapy prolongs survival in metastatic gastro-esophageal cancer compared to best supportive care. A randomised phase III trial from the Arbeitsgemeinschaft Internistische Onkologie (AIO) was the first trial to prove this survival benefit (Thuss-Patience et al. 2011). The positive effect on overall survival and quality of life could be confirmed in two larger subsequent trials (J. H. Kang et al. 2012; Ford et al. 2014). Irinotecan showed similar efficacy to paclitaxel in the second line setting (Hironaka et al. 2013).<br><br>Ramucirumab, a VEGF Receptor 2 antibody has been investigated in two randomized phase III trials in chemorefractory gastric cancer in the second-line setting (REGARD- trial (ramucirumab vs BSC; (Fuchs et al. 2014) and RAINBOW-trial (Wilke et al. 2014; Shitara et al. 2016)). In the RAINBOW trial ramucirumab + paclitaxel was compared to placebo + paclitaxel and showed an improvement of response rate and overall survival. This trial lead to the registration of ramucirumab in combination with paclitaxel, which is now the preferred standard treatment option in second line therapy.<br><br>Due to these data and the current best investigated standard treatment as second line in gastro-esophageal cancer is paclitaxel + ramucirumab.<br><br>Currently PD-1 and PD-L1 inhibitors are a very promising treatment option in gastro-esophageal adenocarcinoma which are investigated in a number of different trials. In patients who are responding to PD-1 blockade astonishingly long lasting responses could be detected (Muro et al. 2016; Chung et al. 2016). In a recently presented randomized phase III trial 493 patients with gastric cancer who were pretreated with at least 2 lines of prior palliative chemotherapy regimens received either nivolumab 3mg/kg or placebo. A clinically highly relevant and statistically significant prolongation of survival could be shown (HR 0.63; p<0,0001) and the rate of survival at 12 months was increased from 10.9% to 26.6% (Y.-K. Kang et al. 2017). In Caucasians similar efficacy of nivolumab can be expected and could be shown in a phase I/II trial (Janjigian et al. 2016). Approval of nivolumab as salvage treatment after available standard therapy can be expected.<br>Chung et al. (Chung et al. 2016) reported promising activity of avelumab monotherapy as maintenance or in second line in advanced gastric cancer patients in a phase Ib trial. Javelin 100 (NCT02625610) investigates in a randomized phase III the value of a maintenance therapy with avelumab after 1st-line FOLFOX therapy, with pending results.<br>In contrast the Javelin 300 (NCT02625623) 3rd line phase III trial investigating avelumab monotherapy compared to paclitaxel or irinotecan has reported no survival benefit in a recent press release. Recently the results of Keynote 061 have also been reported: Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-oesophageal junction cancer with PD-L1 CPS of 1 or higher.(Shitara et al. 2018) These disappointing results emphasize the great need for trials investigating a combination therapy of checkpoint inhibition and chemotherapy to increase the proportion of patients who benefit from the novel immunotherapy (Smyth and Thuss-Patience 2018). |
| KEY INCLUSION CRITERIA | 1. Signed written informed consent<br>2. Male or female ≥ 18 years of age<br>3. Histologically proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction<br>4. Metastatic or locally advanced disease, not amenable to potentially curative resection<br>5. Documented objective radiological or clinical disease progression during or within 6 months of the last dose of first-line platinum and |

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| | fluoropyrimidine doublet with or without anthracycline, docetaxel or trastuzumab. Neoadjuvant/adjuvant treatment is not counted unless progression occurs <6 months after completion of the treatment. In these cases neoadjuvant/adjuvant treatment is counted as first line.<br>6. Measurable or non-measurable but evaluable disease determined using guidelines RECIST 1.1<br>7. ECOG performance status 0-1<br>8. Life expectancy > 12 weeks<br>9. Adequate hematological, hepatic and renal functions:<br>a) Absolute neutrophil count (ANC) ≥ 1.5 x 109/L<br>b) Platelet count ≥ 100 x 109/L<br>c) Hemoglobin ≥ 9 g/dl (may have been transfused)<br>d) Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) and AST and ALT ≤ 2.5 x ULN in absence of liver metastases, or ≤ 5 x ULN in presence of liver metastases; AP ≤ 5 x ULN<br>e) Estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)<br>f) Urinary protein ≤ 1+ on dipstick or routine urinalysis (UA; if urinedipstick or routine analysis is ≥ 2+, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in this protocol)<br>g) Adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1,5 ULN, and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin/phenprocomon must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.<br>10. Women of child-bearing potential must have a negative urine or serum pregnancy test<br>11. Highly effective contraception for both male and female subjects throughout the study and for at least 30 days after last avelumab treatment administration if the risk of conception exists<br>12. Ability to comply with scheduled assessments and with management of toxicities. |
| KEY EXCLUSION CRITERIA | 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 for any other malignancy and disease-free for at least 5 years will be discussed with the sponsor before inclusion<br>2. Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol<br>3. Previous therapy with, paclitaxel or ramucirumab or pretreatment with a PD-1, PD-L1 inhibitor<br>4. Current treatment with any anti-cancer therapy ≤ 2 weeks prior to study treatment start unless rapidly progressing disease is measured<br>5. Previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study<br>6. Major surgical procedure, open biopsy or significant traumatic injury within 4 weeks prior to start of study treatment; anticipation of need for major surgical procedure (e.g. impending bowel obstruction) during the course of the study<br>7. Grade 3-4 GI bleeding within 3 months prior to enrollment<br>8. 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<br>9. 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<br>10. Known brain or leptomeningeal metastases |

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| | 11. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5.0 Grade ≥ 3)<br>12. Other serious illness or medical conditions prior to study drug administration<br>a) Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication<br>b) Uncontrolled or poorly controlled hypertension despite optimal medical therapy<br>c) Current history of chronic diarrhea<br>d) Active disseminated intravascular coagulation<br>e) History of gastrointestinal perforation, fistulae or any clinically relevant arterial thromboembolic event within 6 months<br>f) 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<br>g) Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)<br>h) Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.<br>i) Serious or non-healing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy<br>j) Prior organ transplantation including allogenic stem-cell transplantation<br>k) Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study<br>13. Current use of immunosuppressive medication, EXCEPT for the following:<br>a) intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);<br>b) steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication<br>c) short term steroids to prevent chemotherapy induced nausea<br>14. 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<br>15. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines<br>16. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity<br>17. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to treatment start<br>18. Known drug abuse/ alcohol abuse<br>19. Persisting toxicity related to prior therapy (NCI CTCAE v. 5.0 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 |

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| | not constituting a safety risk based on investigator's judgment are acceptable<br>20. Subject pregnant or breast feeding, or planning to become pregnant within 3 months after the end of treatment<br>21. Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 30 days (male or female) after the end of treatment<br>22. Patients known to have a HER2 positive cancer who have not been treated already with a HER2 targeting agent<br>23. Patients with a psychiatric illness or patients imprisoned or working in the Institution of the treating physician. |
| OUTCOME(S) | Overall survival |
| STATISTICAL ANALYSIS | Primary endopoint: OS rate at 6 months. The following error levels are defined:<br>• Probability to accept the experimental therapy as promising (≥ 65% OS rate) with respect to efficacy, in spite of a true OS rate of ≤ 50%: 0.10 (type I error)<br>• Probability to reject the experimental therapy as not sufficiently efficient (≤ 50%), although the true OS rate is promising (≥ 65%): 0.2 (type II error, corresponding to a power of 80%).<br>A standard two-stage phase II design according to Simon (Simon 1989) is applied. In the first stage, n = 33 patients with the endpoint available are analyzed, and the trial is stopped if the number of "successes" is only 16 or lower. . Otherwise, the study is continued until a total of 53 patients evaluable for efficacy. Including drop-outs a total of 59 patients are estimated to be required. |
| SAMPLE SIZE | N=59 patients (10% drop out rate is included) |
| TRIAL DURATION | 20 months (recruiting period)<br>Maximal treatment duration per patient: 1 year,<br>Maximal Follow-Up after treatment discontinuation: 1 year |
| PARTICIPATING CENTERS | Pending, Planned total number n=18 |
| FURTHER CENTERS DESIRED? | Yes |
| NUMBER of PATIENTS | 0 |
| CURRENT NUMBER of PATIENTS | 0 |

*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**

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

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| Trial type | A randomized, multicenter open label phase II trial |
| Coordinating investigator | Prof. Dr. Sylvie Lorenzen<br>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) | **Arm A (investigational arm)**<br>Paclitaxel 80 mg/m2 on day 1, 8, 15<br>plus<br>Ramucirumab 8 mg/kg i.v. infusion on day 1 and 15<br>Start of next cycle on day 29 (qd 28).<br><br>**Arm B (control arm)**<br>Paclitaxel 80 mg/m2 on day 1, 8, 15<br>Start of next cycle on day 29 (qd 28). |
| Key inclusion and exclusion criteria | Key inclusion criteria:<br>- Histologically proven squamous cell carcinoma of the esophagus<br>- Metastatic or locally advanced disease, not amenable to potentially curative resection<br>- Refractory or intolerant to a combination therapy of platinum and a fluoropyrimidine for esophageal cancer. The definition of refractory should be defined as follows:<br>- 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”.<br>- 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”.<br>- Measurable or non-measurable but evaluable disease determined using guidelines in RECIST 1.1 as confirmed within 28 days before randomization<br>- Adequate blood and biochemistry parameters<br><br>Key exclusion criteria: |

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| | - 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<br>- Patients with significant malnutrition who receive intravenous hyperalimentation or require continuous infusion therapy with hospitalization.<br>- 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.<br>- Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol<br>- Previous therapy with paclitaxel or previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study |
| Outcome(s) | Primary endpoint:<br>OS rate after 6 months<br>Secondary endpoints:<br>- Progression-free survival<br>- Overall survival<br>- Objective response rate (CR + PR)<br>- Tumor control rate (CR, PR, SD)<br>- Safety (according to NCI-CTCAE V 4) and tolerability<br>- Quality of Life (EORTC QLQ C-30) |
| Sample size | 186 (93 per Arm) |
| Trial duration | First patient in to last patient out (months): 48<br>Duration of the entire trial (months): 48<br>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]**

| **AIO-Studie** | |
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| Studiennummer/-Code: | AIO-STO-0117 - RAMONA |
| Status: | Rekrutierung |
| Rekrutierungszeitraum | 2018 - 2019 |
| Weitere Zentren: | nein |
| Letzte Aktualisierung | April 2018 |

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| National Coordinating Investigator (LKP) | Prof. Dr. med. Matthias Ebert<br>II. Medizinische Klinik<br>Universitätsmedizin Mannheim, Heidelberg University<br>Theodor-Kutzer-Ufer 1-3<br>68167 Mannheim<br>Germany<br>Phone: +49621 383 3284<br>Fax: +49621 383 3805 |

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| | E-Mail: Matthias.Ebert@umm.de |
| Sponsor | AIO-Studien-gGmbH<br>Dr. Aysun Karatas<br>Kuno-Fischer-Straße 8<br>14057 Berlin<br>Phone: +49 30 814534431<br>Fax +49 30 322932926<br>E-Mail: info@aio-studien-ggmbh.de |
| Study design | Open label, multicenter phase II trial |
| Duration of study | Enrollment: 12 months<br>total study duration 36 months (incl. follow-up) |
| Indication | Pretreated 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 | 33 initiated |
| Recruitment status | 75 patients planned, 22 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.<br>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:<br>a) to assess additional efficacy and safety parameters of an intensified immunotherapy regimen.<br>b) to assess and explore the predictive value of structured geriatric assessments for treatment-emergent toxicities and treatment discontinuation |
| Inclusion criteria | - 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<br>- Age ≥ 65 years at time of study entry<br>- Histologically confirmed advanced stage non-resectable esophageal squamous cell carcinoma beyond frontline therapy*:<br>○ stage 4 OR<br>○ stage 3 non-responder to radio-chemotherapy OR<br>○ any relapse after after chemo-radiation OR<br>○ any relapse after surgery if patient is ineligible or intolerant to standard frontline therapies OR refuses other treatment<br>* Frontline therapy is defined as chemotherapy (+/- radiotherapy) (e.g. CROSS, FLOT or similar protocols) OR any palliative systemic chemotherapy<br>- Geriatric status: SlowGo or GoGo according to G8 and DAFI assessment (G8 > 14 points or CGA/DAFI 0.2<0.35)<br>- At least 1 measurable lesion according to RECIST 1.1<br>- Karnofski performance status ≥ 50<br>- Sufficient cardiac functional reserve defined as ejection fraction ≥ 50%<br>- Adequate blood count, liver-enzymes, and renal function:<br>- neutrophil count > 1.5 x $10^6$/mL<br>- WBC ≥ 3000/µL<br>- Platelet count ≥ 100 x $10^9$/L (>100,000 per $mm^3$)<br>- hemoglobin ≥ 9 g/dL<br>- INR ≤ 1.5 and PTT ≤ 1.5 x ULN during the last 7 days before therapy<br>- AST (SGOT)/ALT (SGPT) < 3 x institutional upper limit of normal (5 x lower limit in case of liver metastases) |

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| | - bilirubin < 1.5 x ULN<br>- Serum Creatinine ≤ 1.5 x institutional ULN or creatinine clearance (CrCl) ≥ 30 mL/min (if using the Cockcroft-Gault formula below):<br>Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL<br>Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL<br>- 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).<br>- 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 criteria:**<br>• Patients <65 years of age<br>• Frail patients (DAFI score ≥ 0.35)<br>• Esophageal adenocarcinomas, neuroendocrine tumors<br>• 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)<br>• Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lifes of previously used trial medication, whichever is longer<br>• Previous treatment in the present study (does not include screening failure).<br><br>**Medical:**<br>• 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:<br>o Major surgery ≤ 28 days prior first dose of study treatment<br>o 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]<br>o history of interstitial lung disease<br>o known acute or chronic pancreatitis<br>o known active HBV, HCV or HIV infection<br>o active tuberculosis<br>o any other active infection (viral, fungal or bacterial) requiring systemic therapy<br>o history of allogeneic tissue/solid organ transplant<br>o 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.<br>o 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.<br>o Live vaccine within 30 days prior to the first dose of nivolumab-monotherapy treatment or during study treatment.<br>o Other clinically significant active malignancy requiring treatment OR less than 5 years disease free interval of another primary malignancy<br>o Clinically significant or symptomatic cardiovascular/cerebrovascular disease (incl. myocardial infarction, unstable angina, symptomatic |

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| | congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment<br>○ History or clinical evidence of CNS metastases<br>Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:<br>1. are asymptomatic and<br>2. have no requirement for steroids 6 weeks prior to start of nivolumab-monotherapy treament. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases<br><br>**Drug related criteria:**<br>• Medication that is known to interfere with any of the agents applied in the trial.<br>• Has known hypersensitivity to nivolumab or ipilimumab or any of the constituents of the products.<br>• Any other efficacious cancer treatment except protocol specified treatment at study start.<br>• Patient has received any other investigational product within 28 days of study entry.<br>**Safety criteria:**<br>• Patient has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. [Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.]<br>• 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 β-HCG) at screening.<br><br>**Regulatory and ethical criteria:**<br>• Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.<br>• Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>• 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<br>• ipilimumab |
| Treatment schedule | 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).<br>Study subjects without significant TEAEs are eligible to escalate treatment to a nivolumab/ipilimumab combination therapy:<br>**Arm A:** Nivolumab 240 mg fixed dose IV Q2W; Ipilimumab 1mg/kg IV Q6W (starting in week 7 after safety assessment)<br>Subjects with significant TEAEs who still qualify for nivolumab treatment continue nivolumab mono-therapy:<br>**Arm B: Nivolumab 240 mg IV fixed dose Q2W**<br>In both arms treatment continues until progressive disease or intolerable toxicity or withdrawal of consent or death.<br>Tumor assesssments:<br>c) 1st restaging assessment after 12 weeks of therapy<br>d) thereafter Q8W (post-progression nivolumab after 1st assessment included) |

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| Primary endpoint | Overall survival |
| Secondary endpoints | • Time to QoL deterioration defined as a loss of ≥ 10 points in the EORTC QLQ-C30 compared to base-line<br>• PFS<br>• ORR according to RECIST 1.1 and immune related response criteria (modified RECIST)<br>• Duration of Response (DOR)<br>• Duration of treatment<br>• cumulative dose intensity<br>• QoL (EORTC QLQC30 and ELD14)<br>• AEs/SAEs<br>Geriatric assessments:<br>• Evaluation of the predictive value of the GA containing tests (DAFI, G8-Questionaire etc.) for the occurrence of ≥ grade 3 toxicities.<br>• Predictive value of the assessed geriatric tests for treatment discontinuation |
| Exploratory objectives and endpoints | • predictive biomarkers in tumor tissue (pre-treatment and re-biopsies) and blood |
| Rationale<br>Hypothesis | 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 peri-operative chemotherapy and/or chemo-radiation in the front-line setting, mostly according to the CROSS protocol using paclitaxel and carboplatin, the role of subsequent palliative second-line chemotherapy is 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) [3].<br>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].<br><br>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 check-point 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.<br><br>**Research hypothesis:**<br>• Nivolumab in combination with Ipilimumab improves overall survival compared to standard chemotherapy (historical control) in elderly patients with esophageal squamous cell cancer.<br>• Nivolumab alone and in combination with Ipilimumab improves time to QoL deterioration compared to standard chemotherapy (historical control) in elderly ESCC patients. |
| Safety data | • AEs, SAEs and treatment emergent adverse events according to CTC 4.03<br>• Frequency of clinically significant abnormal laboratory parameters |

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| Sample size estimation and<br><br>Statistical analysis considerations | 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%).<br><br>Sample size estimation:<br>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.<br><br>To compensate for uninformative drop-outs a total of **N=75** subjects need to be recruited. |
| Study plan / time lines | First Patient In (FPI): Q1/2018<br>Last Patient In (LPI): after approx. 12 month<br>Last Patient Last treatment (LPLT): after approx. 20 month<br>End of follow-up period after LPI: after approx. 36 month<br>Study report: after approx. 45 month<br>Publication: after approx. 45 month |

# Arbeitsgruppe Pankreaskarzinom

*Pankreaskarzinom – adjuvante Therapie*

**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 | |
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| Studiennummer/-Code: | AIO-PAK-0111/ass - HEAT |
| Status: | unbekannt |
| Rekrutierungszeitraum: | 2013 - 2019 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2017 |

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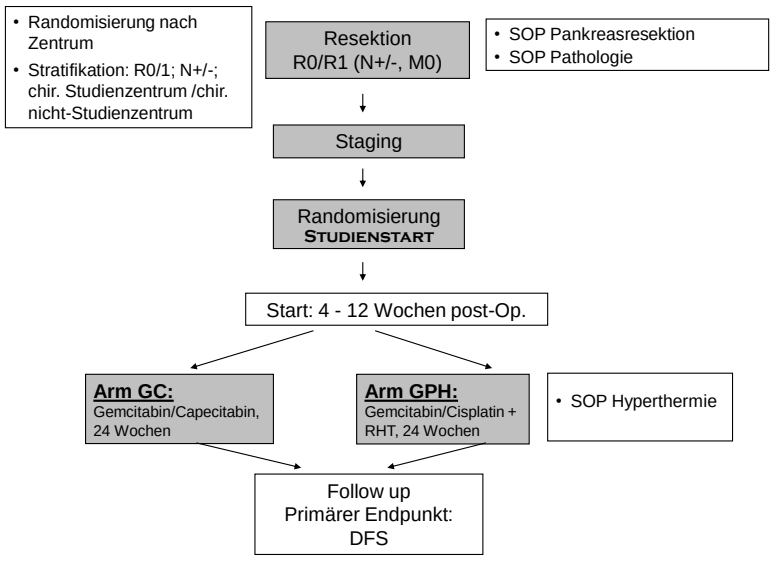
| Study Type | Multicenter, national, randomized (stratification: R0/1; N+/-; surgical study center/surgical non-study center) |
| Sponsor | Klinikum Grosshadern Medical Center, University of Munich<br>represented by the medical director, D-81377 Munich |
| Coordinating Investigator | Prof. Dr. Rolf Issels<br>Dept. Internal Medicine III, Klinikum Grosshadern Medical Center<br>University of Munich, D-81377 Munich |
| Trial Office | Prof. Dr. Rolf Issels / Coordinating center: Nelli Dieterle<br>Phone: +49-89-4400-77776 / -74768<br>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)<br>  |

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| Objektives | *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.* |
| Intervention | Course: A course is defined as a period of 28 days.<br><br>Intervention 1 (GC): Gemcitabine + Capecitabine<br>Gemcitabine: 1000 mg/m² as iv-infusion on days 1, 8 and 15 of each course (Total dose: 18 g/m²)<br>Capecitabine: daily dose of 1660 mg/m²; administered orally for 21 days followed by 7 days' rest (one cycle) for six cycles<br><br>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 27th, 2012)<br><br>Intervention 2 (GPH): Gemcitabine + Cisplatin + regional hyperthermia<br>Gemcitabine: 1000 mg/m² as iv-infusion on days 1 and 15 of each course (Total dose: 12 g/m²)<br>Cisplatin: 25 mg/m² as iv-infusion on days 2, 3* and 16, 17* of each course (Total dose: 600 mg/m²)<br>Regional hyperthermia: 60 minutes on days 2, 3* and 16 ,17* of each course<br><br>* 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.<br><br>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. |
| Number of Patients: | 336 patients (168 per arm) - actually 75 patients recruited (Okt. 2017) |
| Recruitment | Recruitment start: March 2012<br>Recruitment phase: 36 months |
| Further study centers requested? | Yes |
| Inclusion criteria | 1. Any ductal adenocarcinoma of the pancreas confirmed by histology<br>2. Previous R0 or R1 resection of pancreatic tumor with a standardized procedure<br>3. No other previous or concomitant treatment of pancreatic carcinoma like radiation, neoadjuvant therapy or immunotherapy<br>4. No tumor recurrence after surgery<br>5. Performance status ECOG 0-2<br>6. Adequate bone marrow function defined as:<br>• WBC count ≥ 3.5 x $10^9$/L<br>• platelets ≥ 150 x $10^9$/L<br>• hemoglobin ≥ 9 g/dl<br>documented within 1 week prior to randomization<br>7. Adequate renal function defined as:<br>• serum creatinine ≤ 1.2 mg/dl<br>• calculated GFR ≥ 60 mL/min<br>documented within 1 week prior to randomization<br>8. Adequate coagulatory function defined as:<br>• Quick-value ≥ 70%<br>• aPTT ≤ 1.5 x ULN<br>documented within 1 week prior to randomization |

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| | 9. Transaminases (AST, ALT) ≤ 3 x ULN and bilirubin ≤ 2 x ULN documented within 1 week prior to randomization<br>10. At least 18 years of age<br>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.)<br>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)<br>13. Written informed consent |
| Exclusion criteria | 1. Cystic carcinoma of the pancreas<br>2. Periampullary, papillary cancer<br>3. Metastatic disease<br>4. Presence of an active infection grade 3 or higher<br>5. Other severe disease which could impair the patient's ability to participate in the study according to the investigator's opinion<br>6. Pregnant or breastfeeding women<br>7. Known allergies or contraindications with regard to substances or procedures of study therapy<br>8. Severe, non-healing wounds, ulcers or bone fractures<br>9. Participation in another clinical trial during this study or within 4 weeks prior to randomization<br>Exception: participation in a surgical trial prior to this study, for instance RECOPANC trial, comparing two different surgical procedures of pancreas resection (Ethics vote: January 21st,2013)<br>10. Past or current abuse of illegal or legal drugs or alcohol<br>11. 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).<br>12. Permanent cardiac pacemaker<br>13. Gross adiposity defined as BMI > 40 kg/m²<br>14. Treatment with regional hyperthermia not possible for technical reasons (e.g. metal implant)<br>15. *Clinically significant cardiovascular or vascular disease or disorder ≤ 6 months before study enrolment (e.g. myocardial infarction, unstable angina pectoris, chronic heart failure NYHA ≥ grade 2, uncontrolled arrhythmia, cerebral infarction*<br>16. *„Known documented dihydropyrimidine dehydrogenase (DPD) deficiency"* |
| Criteria for evaluation | Primary efficacy criterion: Disease free survival (DFS)<br>Secondary efficacy criterion: Overall Survival (OS)<br>Safety: Adverse events (including abnormal laboratory values) scored according to CTCAE (version 4.0)<br>Quality of Life: EORTC QLQ C30<br>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. |
| Sample size | For sample size calculation we use a group-sequential design with two interim analyses and the following assumptions:<br>Median DFS with treatment group 1 (G): 14 months ($\lambda_G = 0.05$)<br>Median DFS with treatment group 2 (GPH): 19 months ($\lambda_{GPH} = 0.036$) |

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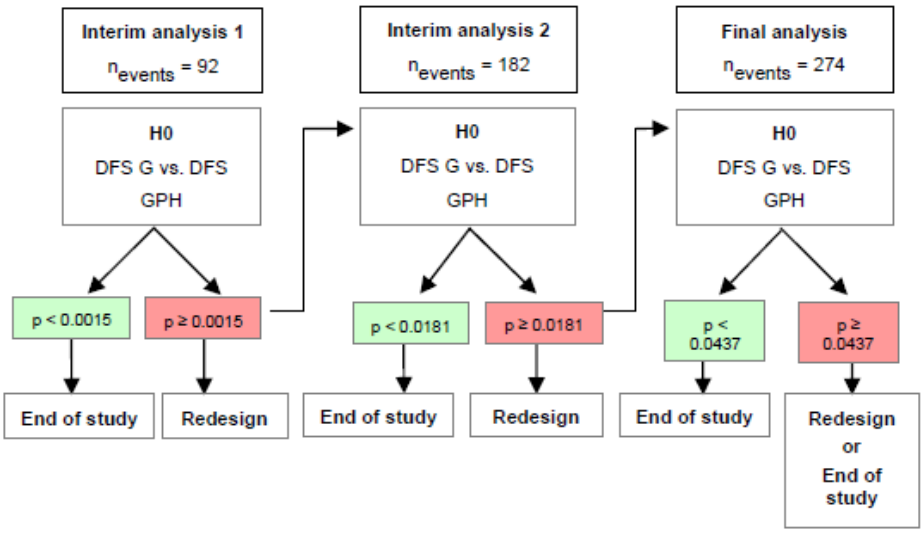
| | For specified alpha = 0.05, hazards $\lambda_G$ = 0.05, $\lambda_{GPH}$ = 0.036 (hazard ratio = 0.737) and power of 80.0% the design would require a maximum of 336 patients to be recruited. Hence, a total number of 168 patients per arm is recruited. Interim analyses are planned after occurring of 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 *estimated to be about* five years. |
| Statistical analysis | Primary efficacy criterion:<br>We test the following null-hypothesis (H0):<br>DFS under treatment group 1 (G) == to DFS under treatment group 2 (GPH)<br>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).<br>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.<br>  <br><br><u>Secondary efficacy criterion:</u><br>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 joint model.<br><u>Prespecified subgroup analyses:</u><br>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.<br><u>Sensitivity analyses:</u><br>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.<br><u>Safety:</u><br>The incidences of adverse events in the treatment arms will be presented by type and severity.<br>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, |

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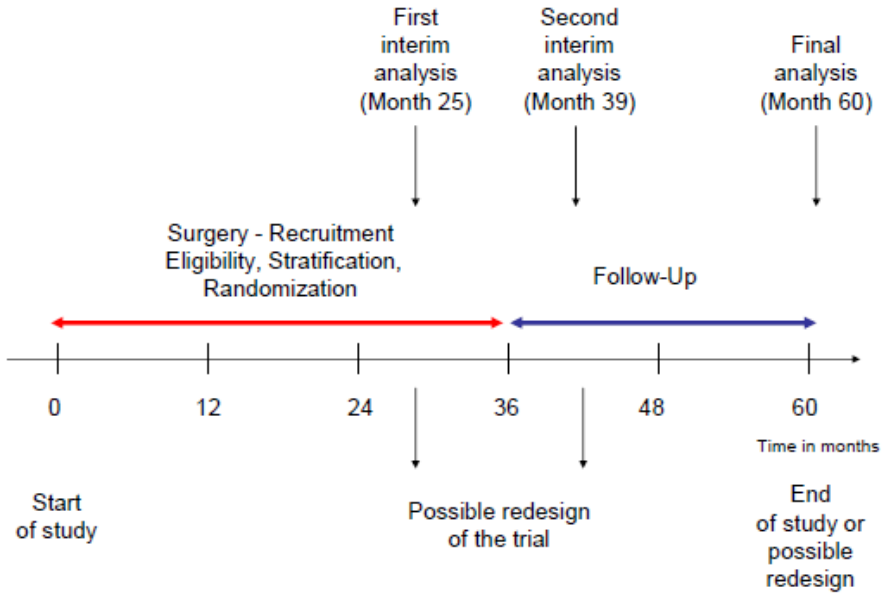
| | loss or gain of centers, etc. The reanalysis will be based on the proposal of Müller & Schäfer (SIM, 2004). |
| Trial duration | First patient in to last patient in: 3 years<br>Duration of the entire trial: 5 years<br>Flow for stage I of trial<br>  |

*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**

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

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| 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<br>Dept. of Internal Medicine I, University of Ulm<br>Albert-Einstein-Allee 23, 89081 Ulm, Germany<br>Phone: +49 731 50044501<br>E-mail: thomas.seufferlein@uniklinik-ulm.de |
| Sponsor: | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany<br>Tel: +49 30-8145 344 32, Fax: +49 30-3229329-26<br>E-Mail: info@aio-studien-ggmbh.de |
| Objectives | Primary objective: |

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| | • 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 ≥ 55 %)<br><br><u>Secondary objectives:</u><br>• 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<br>• Effect of perioperative or adjuvant nab-Paclitaxel/Gemcitabine on DFS and OS 3 year after randomization<br>• Safety of perioperative and adjuvant nab-Paclitaxel/Gemcitabine<br>• Potential association between tumor regression and R0 resection rate, DFS, OS and biomarkers in the perioperative arm<br>• Pre- and postoperative morbidity and mortality<br>• Dropout rate due to toxicity<br>• Disease progression during neoadjuvant therapy<br>• R0 and R1 resection rate as assessed according to the German S3 guidelines<br>• Correlation of tumor regression and R0 resection rate with response according to Recist 1.1 in the perioperative study arm<br>• Overall survival (OS)<br>• First site of tumor recurrence<br>• Health related quality of life (EORTC QLQ-PAN26, QLQ-C30 and HADS-D questionnaires)<br>• Correlation of DFS, OS and tumor regression with pharmacogenomic markers, tumor biomarkers and molecular analyses (cfDNA, transcriptome, miRNA-arrays) |
| Number of patients | **Randomized: 94 patients**<br>To be assessed for eligibility: n = 190<br>To be allocated to trial: n = 166<br>To be analyzed: n = 116 (58 patients per treatment group) |
| Recruitment | Duration of Intervention per patient:<br>Perioperative arm: 37 weeks<br>Adjuvant arm: 34 weeks<br>Start of trial/First patient in (FPI)/Randomization: Q III/2015<br>Last patient in (LPI) Q IV/2019<br>Planned End of Treatment last patient Q III/2020<br>Planned last visit for primary objective last patient Q II /2021<br>LPLV (last patient last visit) date Q III/2023<br>Recruitment period (months): 54 months<br>Follow-up-period: 3 years |
| Number of study centers | 25 study centers in Germany (university hospitals or high-volume centers for PDAC surgery)<br>Number of initiated sites: 30 |
| More centers? | No |
| Key inclusion criteria | • Histologically or cytological proven confirmed, clearly resectable ductal adenocarcinoma of the pancreas (PDAC) ≤ cT3 with no prior tumor specific treatment.<br>• No evidence of metastases to distant organs (e.g. liver, peritoneum, lung).<br>• 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).<br>• Measurable tumor according to RECIST 1.1<br>• ECOG performance status 0 or 1<br>• Creatinine clearance ≥ 30 ml/min |

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| | • Serum total bilirubin level ≤ 2.5 x ULN (not necessary for enrollment or randomization, but before start of neoadjuvant chemotherapy)<br>• ALT and AST ≤ 2.5 x ULN (not necessary for enrollment or randomization, but before start of neoadjuvant chemotherapy)<br>• In case of biliary obstruction, biliary decompression is required. Postinterventional bilirubin levels must be ≤ 2.5 x ULN if the patient was randomized to receive neoadjuvant chemotherapy (arm A)<br>• White blood cell count ≥ 3.5 x $10^6$/ml, neutrophil granulocytes count ≥ 1,5 x $10^6$/ml, platelet count ≥ 100 x $10^6$/ml<br>• Signed informed consent incl. participation in translational research<br>• Age ≥ 18 years |
| Key exclusion criteria | • Borderline resectable PDAC by radiologic criteria<br>• Papillary cancer<br>• Neuroendocrine Cancer<br>• Tumor specific pre-treatment<br>• Local recurrence<br>• Peritoneal or other distant metastases<br>• Radiographic evidence of severe portal hypertension/cavernous transformation<br>• Infiltration of extrapancreatic organs (except duodenum)<br>• Ascites<br>• Gastric outlet obstruction<br>• Global respiratory insufficiency requiring oxygen supplementation<br>• Chronic infectious diseases, immune deficiency syndromes<br>• Premalignant hematologic disorders, e.g. myelodysplastic syndrome<br>• Disability to understand and sign written informed consent document<br>• Past or current history of malignancies except for the indication under this study and curatively treated:<br>- Basal and squamous cell carcinoma of the skin<br>- In-situ carcinoma of the cervix<br>- Other malignant disease without recurrence after at least 5 years of follow-up<br>• Clinically significant cardiovascular disease (incl. myocardialinfarction, unstable angina, symptomatic congestive heart failure ,serious uncontrolled cardiac arrhythmia) 6 months before enrollment<br>• 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.<br>• 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).<br>• Pre-existing neuropathy > grade 1 (NCI CTCAE)<br>• Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy<br>• Severe non-healing wounds, ulcers or bone fractions<br>• Evidence of bleeding diathesis or coagulopathy<br>• Patients not receiving therapeutic anticoagulation must have an INR < 1.5 ULN and PTT < 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)<br>• 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.<br>• Pregnancy or breastfeeding women.<br>• Subjects with known allergies to the study drugs or to any of its excipients.<br>• Current or recent (within the 28 days prior randomization) treatment with another investigational drug or participation in another investigational study. |

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| | • 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 |
| Scheme of therapy | **Arm A (neoadjuvant arm):**<br>2 cycles of nab-Paclitaxel/Gemcitabine (nab-Paclitaxel 125 mg/m$^2$,Gemcitabine 1000 mg/m$^2$ on day 1, 8 and 15 of an 28 day-cycles) 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$^2$, Gemcitabine 1000 mg/m$^2$ on day 1, 8 and 15 of a 28 day-cycles) in the adjuvant setting.<br><br>**Arm B (adjuvant arm):**<br>Tumor surgery followed by adjuvant chemotherapy with 6 cycles of nab-Paclitaxel/Gemcitabine (nab-Paclitaxel 125 mg/m$^2$, Gemcitabine 1000mg/m$^2$ on day 1, 8 and 15 of a 28 day-cycles, starting within 12 weeks after surgery).<br><br>**Duration of intervention per patient:**<br>**Arm A:** Neoadjuvant chemotherapy (8 weeks) preceding surgery (3 weeks after completion of chemotherapy) followed by adjuvant chemotherapy (16 weeks, starting within 12 weeks after surgery).<br>**Arm B:** Surgery followed by adjuvant chemotherapy (24 weeks, starting within 12 weeks after surgery),<br>Follow-up per patient: Until end of study or death. |
| Sample size and statistical analysis | 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 sample size is 166 patients (2 x 83). Sample size was computed by “SWOG One arm survival sample size and power” (http://www.swogstat.org/stat/public/one_survival.htm).<br>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.<br>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.<br>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. |

*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)**

| **AIO-assoziierte Studie** | |
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| 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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| COORDINATING INVESTIGATOR | Prof. Dr. Volker Heinemann<br>Medizinische Klinik III, Campus Großhadern<br>Ludwig-Maximilians-Univ. München<br>Marchioninistr. 15, 81377 München<br>Phone: 089 4400 72208<br>Fax: 089 4400 75256<br>E-mail : volker.heinemann@med.uni-muenchen.de |
| Study coordinator | Dr. Benedikt Westphalen Medizinische Klinik III, Campus Großhadern<br>Ludwig-Maximilians-Univ. München<br>Marchioninistr. 15, 81377 München<br>Phone: 089 4400 75250<br>E-mail : cwestpha@med.lmu.de |
| OBJECTIVE(S) | To determine the optimal first line regimen in metastatic pancreatic cancer. |
| INTERVENTION(S) | **Arm A: Gemcitabine & nab-paclitaxel (Standard)**<br>• *Nab*-paclitaxel 125 mg/m², i.v. infusion over about 30 minutes followed by<br>• Gemcitabine 1000 mg/m² as a 30-minute i.v. infusion on D1, D8, D15 of a 28-day cycle.<br><br>Treatment is given until disease progression or the occurrence of unacceptable toxicity.<br><br>**Arm B: NAPOLI regimen (Investigational 1)**<br>On Day 1 of a 14-day cycle:<br>• Liposomal irinotecan 80 mg/m² i.v. over about 90 minutes followed by<br>• Folinic acid 400 mg/m² i.v. over about 30 minutes followed by<br>• 5-FU 2400 mg/m² i.v. over about 46 h (pump)<br><br>Treatment is given until disease progression or the occurrence of unacceptable toxicity.<br><br>**Arm C: Alternating NAPOLI/mFOLFOX6 (aNAPOLINOX) (Investigational 2):**<br>The NAPOLI regimen and the mFOLFOX6 regimen are applied in an alternating fashion, starting with the NAPOLI regimen.<br><br>***NAPOLI***:<br>On Day 1 of a 14-day cycle:<br>• Liposomal irinotecan 80 mg/m² i.v. over about 90 minutes followed by<br>• Folinic acid 400 mg/m² i.v. over about 30 minutes followed by<br>• 5-FU 2400 mg/m² i.v. over about 46 h (pump)<br><br>***mFOLFOX6:***<br>On Day 1 of a 14-day cycle: |

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| | • Oxaliplatin 85 mg/m$^2$ i.v.<br>• Folinic acid 400 mg/m$^2$ i.v.<br>followed by<br>• 5-FU 2400 mg/m$^2$ i.v. over about 46 h (pump)<br><br>Treatment is given until disease progression or the occurrence of unacceptable toxicity.<br><br>***Recommended second-line regimens:***<br>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:<br><br>**Arm A:** After failure of gemcitabine/*nab*-paclitaxel the recommended second-line treatment would be the NAPOLI regimen.<br><br>**Arms B and C**: After failure of the NAPOLI-regimen, a gemcitabine-based regimen, preferentially gemcitabine/*nab*-paclitaxel, would be recommended. |
| KEY EXCLUSION CRITERIA | • Locally advanced PDAC without metastasis<br>• Known DPD-deficiency (special screening test not required)<br>• Symptomatic clinically significant ascites (expected indication for repeated paracentesis)<br>• 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.<br>• Previous palliative chemotherapy or other palliative systemic tumor therapy for metastatic disease of PDAC<br>• Previous gemcitabine/5-FU treatment ***with exception of*** gemcitabine/5-FU treatment applied in the adjuvant setting (after potential curative R0 or R1 resection) ***and*** if the adjuvant chemotherapy was terminated at least 6 months before study entry<br>• Previous radiotherapy of PDAC<br>• Any major surgery within the last 4 weeks before study entry<br>• Clinical significant decrease in performance status within 2 weeks of intended first application of study medication (by medical history)<br>• Severe tumor-related cachexia and/or known weight loss > 15% within one month before study enrollment<br>• Pre-existing polyneuropathy ≥ grade 2 according to CTCAE version 4.03<br>• 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 ≥ 2<br>• 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 (≤ 6 months before study start), myocardial infarction (≤ 6 months before study start), unstable angina, heart failure ≥ NYHA functional classification system grade 2, severe cardiac arrhythmia requiring medication, metabolic dysfunction, severe renal disorder.<br>• 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<br>• Hypersensitivity to the study drugs or to any of the excipients or to compounds with similar chemical or biologic composition<br>• 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. |

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| | • Patient known to be homozygous for UGT111*28 or strongly suspected to be homozygous for the UGT111*28 allele<br>• Requirement for concomitant antiviral treatment with sorivudine or brivudine<br>• Continuing abuse of alcohol, drugs, or medical drugs<br>• Pregnant or breast-feeding females or FCBPs unable to either perform highly effective contraceptive measures or practice complete abstinence from heterosexual intercourse<br>• 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 |
| KEY INCLUSION CRITERIA | • Adult patients ≥ 18 years of age and ≤ 75 years<br>• 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)<br>• No option for surgical resection or radiation in curative intent<br>• At least one unidimensionally measurable tumor lesion (according to RECIST 1.1)<br>• ECOG performance status 0 - 1<br>• Life expectancy at least 3 months<br>• Adequate hepatic, renal and bone marrow function, defined as:<br>▪ Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L<br>▪ Haemoglobin ≥ 9 g/dL<br>▪ Thrombocytes ≥ 100 x $10^9$/L<br>▪ Total bilirubin ≤ 1.5 x ULN. Patients with a biliary stent may be included provided that bilirubin level after stent insertion decreased to ≤ 1.5 x ULN and there is no cholangitis.<br>▪ AST/GOT and/or ALT/GPT ≤ 2.5 x ULN or in case of liver metastasis ≤ 5 x ULN)<br>▪ Serum creatinine within normal limits or creatinine clearance [1 SEP] ≥ 60 mL/min/1.73 $m^2$ as calculated by CKD-EPI formula for patients with serum creatinine levels above or below the institutional normal value.<br>▪ Acceptable coagulation studies defined as prothrombin time (or INR) and PTT ≤ 1.5 x ULN<br>• 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<br>**and**<br>FCBP must either agree to use and be able to take highly effective contraceptive birth control methods (Pearl Index < 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.<br>A female subject following menarche is considered to be of childbearing potential unless she is naturally amenorrhoeic for ≥ 1 year without an alternative medical reason, or unless she is permanently sterile.<br>• 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.<br>• Signed and dated informed consent before the start of any specific protocol procedures<br>Patient's legal capacity to consent to study participation |
| OUTCOME(S) | **Primary Endpoint:** |

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| | • Progression free survival (PFS)<br>**Secondary Endpoints:**<br>• Overall survival (OS)<br>• Objective response rate (ORR)<br>• Disease control rate (DCR)<br>• Duration of study treatment<br>• Type, incidence, causal relationship and severity of adverse events according to NCI CTCAE version 4.03<br>• Quality of life as assessed by EORTC-QLQ-C30<br>• Treatment with second-line chemotherapy as documented in the patient's medical file |
| STUDY TYPE | **Multicenter randomized phase II** |
| STATISTICAL ANALYSIS | 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 (α = 0,1 & β = 0.2 –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:<br>$H_0$: PFS (arm B) ≤ PFS (arm A)<br>$H_1$: PFS (arm B) > PFS (arm A)<br>and<br>$H_0$: PFS (arm C) ≤ PFS (arm A)<br>$H_1$: PFS (arm C) > PFS (arm A)<br>Both pair of hypotheses will be tested with one-tailed α=0.067 and β=0.2. This leads to a total α 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. |
| 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**

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| Studiennummer/-Code: | AIO-PAK-0216 - PREDICT |
| Status: | Aktiv rekrutierend |
| Rekrutierungszeitraum: | FPI März 2018 // Rekrutierung geplant auf 24 Monate |
| Anzahl initiierter Zentren: | 31 (inkl. der im November neu initiierten Zentren) |
| Weitere Zentren: | Momentan nur Warteliste |
| Anzahl eingeschlossene Patienten: | 15 von geplanten 270 |
| Letzte Aktualisierung: | Oktober 2018 |

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| EudraCT No. | 2016-005147-17 |
| National Coordinating Investigator | Prof. Dr. med. Manfred P. Lutz<br>Internal Medicine<br>Caritasklinikum St. Theresia<br>Rheinstrasse 2, 66113 Saarbrücken |

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| | Phone +49 681 406 1001<br>Fax +49 681 406 1003<br>m.lutz@caritasklinikum.de |
| Sponsor | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431<br>Fax +49 30 322932926<br>E-Mail: info@aio-studien-ggmbh.de |
| Study design | Open label, single arm, multicenter phase IIIb trial |
| Duration of study | Enrollment: 24 month<br>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 1st-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 2nd line treatment with Nal-IRI combination chemotherapy |
| Secondary objectives | Secondary objectives of this study are:<br>• to generate additional efficacy and safety data for the 2nd-line treatment<br>• to assess the Quality of Life and Patient Reported Outcomes during 2nd-line treatment<br>• to assess the impact of the course of the 1st-line treatment on the outcome of the 2nd-line therapy<br>• to explore the impact of physiological and molecular markers on the efficacy of the 2nd-line |
| 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<br>2. Clinical indication for a 2nd-line systemic therapy according to current standard-of-care.<br>3. Age ≥ 18 years at time of study entry<br>4. Patients with histologically or cytologically confirmed pancreatic ductal adenocarcinoma<br>5. Imaging of evaluable lesions within 2 weeks of inclusion (either sonography, X-ray, CT scans, MRI)<br>6. ECOG performance status 0-2<br>7. One line of systemic gemcitabine/Nab-paclitaxel therapy for advanced disease (irrespective of prior adjuvant therapy)<br>OR<br>Previous adjuvant gemcitabine/Nab-paclitaxel chemotherapy with documented progression less than 6 months after termination<br>8. Detailed documentation of prior therapy (duration, dose-intensity, maximum toxicity, reason for discontinuation)<br>9. Adequate blood count, liver-enzymes, and renal function:<br>• neutrophil count > 1.5 x $10^6$/mL<br>• Platelet count ≥ 100 x $10^9$/L (≥100,000 per mm3)<br>• AST (SGOT)/ALT (SGPT) ≤ 5 x institutional upper limit of normal<br>• bilirubin ≤1.5 ULN (<3 x ULN in patients with confirmed mechanical cholestasis)<br>• Creatinine Clearance CLcr ≥ 30 mL/min<br>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. |

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| Exclusion criteria | **Medical criteria:**<br>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:<br>(1) Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes<br>(2) Premalignant hematologic disorders, e.g. myelodysplastic syndrome<br>(3) Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment<br>(4) Prior (<3 years) or concurrent malignancy (other than biliary-tract cancer) which either progresses or requires active treatment.<br>***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].<br>(5) Pre-existing lung disease of clinical significance or with impact on performance status<br>(6) History or clinical evidence of CNS metastases<br>Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:<br>b) are asymptomatic and<br>c) have no requirement for steroids 6 weeks prior to start of study treament. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases<br>(7) Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy<br>(8) Severe non-healing wounds, ulcers or bone fractions<br>(9) Evidence of bleeding diathesis or coagulopathy<br>(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 of the study except for surgery of central intravenous line placement for chemotherapy administration.<br>(11) Known Gilbert-Meulengracht syndrome<br>(12) Known chronic hypoacusis, tinnitus or vertigo<br>(13) Bone marrow depression (e.g., after radiation therapy)<br>(14) Pernicious anemia and other megaloblastic anemias secondary to vitamin B12 deficiency<br>(15) Severe impairment of hepatic function<br>(16) Diarrhea<br><br>**Drug related criteria:**<br>24. Medication that is known to interfere with any of the agents applied in the trial.<br>25. Known dihydropyrimidine dehydrogenase (DPD) deficiency<br>26. History of hypersensitivity to any of the study drugs or any of the constituents of the products.<br>27. Any other efficacious cancer treatment except protocol specified treatment at study start.<br><br>**Safety criteria:**<br>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 |

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| | 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 β-HCG acc. to SOC) at screening.<br><br>**Methodological criteria:**<br>29. Any experimental pretreatment for advanced disease<br>30. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lifes of previously used trial medication, whichever is longer<br>31. Previous enrollment in the present study (does not include screening failure).<br><br>**Regulatory and ethical criteria:**<br>32. Patient who might be dependent on the sponsor, site or the investigator<br>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]. |
| Investigational agents | • Nal-IRI (MM-398, IRINOTECAN LIPOSOME)<br>• 5-Fluorouracil (5-FU)<br>• folinic acid<br>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. |
| Treatment schedule | • Nal-IRI 80 mg/m$^2$ as a 1.5 hour infusion<br>• 5-FU 2400 mg/m$^2$ as 46 hour infusion<br>• Leucovorin 400 mg/m$^2$ as 0.5 hour infusion<br>• all on Day 1 of each cycle; cycle q2w<br><br>Treatment until progressive disease or intolerable toxicity or withdrawal of consent.<br><br>Key study procedures (and routine procedures):<br>• Clinical and toxicity evaluations before each new cycle; Q2W<br>• Disease evaluation (imaging if applicable) after 4 cycles of CTx (Q8W)<br>• QoL assessments Q4W;<br>Assessment tools: EORTC QLQ-PAN26, QLQ-C30; EQ-5D-5L<br>• Tumor tissue analysis at reference pathology<br>• Serum sample for cell-free DNA mutational analysis Q4W<br>• CA19-9 measurement Q2W |
| Primary endpoint | Time to Treatment Failure of second-line treatment (TTF2)<br><br>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) |
| Secondary endpoints | • Overall survival<br>• AEs / SAEs<br>• QoL [EORTC QLQ-PAN26, QLQ-C30; EQ-5D-5L]<br>• Evaluation of time to definitive deterioration of QoL (TDD)<br>• Growth modulation index |
| Exploratory objectives and endpoints | • Time course of individual parameters of QoL during 2nd-line treatment<br>• Correlation index of dose intensity of 1st-line treatment with TTF2<br>• Correlation of reasons for termination of 1st-line (progression or toxicity) with TTF2<br>• Correlation of BMI with TTF2 |

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| | • Comparison of treatment effect on QLQ-C30/Pan26 parameters with PROM (patient-related outcome measures)<br>• Correlation of CA19-9 response with TTF2<br>• Correlation of sequential cell-free DNA mutation levels with TTF2<br>• Correlation of CA19-9 to to TTF2 and OS Evaluate PROM as measure of treatment success<br>• Comparison of QoL as measured by standard tools (i.e. EORTC QLQ-C30 or –PAN26 or EQ-5D-5L) with PROM<br>• Compare variations and applicability of QLQ-C30/-PAN26 and PROM (Gerritsen et al. Europ J Cancer 57:68, 2016) in relation to treatment success<br>• Sequential measure of cell-free DNA in correlation to imaging response at 6-8 weeks according to RECIST1.1 guidelines (if available)<br>• Correlation of decrease in cell-free DNA to OS<br>• Correlation of histology (collection of tumor blocks required) to cell-free DNA and TTF2/OS<br>• Serum cell-free DNA analysis q4w and correlation with TTF2/OS/CA19-9 |
| Rationale<br>Hypothesis | 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).<br>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.<br><br>In summary, it is currently unknown which patients profit most from 2nd-line treatment with Nal-IRI.<br>It is also not known if 2nd-line treatment and its associated toxicities have an impact on symptom control or Quality of Life (QoL).<br>Confounding factors for the efficacy of 2nd-line treatment have only rarely been examined in pancreatic cancer.<br>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 1st-line (> 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).<br>Additional hypothesis can be derived from other tumor types.<br>In soft tissue sarcoma, a good performance status predicts success of 2nd-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, $p<0.04$), 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.<br>In advanced colorectal cancer, early progression during 1st-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.<br>In summary, the success of first-line therapy seems to have a beneficial effect on the efficacy of 2nd-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. |

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| | **Research hypothesis:**<br>Patients profit from 2nd-line therapy with Nal-IRI if they also had a benefit from 1st-line treatment.<br>Benefit from treatment (either 1st or 2nd-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. |
| Safety data | • AEs, SAEs and treatment emergent adverse events according to CTCAE Version 4.03<br>• Frequency of clinically significant abnormal laboratory parameters |
| Sample size estimation and<br>Statistical considerations | • 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 1st-line therapy for advanced disease.<br>• Assumptions: The expected median TTF2 of the whole patient population is 2.3 months (95% CI 1.6-2.8), as derived from another 2nd-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.<br>• 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. |
| Study plan / time lines | First Patient In (FPI): Q4/2017<br>Last Patient In (LPI): after approx. 24 month<br>Last Patient Last treatment (LPLT): after approx. 29 month<br>End of follow-up period after LPI: after approx. 34 month<br>Study report: after approx. 40 month<br>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)**

| **AIO-Studie** | |
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| Studiennummer/-Code: | AIO-PAK-0114 - ALPACA |
| Status: | Aktiv rekrutierend |
| Rekrutierungszeitraum: | 30 Monate (FPI 27.05.2016) |
| Anzahl initiierter Zentren: | 30 |
| Weitere Zentren: | Momentan nur Warteliste |
| Anzahl eingeschlossene Patienten: | 189 von 325 (83 randomisierte Patienten von 228 geplanten) |
| Letzte Aktualisierung: | Oktober 2018 |

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| Study Type | Multicenter, open-label, randomized active-controlled phase II trial |
| Coordinating Investigator | Prof. Dr. Frank Kullmann<br>Kliniken Nordoberfalz AG<br>Klinikum Weiden, Söllnerstraße 16, 92637 Weiden<br>E-Mail: frank.kullmann@kliniken-nordoberpfalz.ag |
| Sponsor | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8, 14057 Berlin, Germany<br>Tel: +49 30-8145 344 31; Fax: +49 30-3229 329 26<br>E-Mail: info@aio-studien-ggmbh.de |
| Number of patients | A total of 325 patients will be enrolled to the trial. (228 randomized) |
| Study duration | **Accrual period:**<br>The accrual period is estimated to last 30 months.<br><br>**Estimated treatment duration of the individual patient:**<br>Treatment duration in the individual patient will differ; estimated average treatment duration will be 6 - 8 months.<br><br>**Duration of follow up after end of treatment:**<br>Until death or the end of the study whichever is sooner and for at least 6 months or until death in each patient<br><br>**Estimated study duration:**<br>3.5 years from the first patient enrolled until the end of study<br><br>**Start of the study:**<br>First patient First visit (FPFV): Date of the written informed consent by the first patient enrolled.<br><br>**End of the study:**<br>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<br>This study is not open for new sites. |
| Background and Rationale | In the MPACT trial nab-paclitaxel in combination with gemcitabine has been shown to significantly improve overall survival ([OS];<br>8.5 vs. 6.6 months; median improvement of 2.1 months; p<0.001) compared to standard gemcitabine monotherapy in metastatic pancreatic adenocarcinoma. |

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| | 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$^2$). 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$^2$). This shorter treatment duration could have contributed to reduced overall survival.<br>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.<br><br>The considerations for the justification of alternating treatment cycles of gemcitabine monotherapy followed by nab-paclitaxel/gemcitabine are as follows:<br><br>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%).<br><br>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. |
| Inclusion criteria | • Adult patients (≥ 18 years of age)<br>• Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Patients with islet cell neoplasms are excluded<br>• Karnofsky performance status (KPS) ≥ 70%<br>• At least one unidimensionally measurable lesion as assessed by CT-scan or MRI according to RECIST 1.1<br>• Total bilirubin ≤ 1,5 x ULN. Patients with a biliary stent may be included provided that bilirubin level after stent insertion decreased to ≤ 1,5 x ULN and there is no cholangitis.<br>• Adequate renal, hepatic and bone marrow function, defined as<br>- Calculated creatinine clearance ≥ 30 mL/min according to CKD-EPI formula<br>- AST/GOT and/or ALT/GPT ≤ 2.5 x ULN and ≤ 5.0 x ULN in case of liver metastasis<br>- Absolute neutrophil count (ANC) ≥ 1.5 x 10$^9$/L |

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| | - Haemoglobin ≥ 9 g/dL<br>- Platelets ≥ 100 x $10^9$/L<br>• 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<br>**and**<br>FCBP must either agree to use and be able to take effective contraceptive birth control measures (Pearl Index < 1) 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 ≥ 50 years and naturally amenorrhoeic for ≥ 2 years, or unless she is surgically sterile.<br>• 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.<br>• Signed and dated informed consent before the start of any specific protocol procedures.<br>Patient's legal capacity to consent to study participation. |
| Exlusion criteria | • Missing histological or cytological confirmation of metastatic adenocarcinoma of the pancreas<br>• Locally advanced pancreatic adenocarcinoma without metastases<br>• 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.)<br>• Known brain metastase/brain metastases. Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients.<br>• Pre-existing polyneuropathy ≥ grade 2 according to CTCAE version 4<br>• Medical history of interstitial lung disease (ILD) or pulmonary fibrosis<br>• Patients with high cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year<br>• Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus)<br>• 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<br>• 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 > 5 years prior to enrolment<br>• Hypersensitivity against nab-paclitaxel, gemcitabine, or any excipients of these drugs<br>• Continuing abuse of alcohol, drugs, or medical drugs<br>• Pregnant females, breast feeding females or females of childbearing potential unable to either perform adequate contraceptive measures or practice complete abstinence from heterosexual intercourse<br>• 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. |
| Treatment regimen | **<u>Induction treatment</u>**<br>All patients will be given:<br>***3 cycles nab-paclitaxel/gemcitabine; duration of each cycle 28 days***<br>nab-paclitaxel 125 mg/$m^2$, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/$m^2$ as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle |

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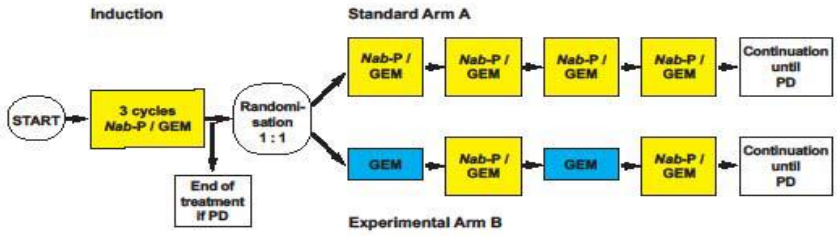
| | Patient with progression or unacceptable toxicity have to discontinue study treatment.<br>After three cycles nab-paclitaxel/gemcitabine tumor evaluation is performed. Randomization in Arm A and Arm B will take place for all patients with at least stable disease (SD).<br><br>**<u>Continuous treatment after randomization</u>**<br>***Standard Arm A***<br><br>Patients randomized in Arm A will receive **continuing application of** nab-paclitaxel/gemcitabine **treatment cycles** until progression or unacceptable toxicity.<br>Duration of each cycle is 28 days and comprises:<br>nab-paclitaxel 125 mg/m$^2$, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m$^2$ as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle<br><br>***Experimental Arm B***<br><br>Patients randomized in Arm B will receive **alternating application of gemcitabine monotherapy and nab-paclitaxel/gemcitabine treatment cycles** 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.<br><br>**Gemcitabine treatment cycle:**<br>Gemcitabine 1000 mg/m$^2$ as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle<br><br>**nab-paclitaxel/gemcitabine treatment cycle:**<br>nab-paclitaxel 125 mg/m$^2$, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m$^2$ as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle<br><br>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.<br><br>  <br><br><br>• GEM = gemcitabine; Nab-P = nab-paclitaxel, PD = progession |
| Statistical and analytical plan and methodology | 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 applied. |
| Endpoints | <u>Primary endpoint:</u><br>Overall survival determined from time of randomization until date of death<br><br><u>Secondary endpoints:</u> |

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| | *Efficacy variables*:<br>• Progression-free survival as time from randomization to objective tumor progression or death from any cause<br>• Overall response rate according to RECISTv1.1 determined from first application of induction treatment<br>• Disease control rate according to RECISTv1.1) determined from first application of induction treatment<br>• Quality of life as determined with EORTC QLQ-C30 determined from randomization<br>*Safety variables:*<br>• Type, incidence, and severity of adverse events according to NCI CTCAE version 4 with explicit consideration of any neurotoxicity<br>• Duration of treatment without toxicity leading to permanent discontinuation<br>Functional assessment of neurotoxicity (with FACT taxane score) |
| Additional exploratory endpoints | **Efficacy and safety during induction phase:**<br>• Overall response rate (according to RECISTv1.1) during induction phase<br>• Disease control rate (according to RECISTv1.1) during induction phase<br>• Overall survival during induction phase<br>• Progression-free survival during induction phase<br>• Duration of treatment during induction phase<br>• Type, incidence, and severity of adverse events according to NCI CTCAE version 4 with explicit consideration of any neurotoxicity during induction phase<br>• FACT taxane score during induction phase<br>• Quality of Life as determined with EORTC QLQ-C30 during induction phase<br>**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:**<br>• OS determined from first application of induction treatment<br>• PFS determined from first application of induction treatment<br>• ORR (according to RECISTv1.1)<br>• DCR (according to RECISTv1.1)<br>• Type, incidence, and severity of adverse events according to NCI CTCAE version 4 with explicit consideration of any neurotoxicity |
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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**

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| Studiennummer/-Code: | AIO-PAK-0117 (PANCHO) |
| Status: | In Einreichung |
| Rekrutierungszeitraum: | Q1/2019 – Q3/2022 (geplant) |
| Weitere Zentren: | sind aktuell leider nicht möglich |
| Letzte Aktualisierung: | Oktober 2018 |

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| National Coordinating Investigator | PD Dr. med. Uwe Pelzer<br>Charité - Universitätsmedizin Berlin<br>Med. Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie<br>Augustenburger Platz 1, 13353 Berlin<br>Phone: +49 30 450553 112 / 222<br>FAX: +49 30 450553 901 / 959<br>E-mail: uwe.pelzer@charite.de |
| Sponsor | AIO-Studien-gGmbH<br>Dr. Aysun Karatas<br>Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431<br>Fax: +49 30 322932926<br>E-mail: info@aio-studien-ggmbh.de |
| 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 | Q1/2019 |
| Duration of study | ~ 44 months<br>Accrual period: 38 month<br>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 nab-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 adverse events. |
| Secondary objectives and endpoints | To evaluate further efficacy data for the combination of *nab*-paclitaxel and gemcitabine in first line patients with advanced pancreatic cancer and cholestatic hyperbilirubinemia:<br>1. Tumor response according to RECIST 1.1<br>2. Progression-free survival (PFS)<br>3. Overall Survival (OS)<br>4. CA19-9 response<br>5. Change in hyperbilirubinemia<br>6. QoL (EORTC QLQ-C30 and Pan26), (Q-Twist analysis)<br>7. Treatment-associated change of patients' nutritional, metabolic and inflammatory status: |

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| | a. CRP and Interleukin-6<br>b. Serum protein levels |
| Exploratory objectives and endpoints | Biomarker exploration on tumor tissue. |
| Planned sample size | Maximum N=60 patients (incl. drop outs)<br>Cohort A: max. 12 pts<br>Cohort B: max. 18 pts<br>Cohort C: max. 24 pts<br>Dropouts: max. 6 pts<br>Maximum numbers per dose cohort always refer to evaluable subjects. |
| Inclusion criteria | 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<br>2. Age ≥ 18 years at time of study entry<br>3. Histological or cytological documentation of an adenocarcinoma of the pancreas<br>4. Metastatic disease not amenable to surgical resection with curative intent<br>5. No prior chemotherapy for metastatic disease<br>6. Measurable disease, defined as at least one unidimensional measurable lesion on a CT scan as defined by RECIST 1.1<br>7. Performance-Status according to Karnofsky Scale ≥ 70%<br>8. Life expectancy of at least 3 months<br>9. Adequate bone marrow, renal, and hepatic function:<br>• Absolute neutrophil count (ANC) ≥ 1,500/$mm^3$<br>• Platelets ≥ 100,000/$mm^3$<br>• Hemoglobin ≥ 8.0 g/dL<br>• Bilirubin from ≥ 1.5 x ULN to ≤ 10 x ULN due to cholestasis measured 3 days after drainage (if possible).<br>Bilirubin level must be decreasing after drainage.<br>10. Male and female subjects of childbearing potential must agree to use highly effective methods contraception from screening, and must agree to continue using such precautions for 6 months after the final dose of investigational product.<br>11. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥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.<br>12. In the assessment of the investigator, patient is able to comply with study requirements.<br>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. |
| Exclusion criteria | 1. Hyperbilirubinemia successfully treatable with internal or external drainage of the choledochus<br>2. Active infection > Grade 2 NCI-CTCAE v5<br>3. Serious systemic disease: uncontrolled hypertension or hyperglycemia, hypoglycemia, congestive heart failure NYHA III – IV, symptomatic coronary heart disease, uncontrolled cardiac arrhythmia > grade II<br>4. Hepatic transaminases elevation > 5 x ULN<br>5. Albumin < 2.0 g/dL<br>6. GFR < 30 mL/min |

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| | 7. International Normalized Ratio (INR) > 2.0 or prolongation of the activated partial prothrombin time (aPTT) > 2 x ULN<br>8. Uncontrolled diabetes type I or II<br>9. Need of immuno-suppressive therapy (e. g. patients after transplantation)<br>10. Subject uses medication known to be strong inducers of CYP3A4 or CYP2C8<br>11. Severe non-healing wounds, ulcers or bone fractures<br>12. Hypersensitivity against *nab*-paclitaxel, gemcitabine, or any of the constituents of the products<br>13. Female subjects who are pregnant, breast-feeding or intend to become pregnant; as well as sexually active male or female patients who are unwilling to employ highly effective methods of contraception.<br>14. Patients with brain metastases are excluded unless the metastases are adequately treated (surgery or radiotherapy) with no evidence of progression for at least 6 weeks and neurologically stable without anticonvulsants and steroids.<br>15. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results<br>16. Participation in another clinical study with an investigational product during the last 30 days before inclusion<br>17. Previous enrollment in the present study (does not include screening failure).<br>1. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. |
| Investigational agent | • *Nab*-paclitaxel<br>• Gemcitabine |
| Treatment plan and schedule | **General treatment regimen (all cohorts and dose levels):**<br>*nab*-Paclitaxel: 50 to 125* mg/m², 30min i.v., d1, 8, 15<br>Gemcitabine: 600 to 1000* mg/m²; 30min i.v., d1, 8, 15<br>Cycle length is 28 days (4 weeks).<br>* Dose depending on dose level and bilirubin cohort<br><br>**Dose escalation design adapted to hyperbilirubinemia**.<br>Three parallel cohorts:<br>• 1 cohort with bilirubin ≥ 1.5 x ULN ≤ 3.0 x ULN (**Cohort A**)<br>• 1 cohort with bilirubin > 3.0 x ULN ≤ 5.0 x ULN (**Cohort B**)<br>• 1 cohort with bilirubin > 5.0 x ULN ≤ 10.0 x ULN (**Cohort C**)<br><br>Bilirubin will be measured 3 days after drainage (if possible) and should be decreasing to indicate successful drainage.<br>Billirubin 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 up to 2 times].<br>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.<br><br>***Dose levels to be tested:*** |

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| | • Level 3: 125 mg/m² nab-paclitaxel followed by 1000 mg/m² gemcitabine weekly, i.v., 30 min.<br>• Level 2 (starting dose for A): 100 mg/m² nab-paclitaxel followed by 800 mg/m² gemcitabine weekly, i.v., 30 min.<br>• Level 1 (starting dose for B): 75 mg/m² nab-paclitaxel followed by 600 mg/m² gemcitabine weekly, i.v., 30 min.<br>• Level 0 (starting dose for C): 50 mg/m² nab-paclitaxel followed by 600 mg/m² gemcitabine weekly, i.v., 30 min. [dose level will only be tested in cohort C]<br><br>***Definition of Dose Limiting Toxicities (DLTs):***<br>• Every grade 3 or 4 non-hematologic toxicity with the exception of nausea, vomiting (and bilirubin levels in cohorts B and C)<br>• Grade 4 thrombocytopenia or grade 3 thrombocytopenia with concomitant bleeding<br>• Grade 4 neutropenia for more than 7 days or febrile neutropenia<br>Grading according to Common Toxicity Criteria for Adverse Events; NCI-CTCAE Version 5<br><br>If the occurrence of DLT toxicity is probably not drug related (e.g. result of a comorbidity or progression of cancer), the investigator should seek advice from the CI for further guidance.<br><br>***Modified 3+3 dose finding strategy:***<br>• No appearance of DLT in 3 pts during cycle 1, then additional 3 pts with higher dose level will be recruited<br>• If there is one patient with DLT in 3 pts during cycle 1, then the cohort must be expanded to 6 pts<br>• 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<br>• 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.<br>• **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), then 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.<br>• **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.<br>• **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/m² 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<br>After the MTD has been established patients may continue further treatment with either the established MTD or an individually tolerated dose.<br><br>***Safety-intra-subject dose modification plan*** |

<table>
<tr><td></td><td>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 5.<br>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.
<table>
<tr><th>Dose Level</th><th>nab-Paclitaxel Dose (mg/m$^2$)</th><th>Gemcitabine Dose (mg/m$^2$)</th></tr>
<tr><td>Level 3</td><td>125</td><td>1000</td></tr>
<tr><td>Level 2</td><td>100</td><td>800</td></tr>
<tr><td>Level 1</td><td>75</td><td>600</td></tr>
<tr><td>Level 0</td><td>50</td><td>600</td></tr>
<tr><td>If more than 2 dose reductions required</td><td>Discontinue treatment</td><td>Discontinue treatment</td></tr>
</table></td></tr>
<tr><td>Rationale</td><td>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 patients with hyperbilirubinemia due to cholestasis exist (1). Nab-paclitaxel in combination with gemcitabine was approved for metastatic pancreatic cancer patients in 2013 (2). However, the SmPC states that treatment with nab-paclitaxel and gemcitabine is not recommended in patients with bilirubin > 1.5 x ULN due to insufficient data (3). This phase I study aims to evaluate the MTD of nab-paclitaxel and gemcitabine in metastatic pancreatic cancer patients with bilirubin levels ≥ 1.5 x ULN and ≤ 10.0 x ULN due to cholestasis despite appropriate stenting to establish a safe treatment option for these patients.<br><br>References:<br>
1) Vogel A, Kullmann F, Kunzmann V, Al-Batran S-E, Oettle H, Plentz R, et al. Patients with Advanced Pancreatic Cancer and Hyperbilirubinaemia: Review and German Expert Opinion on Treatment with nab-Paclitaxel plus Gemcitabine. Oncol Res Treat. 2015;38(11):596–603<br>2) ,Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691–703. Current version of SmPC Abraxane<br>3) Abraxane: EPAR - Product Information - Annex I - Summary of Product Characteristics [Internet]. 2018 [cited 2018 Mar 23]. Available from: http://www.ema.europa.eu/ema/ index.jsp?curl=pages/medicines/human/medicines/000778/human_med_000620 .jsp&mid=WC0b01ac058001d124</td></tr>
<tr><td>Interim analyses</td><td>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 (>1/3 DLTs). The exact escalation and de-escalation strategy depends on the patient cohort/starting dose level.</td></tr>
<tr><td>Safety data</td><td>All safety variables of classical phase I trials, measurements of AEs, SAEs and DLTs</td></tr>
<tr><td>Sample size estimation and<br>statistical analysis considerations</td><td>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 n=54.<br>Subjects withdrawn from the study will not be replaced, unless the investigator can unequivocally ascertain that the reasons for withdrawal of a patient are personal</td></tr>
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| | 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 thus is **N=60**.<br><br>The MTD will be the highest dose for which the frequency of DLTs is <33%.<br><br>All secondary efficacy, safety and QoL endpoints will be analyzed descriptively |
| Study plan/ Timelines | First Patient In (FPI): Q1/2019<br>Last Patient In (LPI): after approx. 38 months<br>Last Patient Last Visit (LSO): after approx. 44 months<br>End of follow-up period after LSO: after approx. 44 months<br>Study report: after approx. 50 months<br>Publication: after approx. 53 months |

**AIO-PAK-0217/ass: 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-assoziierte Studie**

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| Studiennummer/-Code: | AIO-STS-0317/ass |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2017 – 2019 |
| Weitere Zentren: | sind derzeit leider nicht möglich |
| Letzte Aktualisierung | 23.10.2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | The Scandinavian Sarcoma Group (SSG)/<br>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) | **Primary:**<br>• Recurrence-free survival (RFS) after randomisation.<br>**Secondary:**<br>• Overall survival.<br>• GIST-specific survival.<br>• Adverse events (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).<br>• Quality of life<br>**Exploratory:**<br>• Effect of tumour site on RFS.<br>• Effect of tumour mutation type on RFS.<br>• Effect of imatinib dose at randomisation on RFS.<br>• To evaluate tumour tissue and blood molecular markers in prediction of GIST recurrence. |
| INTERVENTION(S) | **Arm A: Imatinib**<br>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 |

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| | 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.<br>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.<br>**Arm B: No imatinib**<br>No imatinib or other anti-cancer treatment will be administered in the adjuvant setting |
| KEY EXCLUSION CRITERIA | 1. Presence of distant metastases or local recurrence of GIST.<br>2. Not willing to donate tumour tissue and/or blood samples for the study molecular studies.<br>3. Presence of a substitution mutation at PDGFRA codon D842 (usually D842V).<br>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.<br>5. Prior adjuvant (+ neoadjuvant) therapy with imatinib mesylate for at least 35 months has not been completed, or the total duration of prior adjuvant (+ neoadjuvant) imatinib administration exceeds the total duration of 38 months.<br>6. Neoadjuvant imatinib for a duration that exceeds 12 months.<br>7. Longer than 4-week break during adjuvant imatinib administration.<br>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.<br>9. Patient has received any investigational anti-cancer agents during adjuvant imatinib or between completion of adjuvant imatinib and the date of randomisation.<br>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, a small (2 cm or less in diameter) nodenegative<br>breast cancer (pT1N0M0), a low Gleason<br>score (<8) local (T1 or T2) prostate cancer. Recent existence of any other malignant disease is not allowed.<br>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).<br>12. Female patients who are pregnant or breast-feeding.<br>13. Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, severe chronic renal disease, or active uncontrolled infection).<br>14. Known diagnosis of human immunodeficiency virus (HIV) infection.<br>15. Patient with a significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.<br>16. Patients with chronic or active hepatitis B.<br>17. Patients that have been committed to an institution by official or judicial order.<br>18. Patients that are dependent upon the sponsor, the trial site or the investigator. |
| KEY INCLUSION CRITERIA | 1. Age ≥ 18 years.<br>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).<br>3. Macroscopically complete surgical resection of GIST (either R0 or R1 resection).<br>4. Mutation analysis of KIT and PDGFR genes has been carried out.<br>5. A high risk of GIST recurrence, either<br>1) gastric GIST with mitotic count >10/50 HPFs, or |

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| | 2) non-gastric GIST with mitotic count >5/50 HPFs, or<br>3) non-gastric GIST treated with neoadjuvant<br>imatinib and initially larger than 10 cm<br>4) tumour rupture<br>Tumour rupture (spillage of the tumour contents into the abdominal cavity) may have occurred either before or at surgery.<br>6. ECOG performance status ≤ 2.<br>7. Adequate organ function, defined as serum total bilirubin <1.5 x ULN (upper limit of normal), serum AST (SGOT) and ALT (SGPT) <2.5 x ULN, creatinine <1.5 x ULN; blood ANC (neutrophil count) ≥1.0 x 109/L, platelet count ≥100 x 109/L.<br>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.<br>9. Patient willing to be followed up at the study site regardless of the result of randomisation.<br>10. Patient has provided a written, voluntary informed consent prior to study-specific screening procedures. |
| OUTCOME(S) | **Primary:**<br>• 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.<br>**Secondary:**<br>• Overall survival (the time period between the date of randomisation and the date of death).<br>• 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).<br>• Safety (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).<br>• Quality of Life (EQ-5D instrument).<br>**Exploratory:**<br>• Effect of the tumour mutation type on RFS.<br>• Effect of tumour site on RFS.<br>• Effect of the imatinib dose at randomisation on RFS.<br>• Tumour tissue and blood molecular markers in prediction of GIST recurrence. |
| STUDY TYPE | Open-label, 2-arm, prospective, randomised,<br>multicentre phase III trial.<br>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<br>imatinib will be randomly allocated to one of the following 2 arms in a 1:1 ratio:<br>**A.** to further 24 months of adjuvant imatinib (i.e. the planned total duration of adjuvant imatinib is 5 years)<br>**B.** to stop imatinib (i.e. the planned total duration of adjuvant imatinib is 3 years)<br>The study participants will be followed up for a minimum of 10 years post-randomisation or until death. |

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| STATISTICAL ANALYSIS | 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). |
| SAMPLE SIZE | 300 patients to be randomised in 1:1 ratio, 150 to imatinib for further 24 months and 150 to stop imatinib |
| TRIAL DURATION | 2 years of recruitment followed by 10 years follow up after randomization |
| current number of patients included | 88 pts..recruited – 7 in Germany – Stand 23.10.2018 |
| Number of sites | 9 German sites, 8 sites opened, 1 planned Q4/2018 |

## *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**

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| Studiennummer/-Code: | AIO-PAK-0118 - SEPION |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum: | 2018 – 2020 |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | 30.10.2018 |

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| PPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. med. Jens Siveke |
| CONTACT | Dep. of Medical Oncology and<br>Division of Solid Tumor Translational Oncology<br>West German Cancer Center<br>University Hospital Essen<br>Hufelandstr. 55, 45147 Essen<br>Phone: +49 201 723-3704<br>Fax: +49 201 723 6725<br>E-mail: jens.siveke@uk-essen.de |
| CONDITION | Patients with metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (stage IV) and no prior chemotherapy for stage IV disease. |

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| OBJECTIVE(S) | **Primary objective(s)**<br>→ The primary objective of the study, including the dose escalating part (Part 1a), the dose expansion part (Part 1b) as well as the consolidation part (Part 2), is to determine the safety and tolerability of Azacitidine (according to visit schedule Arm B) and/or Romidepsin (according to visit scheldule Arm A) 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).<br>→ Moreover, in the dose escalating part of the study (Part 1a), the recommmended dose for expansion (RDE) and dose-limiting toxicity (DLT) of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine will be identified.<br>**Secondary objective(s)**<br>→ 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)<br>→ 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)<br>→ to assess 2nd ORR, 2nd CA19-9 response and 2nd DCR (after start of Part 2), PFS and OS in patients treated with Durvalumab and Lenalidomide as consolidation treatment (Part 2)<br>→ to assess OS in all patients treated at the recommended dose and regimen<br>**Exploratory Translational Sub-studies**<br>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.<br>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-γ) and immuno-phenotyping (e.g. CD8, CD4, Treg, Macrophages). |
| INTERVENTION(S) | 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 **(Part 1a).** Study treatment is given until intolerable toxicity of Romidepsin and/or Azacitidine for a maximum of 3 cycles, whereas in the Standard arm nab-Paclitaxel/Gemcitabine will be administered exclusively. |

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| | 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.<br><br>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) 5.0 will be used to assess toxicities:<br><br>- Absolute neutrophil count < 0.5 x $10^9$/L for ≥7 days<br>- Platelets < 25 x $10^9$/L for ≥7 days (severe thrombopenia)<br>- CTCAE grade ≥3 non-hematologic toxicity related to study treatment despite adequate therapy<br>- Drug-related, non-remitting CTCAE grade 2 or unexpected toxicity may be declared a DLT after thorough consulation between the investigator and the sponsor<br><br>For the dose expansion part **(Part 1b)** 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 (**Fehler! Verweisquelle konnte nicht g efunden werden.**). 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 prefered over Arm A. In case of no determination of RDE in Arm B, Arm A will be selected. In case of no determination of RDE in Arm A, patients will be treated with standard nab-Paclitaxel/Gemcitabine for up to 41 patients with controlled disease after 3 cycles to enter **Part 2** of the trial.<br><br>All patients from **Part 1a and 1b** 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 (complete response [CR], partial response [PR], stable disease [SD]) In case of intolerable toxicity, patients will deescalate to a lower dose level as defined in the protocol.<br><br>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 and a drop-out rate of 10%. |
| KEY EXCLUSION CRITERIA | **Principal exclusion criteria**<br><br>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;<br>2. Patients may not be receiving any other investigational agents;<br>3. Patients who have previously received Romidepsin, Azacitidine, Lenalidomide or Durvalumab;<br>4. Patients with untreated or uncontrolled brain metastases or leptomeningeal disease;<br>5. Presence of other active illnesses;<br>6. Any known cardiac abnormalities such as:<br>• Congenital long QT syndrome<br>• QTc interval ≥ 500 milliseconds;<br>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 |

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| | asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event may participate;<br>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);<br>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;<br>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 <40% by MUGA or <50% by echocardiogram and/or magnetic resonance imaging (MRI);<br>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);<br>12. Concomitant use of any drug known to prolong QT interval;<br>13. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole);<br>14. Patients with human immunodeficiency virus (HIV), hepatitis B or C (requirement for screening);<br>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;<br>16. Diagnosis of immunodeficiency or any condition that requires systemic steroid therapy or other forms of immunosuppressive therapy;<br>17. Prior thromboembolic events;<br>18. History of other malignancies, except:<br>• Malignancy treated with curative intent and with no known active disease present for ≥2 years before the first dose of study drug and felt to be at low risk for recurrence by investigator.<br>• Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.<br>• Adequately treated carcinoma in situ without current evidence of disease (all treatment of which should have been completed 6 months prior to randomization).<br>• Any uncontrolled active systemic infection;<br>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;<br>20. History of stroke or intracranial hemorrhage within 6 months prior to enrollment;<br>21. History of interstitial lung disease, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis;<br>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;<br>23. Concomitant use of warfarin or other Vitamin K antagonists;<br>24. Known hypersensitivity to any study drug;<br>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;<br>26. Pregnant females, breast feeding females or females of childbearing potential unable to perform adequate contraceptive measures or practice complete abstinence from heterosexual intercourse;<br>27. Subject is an employee of GWT-TUD GmbH. |

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| KEY INCLUSION CRITERIA | **Principal inclusion criteria**<br>Subjects must fulfill all of the following criteria before inclusion in the study:<br><br>1. Patients must have histologically confirmed PDAC<br>2. Patients must have metastatic disease (stage IV) and not received prior chemotherapy for stage IV disease (adjuvant/additive chemotherapy is allowed if completed at least 6 months prior to study inclusion)<br>3. Patients must not have received the following drugs before: Azacitidine, Romidepsin, any checkpoint-inhibitor or immunomodulating agents such as IMiDs (Lenalidomide)<br>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 RECIST criteria v. 1.1<br>5. Male or female, age > 18 years<br>6. Body weight > 30 kg for inclusion into Part 2 (according to Durvalumab treatment)<br>7. ECOG performance status 0 or 1<br>8. Patients must have normal organ and marrow function as defined below<br>• Leukocytes ≥ 2,500/mcL<br>• Absolute neutrophil count ≥ 1,500/mcL<br>• Platelets ≥ 100,000/mcL<br>• Haemoglobin ≥ 9 g/dL<br>• Total bilirubin < 1.5 mg/dl<br>• Serum bilirubin ≤ 1.5 x upper limit of normal (ULN). This will not apply to patients 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<br>• Asparate aminotransferase/alanine aminotransferase (AST/ALT) (SGOT/SGPT) ≤ 2.5 x ULN and ≤ 5 in the case of liver metastasis<br>• Measured creatinine clearance (CL) >60 mL/min or calculated creatinine CL>60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance<br>9. Patients must be recovered from the effects of any prior surgery<br>10. Patient 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<br>11. All subjects must agree to refrain from donating blood while on study drug and for 90 days after discontinuation from this study treatment<br>12. All subjects must have a life expectancy of at least 12 weeks<br>13. All subjects must agree not to share medication<br>14. Females of childbearing potential (FCBP) must<br>• Understand the potential teratogenic risk to the unborn child<br>• Understand the need and agree to utilize two reliable forms of contraception (refer to **Fehler! Verweisquelle konnte nicht gefunden werden.**) 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<br>• Understand and agree to inform the investigator if a change or stop of method of contraception is needed<br>• Be capable of complying with effective contraceptive measures<br>• Be informed and understand the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy<br>• Understand the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test<br>• Understand the need and accept to undergo pregnancy testing based on the frequency outlined in this protocol |

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| | • Acknowledges that she understands the hazards Lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of Lenalidomide<br>• Females must agree to abstain from breastfeeding during study participation and for at least 90 days after study drug discontinuation<br>15. Males must<br>• Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP<br>• Agree to use a latex condom during any sexual contact with FCBP or a pregnant female while participating in the study and for 90 days following discontinuation from this study, even if he has undergone a successful vasectomy. For treatment with Gemcitabine and nab-Paclitaxel men must avoid fathering a child/ use condom up to 6 months after their last dose. Depending on duration of Lenalidomide/Durvalumab treatment this period can be loger than 90 days after study discontinuation.<br>• Agree to refrain from donating semen or sperm while on the study drugs and for 90 days after discontinuation from this study treatment. For treatment with nab-Paclitaxel and Gemcitabine mal subject must agree not to fathering a child or donate semen for at least 6 month after last intake of medication.<br>• Agree not to father a child during the course of the trial and for at least 90 days after last administration of study drugs For Gemcitabine and nab-Paclitaxel treatment up to 6 month after last drug intake.<br>16. Females of non-childbearing potential:<br>• 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 amenorrhea for at least 24 consecutive months without an alternative medical cause. The following age-specific requirements apply:<br>Women <50 years of age would be considered post-menopausal if they have been amenorrhea for at least 24 consecutive 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)<br>Women ≥50 years of age would be considered post-menopausal if they have been amenorrhea for at least 24 consecutive months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) |
| OUTCOME(S) | **Primary endpoint(s)**<br>The primary endpoint is the safety and tolerability of Azacitidine (according to visit schedule Arm B) and/or Romidepsin (according to visit schedule Arm A) in combination with nab-Paclitaxel/Gemcitabine, followed by sequential immune targeting with programmed death-ligand (PD-L)1 blockade in combination with low-dose Lenalidomide in patients with advanced PDAC (Part 1 and 2).<br><br>Safety and tolerability will be determined by the following parameters:<br>• Clinical laboratory (clinical chemistry, hematology, urinalysis)<br>• Performance status according to Eastern Cooperation Oncology Group (ECOG)<br>• Recording of AEs and concomitant medication<br>• Physical examination |

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| | • ECG<br>• ECHO (Echocardiography) or MUGA (Multiple-Gated-Acquisition-(MUGA)-Radionuclide-Imaging)<br>• Vital signs (pulse, blood pressure, body temparature)<br><br>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 after completion of 3 treatment cycles. |
| STUDY TYPE | 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. |
| STATISTICAL ANALYSIS | <u>Descriptive analyses</u><br><br>Summary statistics will be presented. Frequency tables for categorical data will be provided. Medical history findings will be summarized using MedDRA terms.<br><br><u>Safety examinations</u><br><br>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 90 days after last study drug administration will be considered as treatment-emergent.<br><br>In summary, the trial design is based on the following assumptions:<br>• The experimental therapy in Part 1b would be rated as insufficiently active, if the true DCR at > 12 weeks is 60% or lower, considered to be futile.<br>• 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.<br>• Probability to accept the experimental therapy as promising (> 83% DCR) with respect to efficacy, in spite of a true DCR of ≤ 60%: 0.05 (type I error)<br>• Probability to reject the experimental therapy as not sufficiently efficient (≤ 60%), although the true DCR is promising (> 83%): 0.1 (type II error, corresponding to a power of 90%).<br><br>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 irRECIST1.1 (Wolchok, 2009) 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. |
| SAMPLE SIZE | 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.<br><br>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 |

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| | 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%.<br>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. |
| TRIAL DURATION | **For the individual patient:**<br>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.<br>**Planned study schedule**<br>First Patient First Visit 01/2019<br>Last Patient First Visit 01/2021<br>Last Patient End of Trial 01/2022<br>Last Patient Last Active Follow up 01/2023<br>Last Patient Last Follow Up of SPMs 01/2025<br>Final Study report (primary data) 10/2023<br>Report of SPMs 04/2025 |
| 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**

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| Studiennummer/-Code: | AIO-PAK-0116 - PANTHEON |
| Status: | Rekrutierung |
| Rekrutierungszeitraum: | 2017 – 2020 (geplant) |
| Weitere Zentren: | Warteliste |
| Letzte Aktualisierung | Oktober 2018 |

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| Study Type | Open label, randomized, sequential cross-over phase II study |
| Verantwortlicher Studienleiter nach AMG | Prof. Dr. med. Helmut Oettle, Praxis und Tagesklinik<br>Friedrichstr. 53, 88045 Friedrichshafen<br>Telefon: +49 7541 289956-0, FAX.: +49 7541 289950-10<br>E-Mail: helmut.oettle@charite.de |

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| Kontaktadresse/<br>Kontaktperson: | AIO-Studien-gGmbH, Dr. Aysun Karatas<br>Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 8145 344 31, Fax +49 30 3229 329 26<br>info@aio-studien-ggmbh.de |
| Studienziele/<br>Objectives | Primäres Studienziel:<br>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 2nd-line therapy.<br><br>Sekundäre Studienziele:<br>Assessment of safety and feasibility of the sequential cross-over treatment approach for advanced treatment lines in PDAC |
| Patientenzahl<br>Number of patients | Geplant: 204 Patienten<br>Bereits eingeschlossen: 14 (18.10.2018) |
| Rekrutierungzeitraum | Start Q1 2018<br>Last Patient In: approx. Q1 2020 |
| Haupt-Einschlusskriterien<br>Key inclusion criteria | 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<br>15. Age ≥ 18 years at time of study entry<br>16. Irresectable adenocarcinoma of the pancreas previously treated in the palliative setting with gemcitabine and *nab*-paclitaxel (Abraxane®)<br>17. Adequatly documented recurrence and disease status after/under 1st line (Best response, duration of treatment, time to progression, preexisting PNP and other side effects)<br>18. Radiologically confirmed disease progression during 1st- line therapy and measurable reference cancer site(s) as defined by RECIST1.1<br>19. Randomization and start of 2nd-line treatment possible within 4 weeks after radiologically documented disease progression duiring 1st-line therapy<br>20. ECOG performance status 0-2<br>21. No prior radiotherapy<br>22. Adequate blood count, liver-enzymes, and renal function:<br>• Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L (> 1500 per $mm^3$)<br>• Platelet count ≥ 100 x $10^9$/L (>100,000 per $mm^3$)<br>• AST (SGOT)/ALT (SGPT) < 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be < 5x ULN<br>• Serum creatinine ≥ CL60 mL/min calcualtions according to local standard<br>• Bilirubin < 3 ULN<br>23. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥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.<br><br>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. |
| Haupt-Ausschlusskriterien /<br>Key exlusion criteria | 1. Serious cardiovascular disease (eg, unstable coronary artery disease or myocardial infarction within 3 months of study start)<br>2. Preexisting polyneuropathy (PNP) ≥ grade 3 |

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| | [National Cancer Institute Common Toxicity Criteria grade 3 or 4 sensory or motor neuropathy]<br>3. Prior or concurrent malignancy (other than pancreatic cancer) which either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin<br>4. History of DPD deficiency<br>5. Morbus Gilbert<br>6. History of hypersensitivity to any of the study drugs or any of the constituents of the products<br>7. Medication that is known to interfere with any of the agents applied in the trial.<br>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)<br>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<br>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:<br>a) chronic inflammatory bowel disease and/or bowel obstruction.<br>b) active uncontrolled infection<br>c) clinically significant bleeding or bleeding diathesis<br>d) clinically significant stomatitis<br>e) active ulceration of the gastrointestinal tract<br>11. Previous enrollment or randomization in the present study (does not include screening failure).<br>12. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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]. |
| Therapieschema<br>Scheme of therapy | The OFF-regimen is an established second line treatment for adenocarcinoma of the pancreas.<br>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.<br><br>OFF:<br>• 5-FU 2000 mg/m$^2$ as 24 hour infusion + Na folinic acid 200 mg/m$^2$ on D1, 8, 15, 22 Oxaliplatin 85 mg/m$^2$ on D8, 22<br>• 3 weeks rest after D22;<br>• Cycle q42d<br><br>FOLFIRI (all on day 1)<br>• Irinotecan 180 mg /m$^2$<br>• 5-FU 400 mg/m$^2$ (bolus) + 2400 mg/m$^2$ as 46 hour infusion<br>• Na folinic acid 200 mg/m$^2$<br>• Cycle q2w |

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| | Treatment until progressive disease or intolerable toxicity or withdrawal of consent. Treatment cross-over is only permitted after radiologically confirmed progression during 2nd-line treatment.<br><br>Key study procedures (and routine procedures):<br>• Tumor assessment according to standard of care q10w<br>• Routine tumormarker asessments<br>• Neurotoxicity assessments |
| Rationale | 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.<br>Nowadays, the combination of gemcitabine and nab-paclitaxel has been approved for first line treatment based on a similar improvement of OS. So far, 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.<br>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.<br>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. |
| Statistik (optional) | Sample size estimation: It is hypothesized that OFF and FOLFIRI chemotherapy show similar efficacy with regard to PFS in 2nd-line treatment of patients with metastatic PDAC. The test hypothesis is formulated to demonstrate non-inferiority of FOLFIRI treatment compared to OFF.<br><br>Under the proportional hazards assumption, the hazard ratio $HR = h_{FOLFIRI} / h_{OFF}$ is constant across time.<br>For a given non-inferiority margin $HR_0$=1.5 (the maximum ratio of clinical insignificance; $PFS_{OFF}$ = 3 month, $PFS_{FOLFIRI}$ = 2 month), the statistical hypotheses tested are:<br><br>$H_0 : HR \geq HR_0$ vs. $H_1 : HR < HR_0$<br><br>A non-inferiority Log-Rank test with an overall sample size of **N=204** subjects (102 in the OFF group and 102 in the FOLFIRI group) achieves 80.1% power at a one-sided α=0.025 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 $h_{OFF}$=0.23 ($PFS_{OFF}$=3 month).<br>Total Follow-up is 40 month (second-line treatment) of which subject accrual (entry) occurs in the first 36 month.<br>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%).<br><br>In order to analyse the primary endpoint **191 events** need to be observed. |

*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**

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| Studiennummer/-Code: | CONKO-007 |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2013 – 2019 |
| Weitere Zentren: | Leider nein, da keine Finanzierung der Deutschen Krebshilfe |
| Letzte Aktualisierung | Oktober 2018 |

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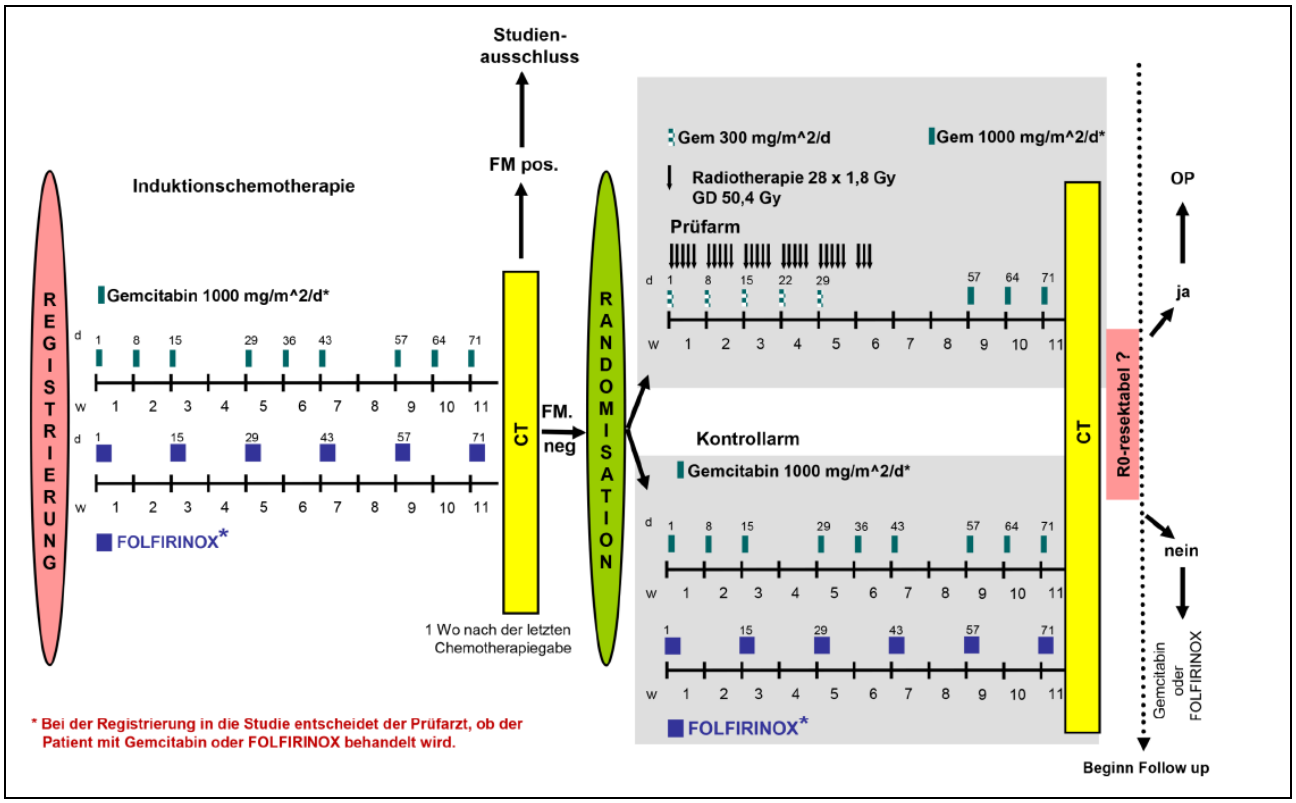
| Kurztitel | CONKO-007, EudraCT-Nr.: 2009-014476-21 |
| Art der Studie | Phase-III |
| Studienleiter nach AMG | Prof. Dr. Rainer Fietkau<br>Universitätsklinikum Erlangen, Strahlenklinik |
| Kontaktadresse/<br>Kontaktperson: | Dr. Dorota Lubgan<br>Universitätsklinikum Erlangen, Strahlenklinik<br>Universitätsstr. 27, 91054 Erlangen<br>Tel.: 09131-85-33968 Fax: 09131/85-33996<br>E-Mail: st-studiensekretariat@uk-erlangen.de |
| Studienziele/<br>Objectives | Primäres Studienziel:<br>• Gesamtüberlebenszeit<br>Sekundäre Studienziele:<br>• Tumorfreie Überlebenszeit<br>• Rate an lokoregionären Rezidiven bzw. Progressionsrate<br>• Rate an Fernmetastasen<br>• Akute und chronische Toxizität der RCT<br>• Lebensqualität<br>• Remissionsraten<br>• Häufigkeit des Erreichens einer Resektion nach Chemotherapie oder Radiochemotherapie<br>• Häufigkeit des Erreichens einer R0-Resektion nach Chemotherapie oder Radiochemotherapie |
| Zielparameter/<br>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: 383 (Stand 22.10.2018) |
| Rekrutierungzeitraum | Q1 2013-Q1 2019 (verlängert) |
| Weitere teilnehmende Zentren erwünscht? | keine weiteren Zentren mehr möglich<br>Ursprünglich 24 Zentren geplant, 52 Zentren eröffnet (Stand 22.10.2018) |




*Registerstudie*

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

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| **AIO-Studie** | Eine Studie der Young-Medical-Oncologists (YMO) |
| Studiennummer/-Code: | AIO-YMO/PAK-0215 - PDAC, PaCaReg |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | Rekrutierunsstart 10/2018 |
| Weitere Zentren: | bitte wenden Sie sich ggfs. an die Studienleitung |
| Letzte Aktualisierung | Okt. 2018 |

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| Studienleitung | Dr. med. Thomas Ettrich<br>Universitätsklinikum Ulm, Klinik für Innere Med. I<br>89081 Ulm, Tel. 0731-500 44774,<br>thomas.ettrich@uniklinik-ulm.de<br>Mentoring *Investigator:*<br>Univ.-Prof. Dr. Thomas Seufferlein<br>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** | |
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| Studiennummer/-Code: | AIO-SUP-0115/ass (CONKO-011) |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2015 – 2019 |
| Weitere Zentren: | Keine weiteren Zentren |
| Letzte Aktualisierung | Oktober 2018 |

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| Study Type | Phase-III |
| Principal investigator | Prof. Dr. med. Hanno Riess<br>Charité – Universitätsmedizin Berlin, Charité Centrum für Tumormedizin<br>CONKO-Studiengruppe<br>Augustenburger Platz 1, 13353 Berlin |
| Study coordinator | PD Dr. med. Marianne Sinn<br>CONKO-Studiengruppe, Augustenburger Platz 1, 13353 Berlin<br>Tel: +49 -030 450–553222, Fax +49-030 450–553959<br>conko-studien@charite.de |
| Sponsor | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>Tel: +49 30 814534431; Fax: +49 30 322932926<br>info@aio-studien-ggmbh.de |
| Study Objectives | Primary objective:<br>• Patient's treatment satisfaction / quality of life measured with the anti-clot treatment scale (ACTS Burden)<br>Secondary objectives:<br>• Newly diagnosed and objectively confirmed acute venous thrombo-embolism<br>• Active malignancy<br>• Life expectancy of at least 6 months<br>• Performance-Status according to Karnofsky Performance Scale ≥ 70 %<br>• 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<br>• platelets ≥ 100.000 /µl, INR < 1.5, PTT < 40 sec.<br>• written informed consent of the patient prior to any procedure in connection with the study |
| 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<br>Currently randomized patients: 209 (Oktober 2018) |
| Anticipated start date | November 2015 |
| Study Centers | Number of sites total: approx.: 40 |
| More centres? | No |

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| Key inclusion criteria | • Newly diagnosed and objectively confirmed acute venous thrombo-embolism<br>• Active malignancy<br>• Life expectancy of at least 6 months<br>• Performance-Status according to Karnofsky Performance Scale ≥ 70 %<br>• 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<br>• Platelets ≥ 100.000 /µl, INR < 1.5, PTT < 40 sec.<br>• written informed consent of the patient prior to any procedure in connection with the study<br>• male and female patients with an age of at least 18 years |
| Key exlusion criteria | • therapeutic anticoagulation 96h prior to study treatment<br>• known allergic reactions against the study drugs or the substances included therein<br>• known conditions associated with high risk of bleeding, known history of hemorrhagic diathesis<br>• acute clinically relevant bleeding in the last 2 weeks<br>• any history of spontaneous major/cerebral bleeding<br>• history of HIT II<br>• pregnant or breast-feeding women. Women of child-bearing potential must have a negative pregnancy test performed < 7 days prior to start of the treatment<br>• severe renal insufficiency (GFR < 30 ml/min)<br>• liver disease with coagulation impairment, including Child B and C cirrhosisacute medical illness<br>• treatment of the underlying cancer with experimental therapies (in Germany not approved) |
| Scheme of therapy | **Arm A:**<br>Rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily<br>**Arm B:**<br>LMWH in therapeutic dosage (1–2× daily s.c.) according to standards of the individual study center, using licensed dosages, e.g.<br>• Enoxaparin 1 mg/kg BW twice daily<br>• Tinzaparin 175 I.E./kg BW once daily<br>• Dalteparin 200 I.E./kg BW once daily |
| Criteria for evaluation | As scheduled for the actual antitumoral treamtment |
| Study rationale | Cancer is one of the major risk factors for venous thrombembolism (VTE) and VTEs are relevant complications in the management and treatment of tumor patients.<br>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).<br>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 |

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| | 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 %).<br>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%).<br>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 thrombembolic event are available so far. Therefore, a study backing up these hypotheses is urgently warranted. |
| Statistics | 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 higherF<br>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%. |

# 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 1st or 2nd generation EGFR TKI therapy (EATON)

**AIO-Studie**

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

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| 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 *EGFR* mutations (*EGFRdel19* or *EGFR p.L858R*) with progression upon treatment with 1st or 2nd generation EGFR TKI and acquired resistance mutation *EGFR p.T790M* |
| Trial design | Phase I, dose escalation, genetically pre-selected, international, multicentre, open-label |
| Trial rational | Mechanisms of resistance to 3rd generation EGFR TKIs recently have been described to be different from those triggering resistance to 1st and 2nd generation EGFR TKIs. Mechanisms described so far in preclinical models and biopsies involve *EGFR p.C797S*, *HER2* amplification, *MET* amplification and others. Multiple mechanisms of activation of the RAS/RAF/MEK pathway, among them, acquired activating mutations in *NRAS* and *KRAS* as well as amplifications and gain of copy number of *KRAS*, *MAPK1* and *NRAS* have been described to contribute to acquired resistance [Eberlein et al., 2015; Ercan et al., 2012; Sharifnia et al., 2014; Thress et al., 2015].<br>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 at 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 3rd generation EGFR TKIs. |
| Summary of the study strategy and aims | The population of interest for this trial is defined by patients with NSCLC harbouring the sensitizing *EGFR* mutation *del19* or *p.L858R* who develop resistance to treatment with EGFR TKIs. The detection of the *EGFR p.T790M* resistance mutation in the rebiopsy tumour tissue is mandatory. High level amplification of *MET* however may not be detected. *EGFR* mutation status is assessed locally by DNA sequencing (e.g. Sanger sequencing, massively parallel sequencing). *MET* status will be assessed locally by FISH.<br>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.<br>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).<br>Preliminary efficacy data of EGF816 and trametinib in the trial population will be generated according to RECIST v1.1.<br>Throughout the study blood samples will be collected to monitor cell free plasma DNA (cfDNA). |

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| | 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<br>2. To characterize the tolerability of EGF816 in combination with trametinib<br>3. To assess the preliminary clinical efficacy of EGF816 in combination with trametinib<br>4. To define PK variables of the combination treatment |
| Secondary endpoints | 1. Incidence, severity and grading of AEs and SAEs<br>2. Dose interruptions, reductions and dose intensity<br>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<br>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<br>2. To determine mechanisms of primary and acquired resistance to a combination treatment of EGF816 and trametinib in post-treatment samples<br>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<br>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<br>3. MPS of cfDNA at baseline, during treatment and at progression<br>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 ≥ 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.<br>At a first stage, 18 (6×3) 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 (2×3) will be treated on the highest (already investigated) dose level (i.e. the actual MTD) equal or below the virtual MTD (extension cohort).<br>No formal statistical sample size calculation was performed for this trial. A total number of 24 patients will be treated. |

**Treatment regimen and dose levels**

Patients will receive continuous doses of EGF816 and trametinib at the designated dose levels.
The starting dose of EGF816 will be 100 mg QD. The dose will be escalated by 50.0% in dose level 3.
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).

*Dose levels and treatment regimen*

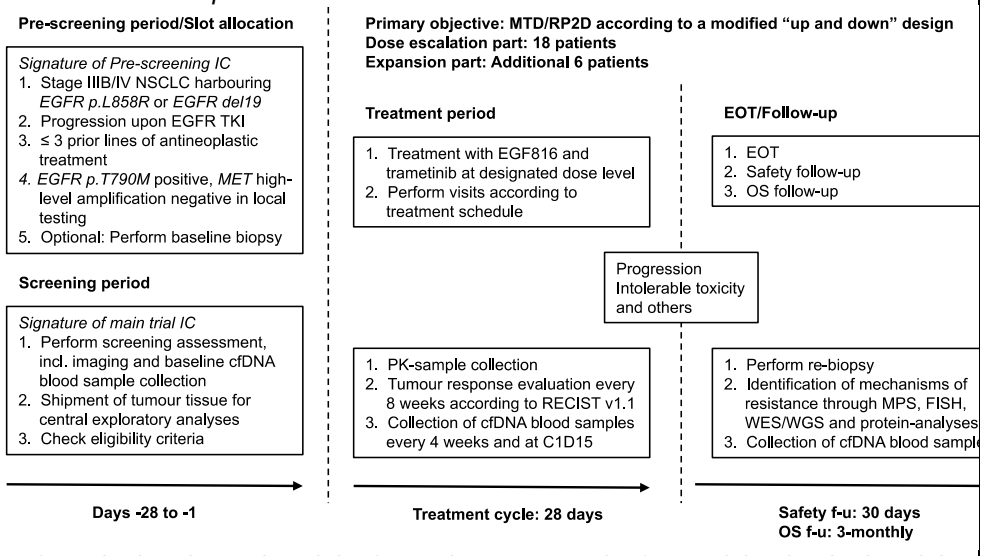
| Dose level | EGF816 daily dose (mg, QD) | trametinib daily dose (mg, QD) |
|---|---|---|
| *1* | 100 | 1.0 |
| *2* | 100 | 1.5 |
| *3* | 150 | 1.5 |
| *4* | 150 | 2.0 |

**Molecular analyses**

Adenocarcinoma patients progressing on 1st or 2nd generation EGFR TKI will be re-biopsied for local *EGFR p.T790M* and *MET* amplification testing (baseline sample).
*EGFR* status will be determined by single gene sequencing (e.g. Sanger sequencing) or massively parallel sequencing (MPS). *MET* status will be determined by fluorescence in-situ hybridisation (FISH). High level *MET* amplification is defined as a tumour fulfilling the following criteria:
a) a MET/CEN7 ratio ≥2.0 or b) an average MET gene copy number per cell of ≥6.0 or c) ≥10% of tumour cells containing ≥15 MET signals [Schildhaus et al., 2015].
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 my predict response or resistance to the combination treatment of EGF816 and trametinib.
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.
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).
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.

**Summary of trial procedures**

*Flow chart of trial procedures.*




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

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| | 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 be collected. Patients whose tumour harbour an *EGFR* p.T790M mutation and no high level *MET* amplification at local testing will be eligible for screening for the main trial.<br>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.<br>Patients will be treated on a continuous schedule of EGF816 and trametinib.<br>Treatment cycles are defined as 28 days (4 weeks) for the purpose of scheduling procedures and evaluation.<br>Tumour response evaluation will be performed by CT and/or MRI scans every 8 weeks and assessed according to RECIST v1.1.<br>Treatment will be conducted until disease progression, occurrence of intolerable toxicity, withdrawal of IC or treatment discontinuation at the discretion of the investigator.<br>At progression a biopsy should be collected to determine potential mechanisms of acquired resistance (*Section 11.3*).<br>At baseline, throughout the trial treatment and at progression blood samples will be collected for analysis of circulating cfDNA by MPS.<br>Treatment beyond progression will be allowed after approval by the PI, as long as the patient clinically derives benefit from the treatment. |
| Inclusion criteria | 1. Written informed consent must have been obtained prior to any screening procedures.<br>2. Patients (male or female) ≥ 18 years of age.<br>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.<br>4. Presence of at least one measurable lesion according to RECIST v.1.1.<br>5. ECOG performance status ≤ 2<br>6. Patients must have NSCLC harbouring EGFR p.L858R or EGFR del19.<br>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).<br>8. EGFR p.T790M mutation must have been detected by local testing in the tumour sample fulfilling the requirements of inclusion criterion 7.<br>9. Documented progression of disease according to RECIST v1.1 while on continuous treatment with 1st or 2nd EGFR TKI (e.g. erlotinib, gefitinib or afatinib). |
| Exclusion criteria | 1. History of allergic reactions or hypersensitivity to one of the study drugs or to any component of the study drugs.<br>2. Prior treatment with any investigational agent known to inhibit EGFR (mutant or wild-type) or any 3rd generation EGFR TKI<br>3. Prior treatment with any agent known to inhibit MEK/ERK or other mediators of KRAS pathway.<br>4. Prior treatment with more than 3 lines of antineoplastic therapy in the advanced setting including EGFR TKI treatment.<br>5. Patients with high level *MET* amplification in the archival or newly obtained biopsy sample as determined by local testing<br>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.<br>7. Patients with presence or history of carcinomatous meningitis.<br>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 |

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| | 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<br>10. Known HIV infection or history of HIV infection independent from the cellular immune status<br>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<br>12. Patients who underwent bone marrow or solid organ transplantation, including patients who do not receive any immunosuppressive treatment.<br>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<br>14. Any of the following within 6 months prior to first trial drug administration: Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure (> NYHA II), uncontrolled hypertension, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack<br>15. Aortic valve stenosis with mean gradient ≥ 25 mmHg and aortic valve area of ≤ 1.5 $cm^2$<br>16. Any other cardiac valve abnormality of more than mild degree/stage<br>17. Left ventricular ejection fraction (LVEF) of < 50 %<br>18. Atrial fibrillation of any Grade or ongoing cardiac dysrhythmias of CTCAE Grade ≥ 2, including corrected QTcF prolongation of > 480 ms, history of congenital long QT-syndrome or Torsades de Pointes<br>19. History of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED)<br>20. Unable or unwilling to swallow tablets or capsules<br>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<br>22. Patients have received anticancer treatment within the following time frames prior to the first dose of study treatment:<br>a. Conventional cytotoxic chemotherapy: ≤ 4 weeks (≤ 6 weeks for nitrosoureas, mitomycin-C and suramin)<br>b. Biological therapy (e.g., antibodies, excluding PD-1 or PD-L1 antibodies): ≤ 4 weeks<br>c. PD-1/PD-L1 antibodies (e.g., nivolumab, pembrolizumab): ≤ 5 half-times<br>d. Non-cytotoxic anti-cancer therapeutic (e.g., tyrosine kinase inhibitors): ≤ 5 half-times or ≤ 1 weeks (whichever is longer)<br>e. Other investigational agent: ≤ 4 weeks<br>f. Radiation therapy (excluding palliative radiation, e.g., of bone metastases): ≤ 4 weeks<br>g. Major surgery (excluding minor surgical interventions, e.g., vascular device implantation): ≤ 2 weeks<br>23. Laboratory values as listed below, that cannot be corrected to normal limits within screening :<br>a. Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L<br>b. Haemoglobin (Hb) < 9 g/dL<br>c. Platelets (PLT) < 100 x 10^9/L<br>d. Total bilirubin > 1.5 x upper limit of normal (ULN). For patients with confirmed Gilbert's disease total bilirubin > 2.5 x ULN<br>e. AST and/or ALT > 3 x ULN<br>f. AST and/or ALT > 5 x ULN in patients with liver involvement<br>g. Serum creatinine > 1.5 x ULN<br>h. Measured or calculated creatinine clearance ≤ 45 mL/min<br>i. Serum amylase and/or lipase CTCAE Grade > 2<br>j. Potassium, magnesium, phosphorus, total calcium (corrected from serum albumin) > ULN<br>24. Patients receiving treatment with any medication that are known to be<br>a. Strong inhibitors or inducers of CYP3A4/5<br>b. Substrates of CYP2D6 with narrow therapeutic index<br>c. and that cannot be discontinued at least 7 days prior to the first dose of the study drugs. |

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| | 25. Patients with a history of or presence of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis<br>26. Pregnancy or breastfeeding/nursing women<br>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<br>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. |
| Trial duration / timelines | Inclusion first patient (FPFV): 04/2018<br>Inclusion last patient: 01/2020<br>Last patient last visit (LPLV): 01/2021 |

*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**

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| Studiennummer/-Code: | AIO-TRK-0115 - PRIMUS |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | Q4/2015 – Q2/2017 (geplant) |
| Weitere Zentren: | in Abhängigkeit vom weiteren Studienverlauf |
| Letzte Aktualisierung | Oktober 2018 |

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| Principal Investigator | Prof. Dr. Martin Reck<br>LungenClinic Grosshansdorf, Wöhrendamm 80, 22927 Großhansdorf |
| Sponsor | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany<br>Phone: +49-30-322932931, Fax: +49-30-322932926<br>info@aio-studien-ggmbh.de |
| Study design | Randomized, double-blind, placebo-controlled study |
| Indication | Metastatic squamous non-small cell lung cancer |
| Countries<br>Total number of sites | Germany<br>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 | 32 randomized patients (10/2018) |
| Target population | Patients with metastatic squamous NSCLC and disease control following first-line platinum-based chemotherapy |
| Inclusion Criteria | 15. Male or female patient, age ≥ 18 years<br>16. Signed informed consent |

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| | 17. Ability to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations<br>18. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1<br>19. At least one measurable tumor lesion according to RECIST 1.1<br>20. Histologically or cytologically confirmed diagnosis of stage IV (AJCC Version 7) squamous non-small cell lung carcinoma<br>21. Complete response, partial response or stable disease after at least 2 cycles of first-line chemotherapy with cisplatin or carboplatin<br>22. Last administration of platinum based first-line chemotherapy ≥3 weeks and ≤ 8 weeks prior first dose of study treatment<br>23. Tumor specimen available for central PD-L1 testing. Tumor specimen must be a tumor block not pre-cut slides.<br>24. Adequate bone-marrow and organ function:<br>a. Absolute neutrophil count ≥ 1.5 x $10^9$/L and<br>b. Thrombocytes ≥ 100 x $10^9$/L and<br>c. Hemoglobin ≥ 9 g/dL<br>d. INR ≤ 1.5 and PTT ≤ 1.5 x upper limit during the last 7 days before therapy<br>e. Bilirubin < 1.5 x ULN and<br>f. AST (GOT) and ALT (GPT) < 3 x ULN (5 x ULN in case of liver metastases)<br>g. Creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 45 mL/min (after first line chemotherapy)<br>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<br>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 |
| Exclusion Criteria | 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 permissable that a patient participates in a follow-up phase of any previous study.<br>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<br>21. History of allogeneic tissue/solid organ transplant<br>22. History of pneumonitis or interstitial lung disease that has required oral or i.v. steroids<br>23. Radiotherapy of target lesion ≤ 28 days prior first dose of study treatment<br>24. Major surgery ≤ 28 days prior first dose of study treatment<br>25. Minor surgery (e.g. venous catheter) ≤ 24 hours prior first dose of study treatment<br>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).<br>27. Severe wound healing disorders, active ulcus ventriculi/duodenal ulcer, bone fracture<br>28. Known active HBV, HCV or HIV infection<br>29. Has any other active infection requiring systemic therapy.<br>30. Patients with active tuberculosis<br>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] |

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| | 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)<br>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<br>33. Indications of a neurological or other disease, which may influence the feasibility of the study or may seriously disturb tolerability<br>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.<br>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.<br>36. Patient has not recovered (i.e., ≤ Grade 1 or at baseline) from side effects due to agents administered more than 4 weeks earlier. [Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.]<br>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.<br>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.<br>39. Has received a live vaccine within 30 days prior to the first dose of trial treatment.<br>40. Has known hypersensitivity to pembrolizumab or any of its insipients.<br>41. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. |
| Investigational Medicinal Product | Pembrolizumab 200 mg fixed<br>Placebo |
| Treatment schedule after randomization | **Arm A:**<br>Pembrolizumab 200 mg every three weeks until disease progression (maximum 2 years)<br><br>**Arm B:**<br>Placebo i.v. every three weeks until disease progression (maximum 2 years) |
| Primary endpoint | • Progression-free-survival (RECIST 1.1) |
| Secondary endpoints | • Overall response rate<br>• Overall survival<br>• PD-L1 expression in tumor samples<br>• Tolerability and safety<br>• Quality of life (FACT-L, LCSS) |
| Randomization procedure | Permuted block randomization will be applied to guarantee balanced group numbers. |

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| Scientific rationale | 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.<br>Specific interest should be drawn to the potential correlation between PD-L1 expression and efficacy of Pembrolizumab. |
| Interim analysis | No interim analysis is planned for this study. |
| Statistical considerations and sample size calculation | **Sample Size Estimation:**<br>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.<br><br>**Statistical Analysis Outline:**<br>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.<br>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.<br>Adverse Events and Serious Adverse Events will be summarized overall and by severity; 90% confidence intervals for event rates will be calculated. |
| Translational research | PD-L1 expression will be assessed on tumor tissues of both patient groups (Arm A and Arm B)<br>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. |
| Study plan | FPI: Q4/2015<br>LPI: after approx.18 month<br>Duration of treatment: approximately 7 months<br>Follow up period for the last patient: 10 months after EOT<br>LPLV: Q4/2018<br>Study report: Q3/2019 |
| Further sites required? | Depends on actual recruitment |

*Metastatic non-small cell lung cancer (NSCLC)*

**AIO-YMO/TRK-0416: DURvalumab (MEDI4736) in frAil and elder PaTIents with metastatic Nsclc (DURATION)**

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| **AIO-Studie** | 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 | Oktober 2018 |

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| 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<br>Röntgenstrasse 1, 69126 Heidelberg, Germany<br>jonas.kuon@med.uni-heidelberg.de<br>**Mentoring Investigator:**<br>Univ.-Prof. Dr. Michael Thomas, Thoraxklinik at Heidelberg University Hospital<br>E-mail: michael.thomas@med.uni-heidelberg.de |
| Sponsor | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431, Fax +49 30 322932926<br>info@aio-studien-ggmbh.de |
| Die vollständige Synopse ist zu finden unter den Kurzprotokollen der Young-Medical Oncologists! | |

*Metastatic adenocarcinoma of the lung (non-squamousNSCLC), second line and beyond*

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

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| **AIO-Studie** | 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 | Oktober 2018 |

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| Study Type | Open-label, randomized Phase-II |
| Coordinating investigator (LKP) | Dr. med. Farastuk Bozorgmehr, Department of Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital<br>Röntgenstrasse 1, 69126 Heidelberg, Germany<br>Phone: +49 6221 396-1301, Fax: +49 6221 396-1302<br>E-mail: farastuk.bozorgmehr@med.uni-heidelberg.de<br>**Mentoring Investigator:**<br>Univ.-Prof. Dr. Michael Thomas, Thoraxklinik at Heidelberg University Hospital<br>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 rezidivierten Lungenkrebs und zur Evaluierung von Biomarkern welche für das Ansprechen auf Immuncheckpointinhibition prädiktiv sind (BIOLUMA)**

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| **AIO-Studie** | |
| Studiennummer/-Code: | AIO-TRK-0116 - BIOLUMA |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2017 - 2020 |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | November 2018 |

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| Kurztitel | BIOLUMA: Biomarker für Nivolumab und Ipilimumab und Evaluierung der Kombinationstherapie bei Patienten mit Lungenkrebs |
| Sponsor | Universität zu Köln, Albertus-Magnus-Platz, 50923 Köln, Deutschland<br>Vertreten durch:<br>Prof. Dr. Jürgen Wolf, Medizinische Klinik I, Centrum für Integrierte Onkologie (CIO), Uniklinik Köln, Kerpener Strasse 62, 50937 Köln, Germany |
| Indikation | Kohorte 1: Nicht-kleinzelliges Lungenkarzinom, Adenokarzinom (AD-NSCLC)<br>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.<br>Kohorte 2: Kleinzelliges Lungenkarzinom (SCLC)<br>Patienten mit hoher Tumormutationslast (TMB high) und kleinzelligem Lungenkarzinom in frühen oder fortgeschrittenen Stadien erhalten nach |

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| | 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<br>(II) Ipilimumab |
| Konzept der Studie | Der monoklonale IgG4-Antiköper 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 rezidiviertem 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 rezidivierten NSCLC[1,2].<br>Allerdings machen Ansprechraten von rund 20% auch deutlich, dass ein hoher Bedarf an genauerer 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.<br>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[1,3]. Zudem haben frühe Studien gezeigt, dass die PD-L1 IHC zwar beim malignen Melanom eine Wertigkeit bezüglich der Frage besitzt, welche Patienten von eine Kombinationstherapie mit Nivolumab und Ipilimumab profitieren können[4], aber dies gilt vermutlich eher nicht bei Patienten mit SCLC[5]. Daher wird der klinische Wert der PD-L1 IHC derzeit kontrovers diskutiert.<br>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. Da aktuelle Daten beim SCLC darauf hindeuten, dass das Ansprechen vor allem von der Tumor-Mutationslast abhängig ist, werden nur Patienten mit hoher Tumor-Mutationslast in diese Kohorte eingeschlossen. Der primäre Endpunkt der Studie ist für beide Kohorten die Ansprechrate der Kombinationstherapie.<br>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).<br>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 |

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| | 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. |
| Studientyp | 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. |
| Studiendesign | 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) mit TMB high in frühen oder fortgeschrittenen Tumorstadien (Kohorte 2).<br>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 gefrorenes Tumormaterial zur DNA- (whole genome/ whole exome) und RNA-Sequenzierung. Archivierte, in Paraffin-eingebettete Tumorproben werden zur Kompelttierung der Daten ebenfalls untersucht. In der SCLC Kohorte wird das zum Zeitpunkt der Erstdiagnose gewonnene Tumormaterial bezüglich Tumor-Mutationslast analysiert. Nur Patienten mit hoher Tumor-Mutationslast kommen für den Studieneinschluss im Rahmen der Zweitlinientherapie in Frage.<br>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. |
| Primäre Zielsetzung | <u>Kohorte 1:</u><br>Erhebung der Ansprechrate der Kombinationstherapie aus Nivolumab und Ipilimumab nach Tumorprogress unter Nivolumab-Monotherapie bei Patienten mit rezidiviertem AD-NSCLC in der Zweitlinientherapie.<br><u>Kohorte 2:</u><br>Erhebung der Ansprechrate der Kombinationstherapie aus Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC in der Zweitlinientherapie und TMB high |
| Primärer Endpunkt | <u>Kohorte 1:</u><br>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.<br><u>Kohorte 2:</u> |

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| | Die nach RECIST 1.1 durch den Prüfer erhobene Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC und TMB high |
| Sekundäre Zielsetzungen | Erhebung der Wirksamkeit der Nivolumab-Monotherapie und der Kombinationstherapie mit Nivolumab und Ipilimumab<br>Charakterisierung der Sicherheit und Tolerabilität der Nivolumab-Monotherapie und der Kombinationstherapie mit Nivolumab und Ipilimumab<br>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<br>Korrelation von Mutationslast und Neoepitop-Signaturen mit demklinischen Therapieansprechen in der NSCLC-Kohorte und in der SCLCKohorte welche vor der Beschränkung auf Patienten mit TMB high eingeschlossen wurden<br>Korrelation von Neoepitop-Signaturen mit dem klinischen Therapieansprechen in der SCLC-Kohorte mit TMB high |
| Sekundäre Endpunkte | • OS, PFS, DCR und DOR unter der Nivolumab-Monotherapie und unter der Kombinationstherapie mit Nivolumab und Ipilimumab<br>• Inzidenz und Schweregrad von unerwünschten Ereignissen (UEs) und schwerwiegenden unerwünschten Ereignissen (SUEs) unter der Nivolumab-Monotherapie und unter der Kombinationstherapie mit Nivolumab und Ipilimumab<br><br>Alle Biomarker-bezogenen sekundären Endpunkte werden sowohl für die Nivolumab-Monotherapie, als auch für die Kombinationstherapie mit Nivolumab und Ipilimumab erhoben:<br><br>• Prädiktiver Wert der PD-1/PD-L2-Positivität der Tumorzellen vor der Studientherapie für ORR, DCR, PFS, OS, TTR und DOR (Grenzwerte ≥1%, ≥5%, ≥10%, ≥25% und ≥50%)<br>• Korrelation der PD-L1/PD-L2/PD-1-Positivität der Tumor-assoziierten Immunzellen vor der Studientherapie mit ORR, DCR, PFS, OS, TTR und DOR<br>• Prädiktiver Wert der Zusammensetzung des Immunzellinfiltrates vor der Studientherapie für ORR, DCR, PFS, OS, TTR und DOR<br>• Prädiktiver Wert von zusätzlichen ko-inhibitorischen Molekülen für ORR, DCR, PFS, OS, TTR und DOR<br>• Prädiktiver Wert der RNA-Expression von PD-L1 und PD-L2 für ORR, DCR, PFS, OS, TTR und DOR<br>• Prädiktiver Wert der Tumormutationslast und der vorherberechneten Neoepitope für. ORR, PFS und OS in der NSCLC-Kohorte und in der SCLC-Kohorte, welche vor der Beschränkung auf Patienten mit hoher Tumor-Mutationslast eingeschlossen wurden.<br>• Prädiktiver Wert von Neoepitop-Signaturen mit ORR, PFS und OS in der SCLC-Kohorte mit hoher/mittlerer/niedriger Tumor-Mutationslast |
| Explorative Zielsetzungen | • Beschreibung von Immunsystem-assoziierten Expressionsprofilen in Tumorbiopsaten und Korrelation mit dem klinischen Verlauf<br>• Beschreibung der Zusammensetzung des Immunzellinfiltrates in Tumorbiopsaten und Korrelation mit dem klinischen Verlauf<br>• Beschreibung der Zusammensetzung der Immunzellpopulationen im peripheren Blut vor, während und nach der Studientherapie und Korrelation mit dem klinischen Verlauf<br>• Korrelation von Veränderungen des C-reaktiven Proteinwertes und der Leukozytenzahl mit dem klinischen Verlauf<br>• Beschreibung der Zusammensetzung des Mikrobioms vor, während und nach der Studientherapie und Korrelation mit dem klinischen Verlauf<br>• Charakterisierung der molekularen Heterogenität der Tumorzellen in den Biopsaten<br>• Korrelation des genetischen Subtyps (definiert nach gezielt behandelbaren Mutationen) mit dem klinischen Verlauf<br>• Korrelation von bekannten Treibermutationen mit dem klinischen Verlauf |

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| | 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:<br>• Analyse der Mutationslast mittels DNA-Sequenzierung (Whole Genome Sequencing oder, je nach DNA-Gehalt der Biopsate, Whole Exome Sequencing)<br>• Charakterisierung der Transkriptom-Expression mittels Whole Transcriptome Sequencing (RNAseq)<br>• Muster der Infiltrate von Immunzellsubpopulationen mittels IHC<br>• Proteinexpression von PD-L1 und PD-L2, mRNA-Expression und Muster der Immunzellsubpopulationen<br>• Immunzellinfiltrat im Tumormikromilieu und Verhältnisse der Immunzellpopulationen im peripheren Blut<br>• Evaluierung der Funktionsveränderung von T-Zellen des peripheren Blutes mittels Analyse von Aktivierungsmarkern und Änderungen der Zytokinlevel<br>• 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 |
| Statistische Analysen | Kohorte 1:<br>Die Studie folgt einem “one-stage A’Hern design” mit Ansprechverhältnissen (das heißt ORR der Kombinationstherapie) $\pi_0 = 0.075$ und $\pi_1 = 0.2$, $\alpha = 0.1$ und $\beta = 0.2$. Demnach werden 33 evaluierbare Patienten benötigt. Die Nullhypothese $H_0: \pi \leq 0.1$ ist verworfen, wenn mindestens 5 von 33 Patienten ansprechen[6].<br>Unter der Annahme einer Ausfallrate von 5% aufgrund von Therapieabbruch in Therapiephase A[2] und einer erneuten Ausfallrate von 35% in Therapiephase B[5] müssen etwa 53 Patienten (das heißt ≈33/0.95/0.65) eingeschlossen werden.<br>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.<br>In jedem Falle wird die Rekrutierung solange erfolgen, bis 33 Studienpatienten für die Analyse des primären Endpunktes evaluierbar sind UND von 40 Patienten evaluierbare Rebiopsien im Rahmen des Screenings, sowie nach Versagen der Nivolumab-Monotherapie vor Einleitung der Therapiephase B gewonnen wurden.<br>Die statistischen Methoden sind überwiegend deskriptiv, so auch die Methodik für Raten, Verhältnisse, zusammenfassende Statistik (Durchschnitt, 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.<br>Die Subgruppenanalysen erfolgen nach PD-L1-Positivität (ja/nein), Geschlecht und Therapieansprechen unter Nivolumab (primäre/sekundäre Resistenz).<br>Kohorte 2:<br>Die Studie folgt einem “one-stage A’Hern design” mit Ansprechverhältnissen (das heißt ORR der Kombinationstherapie) __ = 0.075 und __ = 0.3, = 0.05 und _ = 0.1. Demnach werden 25 evaluierbare Patienten benötigt. Die Nullhypothese _: _ ≤ 0.1 ist verworfen, wenn mindestens 5 von 25 Patienten ansprechen<br>Unter der Annahme einer Prävalenz von 30% hoher Tumor-Mutationslast erwarten wir 84 Patienten zu screenen, um 25 Patienten mit hoher Tumor-Mutationslast zu identifizieren; 108 Patienten müssen gescreent werden, um eine 95%ige Wahrscheinlichkeit zu erreichen, 25 Patienten zu identifizieren (auf der Binominalverteilung basierend), Da jeweils im Rahmen der Erstlinientherapie sowie im Rahmen des Screenings von einer Dropout-Rate |

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| | von 50% auszugehen ist, schätzen wir die Screening-Zahl auf 300, um 25 Patienten mit hoher Tumormutationslast einzuschließen.<br>Im Falle eines Therapieende wird kein auswertbarer Patient ersetzt.<br>Die weiteren statistischen Methoden werden analog zur Kohorte 1 durchgeführt (siehe oben). |
| Haupteinschlusskriterien | • 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.<br>• Kohorte 2: Zweitlinientherapie für Patienten mit histologisch oder zytologisch gesichertem SCLC und TMB high in frühem oder fortgeschrittenem Stadium mit Tumorprogress nach Platin-haltiger Erstlinientherapie.<br><br>Die folgenden Einschlusskriterien gelten für die Kohorte 1 und 2:<br>• Unterschriebene und datierte Patienteneinwilligung, welche vor jeglicher Studien-spezifischen Maßnahme eingeholt werden muss und welche zuvor von einer unabhängigen Ethikkommission genehmigt wurde<br>• Männliche oder weibliche Patienten ≥18 Jahre<br>• Eastern Cooperative Oncology Group (ECOG) Performance Status von 0-1<br>• Studienpatienten müssen bereit sein, mindestens zwei Tumorbiopsien durchführen zu lassen (Baseline und vor Einleitung der Therapiephase B)<br>• Der jeweilige Prüfarzt muss den Studienpatienten für fähig erachten, zwei Tumorbiopsien durchführen zu lassen (Baseline und bei Einleitung der Therapiephase B)<br>• Mindestens eine nach RECICT 1.1 auswertbare Tumorläsion im CT oder MRT. Zielläsionen können in einer zuvor bestrahlten Region liegen, wenn ebendort ein Tumorprogress nach Vollendung der Bestrahlung dokumentiert wurde<br>• 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 ≤ 10 mg Predisonäquivalent. |
| Hauptausschlusskriterien | • Patienten mit Plattenpithelkarzinom der Lunge<br>• Betrifft nur die Kohorte 1: aktivierende EGFR-Mutation oder ALK-Translokation<br>• Mehr als eine vorhergehende Chemotherapielinie beim fortgeschrittenen NSCLC<br>• Vorliegen eines medizinischen Zustandes, der mit signifikant erhöhtem Risiko für Blutungskomplikationen im Rahmen der Tumorbiopsie einhergeht (z.B. bekannte Koagulopathie, therapeutische Antikoagulation)<br>• 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 mindestens zwei Wochen vor Studientherapiegabe keine Notwendigkeit einer systemischen Therapie mit Corticosteroiden > 10 mg Prednisonäquivalent täglich bestehen<br>• Aktuell vorliegende, oder innerhalb der letzten fünf Jahre vor Studieneinschluss zurückliegende, weitere Malignomerkrankung, mit Ausnahme von adäquat behandeltem Basalzellkarzinom oder |

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| | Plattenepithelkarzinom der Haut, oder jedes anderen adäquat behandelten Carcinoma in situ<br>• 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<br>• Aktive oder chronische Hepatitis B- oder Hepatitis C-Infektion<br>• Bekannte Infektion mit dem humanen Immundefizienzvirus (HIV) oder positiver HIV-Test, oder bekannte AIDS-Erkankung (acquired immunodeficiency syndrome)<br>• Jedweder Zustand, der eine systemische Therapie mit entweder Corticosteroiden (> 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 > 10 mg Prednisonäquivalent pro Tag sind bei Abwesenheit einer aktiven Autoimmunerkrankung erlaubt<br>• Patienten mit interstitieller Lungenerkrankung, die symptomatisch ist, oder sich störend auf die Detektion oder das Management von Therapie-bezogenen pulmonalen Toxizitäten auswirken könnte<br>• 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<br>• 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 beeinträchtig, erheblich das Patientenrisiko erhöht, oder sich negativ auf die Interpretation der Studienergebnisse auswirkt<br>• Bekannte Allergie oder schwere Hypersensitivitätsreaktion gegen einen Bestandteil der Studienmedikation, oder gegen jeglichen monoklonalen Antikörper |
| Studienuntersuchungen | Kohorte 1:<br><br>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).<br><br>Kohorte 2:<br><br>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 Woche) statt und im Anschluss daran alle 8 Wochen bis Woche 47 (C24D1), im weiteren Verlauf alle 12 Wochen (+/- 1 Woche). |
| Studiendauer | Kohorte 1, NSCLC:<br>Erster Patient erste Visite (FPFV): April 2017<br>Letzter Patient erste Visite (LPFV): April 2019 |

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| | Letzter Patient letzte Visite (LPLV): Oktober 2020<br>Studienabschlussbericht: Oktober 2021<br>Kohorte 2, SCLC:<br>Erster Patient erste Visite nach Amendment Tumor-Mutationslast: November 2018<br>Letzter Patient erste Visite: Juni 2020<br>Letzter Patient letzte Visite: Dezember 2021<br>Studienabschlussbericht: Dezember 2022 |

*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)**

**AIO-Studie**

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| Studiennummer: | AIO-TRK-0117 - NintNivo |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2018 - 2020 |
| Weitere Zentren: | sind aktuell für Dosisfindungsphase leider nicht möglich. Ja, für Erweiterungsphase (2019) |
| Letzte Aktualisierung: | 31.10.2018 |

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| Prüfplan Version | V 3.0 |
| Leiter der klinischen Prüfung | Prof. Dr. med. Martin Reck<br>LungenClinic Grosshansdorf GmbH<br>Wöhrendamm 80, 22927 Großhansdorf, Germany<br>Tel.: +49 4102 - 601 2101<br>Fax: +49 4102 - 601 7101<br>E-mail: m.reck@lungenclinic.de |
| Sponsor | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8, 14057 Berlin<br>Tel: +49 30 814534431<br>Fax: +49 30 322932926<br>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. |

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| Geplante Fallzahl | N = 56-62 Patienten<br>• Safety run-in: N = 6-12 (3-6 Patienten je Dosislevel, nach einem 3+3 Design)<br>• Phase-1b-Erweiterung: N = 50 |
| Einschlusskriterien | 14. Vorliegen einer vom Patienten unterschriebenen und datierten Einwilligungserklärung einschließlich aller lokal benötigten Genehmigungen (z.B. EU-Datenschutzricht-linie) bevor jedwede studienspezifische Maßnahme, einschließlich Screening durchgeführt wird.<br>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<br>16. Alter ≥ 18 Jahre zum Zeitpunkt des Studieneinschlusses<br>17. Histologisch bestätigtes Adenokarzinom der Lunge des Stadiums IIIB/IV nach UICC7<br>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.<br>19. Allgemeinzustand nach ECOG 0-1<br>20. Angenommene Lebenserwartung von mindestens 3 Monaten<br>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.<br>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 Vakuumsbiopsie handeln. Eine Feinnadelpunktion ist unzureichend.<br>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.<br>*24.* Adäqute Blut-, Leber- und Nierenwerte (bis spätestens 14 Tage vor Beginn der Behandlung erhalten):<br>• Anzahl weißer Blutzellen ≥ 2000/µl<br>• Anzahl Neutrophile ≥ 1500/µl<br>• Anzahl Blutplättchen ≥ 100 x $10^3$/µl<br>• Haemoglobin > 9,0 g/dl<br>• Serum-Kreatinin ≤ 1,5 x ULN oder Kreatinin- Clearance (CrCl) ≥ 40 ml/min (nach der Cockcroft-Gault Formel)<br>• AST/ALT ≤ 1,5 x ULN ( < 3 x ULN im Falle von Lebermetastasen)<br>• Gesamt-Bilirubin ≤ 1,5 x ULN<br>25. Frauen im gebährfähigen Alter müssen geeignete Methode(n) zur Empfängnisverhütung anwenden. Frauen im gebährfähigen Alter sollten eine geeignete Schwangerschaftsverhütungsmethode für 5 Monate (30 Tage plus die Zeit, die Nivolumab benötigt um 5 Halbwertzeiten zu durchlaufen) nach der letzten Gabe von Nivolumab. Da der Effekt von Nintedanib auf den Metabolismus und die Wirksamkeit von Verhütungsmitteln micht untersucht ist, sollen zur Vermeidung von Schwangerschaften Barrieremethoden als zusätzliche Form der Empfängnisverhütung angewendet werden.<br>26. Frauen im gebährfähigen Alter müssen einen negativen Schwangerschaftstest (Serum oder Urin) innerhalb von 24 Stunden vor Studienbehandlung, monatlich während der Behandlung und bis 5 Monate |

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| | nach der letzten Verabreichung der Prüfmedikation, vorweisen (minimale Sensitivität 25 IU/l oder äquivalente Einheiten des HCG)<br>27. Männliche Patienten, die mit einer gebährfähigen Frau sexuell aktiv sind, müssen eine geeignete Empfängnisverhütungsmethode anwenden (Fehlerrate < 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. Nichtgebährfähige Frauen (z.B. postmenopausal oder durch operative Sterilisation) und Männer mit Azoospermie benötigen keine Empfängnisverhütung. |
| Ausschlusskriterien | 34. Mehr als eine vorhergehende Behandlungslinie für fortgeschrittenes oder metastasiertes NSCLC<br>35. Patienten mit aktiven ZNS-Metastasen sind ausgeschlossen. Patienten sind einschlussfähig, 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 ≤ 10 mg täglichem Prednison (oder gleichwertig) sein.<br>36. Leptomeningeale Erkrankung, karzinomatöse Meningitis, chronischer Diarrhö oder Kurzdarmsyndrom<br>37. Bekannte aktivierende EGFR-Mutation oder bekannte ALK-Translokation<br>38. Patienten mit symptomatischer interstitieller Lungenerkrankung<br>39. Jede vorherige Behandlung mit Anti-Tumor-Impfstoffen oder immun-stimulatorischen 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.<br>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.<br>41. Größere Verletzungen innerhalb von 4 Wochen vor Beginn der Studienbehandlung mit unvollständiger Wundheilung und/oder geplante Operation während der Studienbehandlungsphase.<br>42. Patienten mit aktiver, bekannter oder vermuteter Autoimmunerkrankung sind nicht einschlussfähig. **HINWEIS**: 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 einschlussfähig.<br>43. Patienten, die aufgrund einer Erkrankung eine systemische Behandlung entweder mit Kortikosteroiden benötigen (> 10 mg pro Tag Prednisonäquivalente) oder andere immunsuppressive Medikamenten innerhalb von 14 Tagen vor der ersten Gabe der Studienmedikation. **HINWEIS:** inhalierte oder topikale Steroide oder Nebennierenersatz mit einer Dosis von > 10 mg / Tag Prednisonäquivalente, sind in Abwesenheit einer aktiven Autoimmunerkrankung erlaubt.<br>44. Positiver Test auf Hepatitis-B-Viurs 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)<br>45. Vorgeschichte einer schweren Überempfindlichkeitsreaktion gegen andere monoklonale Antikörper oder jegliche Inhaltsstoffe. Bekannte Überempfindlichkeit gegen Nintedanib, Erdnüsse, Soja oder jegliche Inhaltsstoffe oder Kontrastmittel.<br>46. Strahlentherapie der Zielläsion innerhalb der letzten 3 Monate vor Baseline-Imaging (siehe auch Einschlusskriterium Nr. 8).<br>47. Radiographischer Nachweis von kavitären oder nekrotischen Tumoren<br>48. Zentral gelegene Tumore mit radiographischen Nachweis (CT oder MRT) einer lokalen Invasion der großen Blutgefäße |

<table>
<tr><td></td><td>
49. Therapeutische Antikoagulation mit Medikamenten, die eine INR-Überwachung erfordern (außer niedrig dosiertem Heparin und / oder Heparinspülung, wie es für die Aufrechterhaltung einer intravenösen Verweilkanüle erforderlich ist) oder Anti-Thrombozyten-Therapie (mit Ausnahme der Niedrigdosis-Therapie mit Acetylsalicylsäure < 325 mg pro Tag)<br>
50. Vorgeschichte eines klinisch signifikanten hämorrhagischen oder thromboembolischen Ereignisses in den letzten 6 Monaten<br>
51. Bekannte vererbte Prädisposition für Blutungen oder Thrombosen<br>
52. Signifikante Herzerkrankung (d.h. unkontrollierter Bluthochdruck, instabile Angina pectoris, vorhergehender Infarkt innerhalb der letzten 12 Monate vor Beginn der Studienbehandlung, kongestive Herzinsuffizienz > NYHA II, schwere Herzrhythmusstörungen, perikardialer Erguss)<br>
53. Aktiver Alkohol- oder Drogenmissbrauch<br>
54. Signifikanter Gewichtsverlust (> 10 % des Körpergewichts) innerhalb der letzten 6 Monate vor Studieneinschluss<br>
55. Vorgeschichte einer malignen Erkrankung (die sich vom NSCLC unterscheidet), die entweder fortschreitet, oder eine aktive Behandlung erfordert<br>
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.<br>
57. Schwangere, stillende, gebährfähige Patientinnen oder gebährfähige Patienten, die keine hocheffektive Empfängnisverhütungsmethode anwenden (Fehlerrate von weniger als 1% pro Jahr)<br>
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<br>
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.<br>
60. Vom Sponsor, Prüfzentrum oder Prüfarzt abhängige Personen<br>
61. Patienten, die auf gerichtliche oder behördliche Anordnung in einer Anstalt untergebracht sind (§ 40 Abs. 1 S. 3 Nr. 4 AMG).
</td></tr>
<tr><td>Prüfmedikation</td><td>
• Nintedanib<br>
• Nivolumab
</td></tr>
<tr><td>Behandlungsablauf</td><td>
Safety run-in – Dosisfindung<br>
Die safety run-in Phase wird nach einem Standard-3+3-Design zur Dosiseskalation/-deeskalation erfolgen, in das, je nach Auftreten von dosisbegrenzenden Toxizitäten, 3 bis 6 Patienten in jeder Kohorte nacheinander eingeschlossen werden.<br>
Die folgenden Dosisstufen werden untersucht:
<table>
<tr><th>Dosislevel A</th><th>Dosislevel B</th><th>Dosislevel C</th></tr>
<tr><td>• Nintedanib 150 mg bid<br>• Nivolumab 240 mg Q2W</td><td>• Nintedanib 200 mg bid<br>• Nivolumab 240 mg Q2W</td><td>• Nintedanib 100 mg bid<br>• Nivolumab 240 mg Q2W</td></tr>
</table>
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.<br>
Erweiterungsphase
</td></tr>
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| | • Nintedanib RP2D + Nivolumab 240 mg Q2W<br>• Wenn die Behandlung aufgrund von Toxizitäten dauerhaft unterbrochen wird und die Toxizitäten eindeutig eines der Studienmedikamente zugeordnet werden können, kann die Studienbehandlung als Monotherapie fortgesetzt werden. |
| Endpunkte | Primäre Endpunkte:<br>• Sicherheit und Verträglichkeit, bestimmt durch die Häufigkeit und Schwere von unerwünschten Ereignissen<br>• progressionsfreie Überlebensrate bei 6 und 9 Monaten<br>Sekundäre Endpunkte:<br>• Ziel-Ansprechrate (ORR)<br>• Progressionsfreies Überleben (PFS)<br>• Zeit bis zur Tumor-Progression (time to progression, TTP)<br>• Gesamtüberleben (OS)<br>• AEs/SAEs und therapiebedingte Nebenwirkungen nach CTC 4.03<br>• Dauer des Ansprechens (duration of response, DoR) und Zeit des Ansprechens (time to response, TTR)<br>Exploratorische Endpunkte:<br>• PD-L1 Expressionsstatus<br>• Korrelation der Wirksamkeit und PD-L1 Expression und andere Biomarker<br>• Korrelation von Wirksamkeit und Zeit seit Beginn der Erstlinien-Therapie |
| Rationale | 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), *Lancet Oncol.*]. 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).<br>Kombinationsstrategien haben das Potential das Ansprechen auf Immuntherapien zu erhöhen, indem sie die endogene Antitumor-reaktion auf verschiedenen Ebenen stimulieren.<br>Es gibt zunehmendes Verständnis dafür, dass vaskuläre Endothelzellen und VEGFR-Signalisierung nicht nur für die Tumorangiogenese 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.<br>Es wurde gezeigt, dass<br>• VEGFR 1 und 2 eine Rolle bei der dendritischen Zellreifung spielen (VEGF hemmt die Reifung von DCs) [Dikov et al. (2005), *Journal of Immunol*.]<br>• eine Inhibition der VEGFR1-Signalisierung unter Verwendung eines neutralisierenden VEGFR1-spezifischen monoklonalen Antikörpers die DC-Funktion wiederherstellt [Tartour et al. (2011), *Cancer Metastasis Rev*.; Bruno et al. (2014), *Front Oncol.*]<br>• unreife DCs die Immuntoleranz fördern und regulatorische T-Zellen induzieren<br>• die Inhibition von VEGFR verhindert, dass Lungenendothelzellen induziert werden, um T-Zell-Funktionen zu unterdrücken [Mulligan (2010), *J Immunother*.]<br>• eine Blockade von VEGFR2 die Akkumulation von MDSCs reduziert [Finke et al. (2011), *Int Immunopharmacol*.]<br>• MDSCs und regulatorische T-Zellen eine wichtige Rolle bei der Unterdrückung der Entwicklung einer Antitumor-Immunität bei Krebspatienten spielen<br>• die anti-angiogene Behandlung die Verfügbarkeit von Glukose und Sauerstoff erhöht (durch die vaskuläre Normalisierung, wie für Nintedanib gezeigt [Kutluk et al. (2013), *Mol Cancer Ther*.; Mross et al. (2014), *BMC Cancer*] gezeigt) und den Verlust von ICAM-1 und VCAM-1 auf Endothelzellen verhindert, wodurch die T-Zell-Migration und Infiltration |

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| | erhöht werden [Kamrava et al. (2009), *Molecular bioSystems*; Voron et al. (2014), *Front Oncol.*; Dirkx et al. (2006), *The FASEB Journal*]<br>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.<br>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. |
| Sicherheitsdaten | • Sichere Dosis und Dosis-limitierende Toxizitäten<br>• AEs / SAEs / therapiebedingte Nebenwirkungen nach CTC 4.03<br>• Häufigkeit abnormer Laborparameter |
| Rationale für die Fallzahl und Statistik | 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.<br>Deskriptive statistische Instrumente werden verwendet, um die Wirksamkeit und Verträglichkeit zu beschreiben.<br>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.<br><br>Die zu rekrutierende Anzahl von Patienten beträgt N = 56-62 |
| Zeitplan | Einschluss erster Patient (FPI) — Q2 /2018<br>Einschluss letzter Patient (LPI) — nach ca. 29 Monaten<br>Letzter Patient letzte Behandlung (LPLT) — nach ca. 35 Monaten<br>Studienende (Ende der Nachbeobachtungsphase nach LPLT) — nach ca. 47 Monaten<br><br><u>Q2-Q3 2022</u><br>Studienreport — nach ca. 57 Monaten<br>Publikation — nach ca. 60 Monaten |

## *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**

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| Studiennummer/-Code: | AIO-TRK-0315 - CRISP |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2015 - 2019 |
| Weitere Zentren: | auf Anfrage |
| Letzte Aktualisierung | September 2018 |

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

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| Purpose and rationale | 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 non-small cell lung cancer (NSCLC).<br>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 NSCLC. A particular focus is on molecular biomarker testing before the start of first-line treatment of patients with advanced or metastatic NSCLC. The data shall be used to assess the current state of care and to develop recommendations concerning topics that could be improved.<br>PRO assessment will provide large-scale data on quality of life and anxiety/depression for real-life patients with NSCLC 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.<br>Furthermore CRISP will set up a decentralized clinically annotated tissue repository for future collaborative, investigational scientific biomarker testing. |
| Objectives | To assess molecular biomarker testing, treatment and outcome of patients with NSCLC in Germany, in particular:<br>• To collect data on the frequency, methodology and results of molecular biomarker testing before first-line and later-line treatment<br>• To describe types of surgeries, systemic treatments, radiochemotherapies, radiation therapies and sequential treatments thereof applied in real-life practice<br>• To assess effectiveness of treatments in regards to response rate, progression-free survival and overall survival<br>• To describe physician-reported factors affecting treatment decision making besides biomarker profiling<br>• To collect key data on specific supportive therapies<br>• To investigate changes in diagnostics, treatment or outcome during the course of the project<br>• 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 |
| Population / Number of patients | Main project:<br>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).<br>Patients included: **2799** (September 2018)<br><br>Satellite Stage II/III:<br>400 patients with NSCLC stage II, and 400 patients with NSCLC stage IIIA or with NSCLC stage IIIB if they are eligible for curative surgery and/or radiochemotherapy will be recruited (CRISP satellite II/III patients). 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.<br>Satellite Stage II/II started in August 2018. Patients included: 38 (September 2018) |
| Number of sites | 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.<br>Target number: 150, 156 Initiated |

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| Inclusion criteria | Patients who meet all of the following criteria are eligible for the project:<br>• Histologically confirmed non-small cell lung cancer (NSCLC)<br>• Informed consent no later than four weeks after start of first-line treatment<br>• Age ≥ 18 years<br>• Able to understand and willing to sign written Informed Consent and to complete patient-reported-outcome assessment instruments<br>Main project:<br>• Stage IV, IIIC or stage IIIB (UICC8) if patient is ineligible for curative surgery and/or radiochemotherapy<br>• Systemic therapy<br>Satellite Stage II/III:<br>• Stage II, stage IIIA or stage IIIB (UICC8) if patient is eligible for curative surgery and/or radiochemotherapy<br>• systemic (chemo)therapy and/or radiation therapy and/or surgery<br><br>Main project: It is strongly recommended that patients' tumor samples are tested for EGFR mutation in exons 18-21, ALK rearrangement and ROS1 rearrangement as well as PD-L1 expression 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.<br>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)<br><br>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 | Main Project:<br>First Patient In (FPI) Q4/ 2015<br>Last Patient In (LPI) Q4/ 2019<br>Last patient out (LPO) Q4/ 2022<br>Interim analysis Annually<br>Final analysis 2023<br><br>Satellite Stage II/III<br>First Patient In (FPI) Q2/ 2018<br>Last Patient In (LPI) Q2/ 2020<br>Last patient out (LPO) Q2/ 2023<br>Interim analysis Annually<br>Final analysis 2023<br><br>The individual observation time is until death or end of project (LPO).<br><br>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**

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

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| Study type | prospective, explorative, single arm non-interventional trial |
| Background | 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%.<br>Precision medicine raises hope of improved cancer survival rates.<br>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.<br>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.1 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.2 A direct translation of organoid screening into clinical practice has, however, not been established so far.<br>References:<br>1. Iorio, F. et al., Cell (2016). doi:10.1016/j.cell.2016.06.017<br>2. Van de Wetering, M. et al., Cell 161, 933–945 (2015). |
| 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: |

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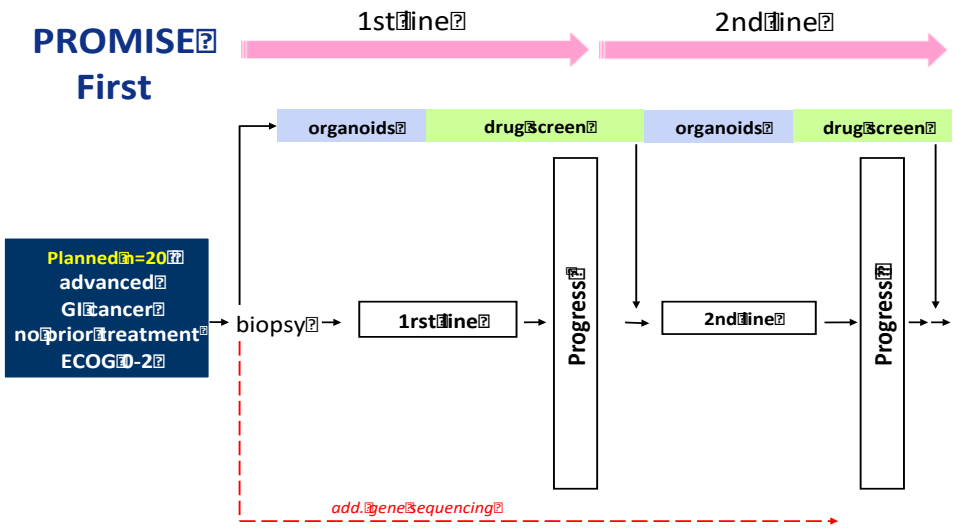
| | - To establish individual patient derived organoids of tumor and normal tissue<br>- To treat the individual tumor organoid with the same substances as the patient<br>- To characterize molecular alterations of the tumor organoid emerging under treatment<br>- To analyze gene-drug-response associations as potential predictive biomarkers<br>- To assess the efficacy of systemic chemotherapy in regards to response rate and progression-free survival<br>- To compare systemic chemotherapy in the patient with treatment results of the corresponding organoid |
| 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 | - Patients ≥ 18 years of age.<br>- Performance status ECOG 0-2<br>- Histologically confirmed advanced stage* gastrointestinal cancer prior last line therapy<br>- Tumor accessible to biopsy and patient willing to undergo biopsy<br>- Absence of HIV, HBV and HCV infection<br>- At least one measurable lesion of disease according to RECIST criteria.<br>- Adequate end organ function:<br>  - renal function: serum creatinine ≤ 1.5 x ULN or GFR ≥ 30mL/min.<br>  - hematopoietic function: white blood cell (WBC) count ≥3000/µL, absolute neutrophil count (ANC) ≥1500/µL, platelets ≥100000/µL, hemoglobin level >9.0 g/dL<br>  - Liver function: total bilirubin ≤1.5 x ULN, AST / ALT ≤3.0 x ULN<br>- Signed informed consent prior to any screening procedures |
| Study design |  <br>Fig. 1. Scheme of the PROMISE-First study.<br>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.<br>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 the cancer in the patient reaches the stage of non-responsiveness. |

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| Clinical part | 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.<br><br>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:<br>Efficacy data:<br>• tumor response evaluation according to RECIST 1.1<br>• Best overall response<br>• Time-to-response (TTR)<br>• Duration of response (DOR)<br>• Time-to-failure of treatment strategy (TTFS)<br>• PFS, OS<br>Safety data:<br>• AEs / SAEs<br>• dose density administered<br>• dose modifications due to toxicity<br>Follow-up after discontinuation of first-line therapy:<br>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. |
| Clinical Data assessment, study visits and re-stagings | 1. Inclusion:<br>- Patients with metastasized CRC before the start of palliative chemotherapy are identified by screening inpatients and endoscopy-patients<br>- Patients undergo endoscopic biopsy of their CRC and organoid lines are established before start of Treatment<br>2. First study visit: Chemotherapy informed consent / chemotherapy initiation<br>- Obligatory assessments: ECOG-Status, weight, clinical examination<br>- Obligatory Lab tests: Diff-BB, CEA, CA-19-9, CRP, LDH, (Na, K, Krea, Billi-Gesamt, AP, yGT, ALAT, ASAT, Quick)<br>- 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<br>- 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<br>3. Follow-up visits<br>- 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.<br>- after week 3, study nurses are informed if organoid culture was successful and if patient remains “on-study”<br>- Obligatory assessment and documentation every visit (bi-weekly):<br>-- Therapy protocol (including regimen, dose reductions)<br>-- ECOG status, weight, clinical examination (as above)<br>-- Lab (as above)<br>-- Chemotherapy side-effects (according to CDC)<br>4. Re-Staging<br>Re-staging CT (thorax, abdomen, pelvis) is performed every 3 months (week 13-14).<br>- CT-results are assessed according to RECIST-criteria<br>- Both CT images and CT report have to be saved in the clinical documentation system |

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| | - 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<br>- obligatory documentation after re-staging (in addition to basic documentation in every visit):<br>-- Response according to RECIST, size and number of metastases in affected organs, primary tumor size<br>-- relevant new co-morbidities |
| Sample size | 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.<br>A sample size of n=20 shall suffice to generate informative pilot data on the feasibility and utility of the Avatar approach. |
| Data analysis | 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.<br>Half-yearly interim analyses will be performed concerning patient characteristics, response evaluation, organoid drug response, molecular analysis, toxicity and outcome. |
| Planned timelines | First Patient In: Q2 2017<br>Last Patient In: Q2 2020<br>Last Patient Out: 2022<br>Individual observation time: 24 months<br>Interim-analysis: every 6 months<br>Final Analysis: 2022 |
| Contact details | Prof. Dr. M. Ebert, Universitätsklinik Mannheim, Universität Heidelberg, matthias.ebert@medma.uni-heidelberg.de<br>Prof. Dr. M. Boutros, DKFZ Heidelberg, m.boutros@dkfz.de<br>Dr. J. Betge, johannes.betge@medma.uni-heidelberg.de |

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

**AIO-Studie**

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

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| 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 (≤5% vs. ≥20%, primary end-point) 3) To characterize molecular alterations of the PDOs and tumor and analyze gene-drug associations as potential predictive biomarkers |

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| INTERVENTION(S) | Experimental intervention:<br>1. Biopsy to establish PDOs, 2. Treatment of the patient with best performing drug in PDO-based drug-screen<br>Control intervention:<br>No control intervention is performed<br>Duration of intervention per patient:<br>1. Biopsy: 30-60minutes, 2. Treatment after last line therapy (until disease progression)<br>Follow-up per patient:<br>24 months |
| KEY INCLUSION AND EXCLUSION CRITERIA | Key inclusion criteria:<br>1. Patients ≥ 18 years of age. 2. Performance status ECOG 0-2. 3. Histologically confirmed metastatic or locally recurrent colorectal cancer prior last line therapy.<br>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<br>Key exclusion criteria:<br>1. HIV, HBV or HCV infection. 2. Inadequate end organ function |
| OUTCOME(S) | Primary efficacy endpoint:<br>Best objective response rate (ORR) per central review in last-line treated subjects (≤5% vs. ≥20%) determined by RECIST criteria<br>Key secondary endpoint(s):<br>Progression-free survival, overall survival, toxicity, quality of life (QoL), predictive value of PDO screens for treatment efficiency, treatment duration and dose intensity<br>Assessment of safety:<br>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:<br>Objective response rate (≤5% vs. ≥20%, primary end-point)<br>Description of the primary efficacy analysis and population:<br>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). H0 : P ≤ P0 HA : P ≥ PA<br>Safety:<br>Rates of complications, adverse events and serious adverse events will be calculated with 95% confidence intervals for group comparisons.<br>Secondary endpoint(s):<br>Progression-free survival, Toxicity, QoL |
| SAMPLE SIZE | To be assessed for eligibility: (n = 70)<br>To be allocated to trial: (n = 40)<br>To be analyzed: (n = 30) |
| TRIAL DURATION | Time for preparation of the trial (months): 6<br>Recruitment period (months): 24<br>First patient in to last patient out (months): 48<br>Time for data clearance and analysis (months): 3<br>Duration of the entire trial (months): 57 (6 preparation, 48 study, 3 analysis) |
| PARTICIPATING CENTERS | To be involved (n): 3<br>High volume centers with expertise in treatment of advanced gastrointestinal cancer |

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

**AIO-STS/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-assoziierte Studie**

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| Studiennummer/-Code: | AIO-STS/TF-0117/ass - NCT-PMO-1603 |
| Status: | rekrutierend |
| Rekrutierungszeitraum: | 2018 – 2020 |
| Weitere Zentren: | sind möglich |
| Letzte Aktualisierung | November 2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk<br>National Center of Tumor diseases, Heidelberg |
| CONDITION | • Advanced or recurrent solid tumors harboring DNA repair deficiencies<br>• Relapsed and metastatic solid tumors with homologous recombination DNA repair deficiency |
| OBJECTIVE(S) | **Primary objective**<br>To assess clinical activity of combination therapy with trabectedin and olaparib in adult patients with advanced or recurrent solid tumors harboring DNA repair deficiency. Clinical efficacy is determined by disease control rate (DCR) at week 16 after five 21-days cycles of treatment in the experimental arm and either also after five 21-days cycles or alternatively four 28-days cycles in the physician's choice arm.<br><br>**Secondary objectives**<br>• To assess progression-free survival (PFS) of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice in adult patients with advanced or recurrent solid tumors harboring DNA repair deficiency.<br>• To assess overall survival (OS) of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice in adult patients with advanced or recurrent solid tumors harboring DNA repair.<br>• To assess Tumor Response Rate (TRR) including CR and PR according RECIST v1.1 criteria after 16 weeks of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice in adult patients with advanced or recurrent solid tumors harboring DNA repair deficiency.<br>• Safety/tolerability of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice.<br>• Quality of life of patients treated with combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice. |
| INTERVENTION(S) | combination therapy with trabectedin and olaparib vs. physician´s choice |
| KEY EXCLUSION CRITERIA | • Hematological 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 symptomatic uncontrolled brain metastases and patients with symptomatic uncontrolled spinal cord compression are not eligible. Patients with previously treated brain metastases are eligible, provided that the patient |

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| | has not experienced a seizure or had a clinically significant change in neurological status within the three months prior to enrollment. All patients with previously treated brain metastases 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<br>• Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years<br>• Concurrent or previous treatment within 28 days in another interventional clinical trial<br>• Treated with an investigational anticancer therapy less than 6 weeks prior to study enrollment<br>• Prior treatment with PARP inhibitors<br>• Persistent toxicity (≥Grade 2 according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) caused by previous cancer therapy, excluding alopecia<br>• Clinical signs of active infection (>Grade 2 according to CTCAE version 5.0)<br>• History of HIV infection and immunocompromised patients<br>• Viral active or chronic hepatitis (HBV or HCV)<br>• Dementia or significant impairment of cognitive state<br>• Epilepsy requiring pharmacologic treatment<br>• Pregnancy and breast feeding (women)<br>• Inability to take oral medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication<br>• Major surgery within 4 weeks of starting study treatment. Patients must have recovered from any effects of any major surgery.<br>• Patients receiving any systemic chemotherapy or radiotherapy within 2 weeks prior to study treatment or a longer period depending on the defined characteristics of the agents used<br>• Known hypersensitivity to any of the study drugs or other ingredients of the investigational medicinal products<br>• Resting ECG with QTc > 450 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome<br>• Heart failure NYHA III/IV<br>• Severe obstructive or restrictive ventilation disorder<br>• Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.<br>• Concomitant use of known strong CYP3A inducers (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort ) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. |
| KEY INCLUSION CRITERIA | • Provision of a written informed consent |

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| | • Patients is able to understand and comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations<br>• Diagnosis of locally advanced or metastatic malignancy<br>• At least one measurable lesion that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment<br>• Prior administration of at least one standard treatment for primary and/or relapsed malignancy according to current guidelines<br>• Eastern Cooperative Oncology Group Performance Status ≤ 1<br>• Male or female patient aged ≥ 18 and ≤ 70 years<br>• Postmenopausal or evidence of non-childbearing status. For women of childbearing potential: negative urine or serum pregnancy test within 14 days prior to study treatment and confirmed prior to treatment on day 1 of every cycle.<br>Postmenopausal or evidence of non-childbearing status is defined as:<br>o Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments<br>o Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the postmenopausal range for women under 50<br>o Radiation-induced oophorectomy with last menses >1 year ago<br>o Chemotherapy-induced menopause with >1 year interval since last menses<br>o Surgical sterilisation (bilateral oophorectomy or hysterectomy)<br>• Female patients of child bearing potential and male patients with partners of child bearing potential, who are sexually active, must agree to the use of highly effective forms of contraception. This should be started from the signing of the informed consent and continue throughout period of taking study treatment and for 1 month (female patients) / 3 months (male patients) after last dose of study drug.<br>• Identification of defective DNA repair via Homologous Recombination, as determined by molecular analysis within NCT/DKTK MASTER (Heidelberg Ethics Committee Reference No.: S-206/2011). Eligibility for the study is defined based on whole-exome/genome sequencing and the presence of “BRCAness” as defined in chapter **Fehler! Verweisquelle konnte nicht g efunden werden.**<br>• Adequate bone marrow, renal, and hepatic function defined by laboratory tests within 14 days prior to study treatment:<br>o Hemoglobin ≥ 10 g/dl with no blood transfusion in the past 28 days<br>o Neutrophil count ≥ 1,500/mm$^3$<br>o Platelet count ≥ 100,000/µl<br>o Bilirubin ≤ 1.0 x upper limit of normal (ULN)<br>o ALT and AST ≤ 2.5 x ULN<br>o Alkaline phosphatase ≤ 2.5 x ULN<br>o PT-INR/PTT ≤ 1.5 x ULN<br>o Albumin ≥ 25 g/l<br>o Creatine kinase ≤ 2.5 x ULN<br>o Serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 ml/min [3] |
| OUTCOME(S) | Clinical efficacy, determined by disease control rate (DCR) at week 16 after five 21-days cycles of treatment |

[3] $Estimated\ creatinine\ clearence = \frac{(140 - age\ [years]) \times weight\ [kg] \times F}{serume\ creatinine\ \left[\frac{mg}{dL}\right] \times 72}$

where $F = 0.85$ for females and $F = 1$ for males

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| 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.<br>Efficacy evaluation involves a two-group comparison of DCR between experimental arm E (DCRE) and control arm C (DCRC). The null hypothesis is H0: DCRE - DCRC ≤ 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<br>Duration of the clinical phase: 34 months<br>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 | 1. NCT Heidelberg, Prof. Dr. Stefan Fröhling, Dr. Stefan Gröschel<br>2. Universitätsklinikum Dresden, Dr. Gunnar Folprecht, Dr Stephan Richter<br>3. Charité Berlin, Prof. Dr. Ulrich Keilholz, Dr. Sebastian Ochsenreither<br>4. Uniklinik Essen, Prof. Dr. Sebastian Bauer, Prof. Dr. Jens Siveke<br>5. Universitätsmedizin Mainz, Dr. Thomas Kindler<br>6. Universitätsklinikum Frankfurt, Prof. Dr. Christian Brandts<br>7. Universität Tübingen, Dr. Hans-Georg Kopp<br>8. Universitätsklinikum Freiburg, Prof. Dr. Nikolas von Bubnoff<br>9. LMU München, Prof. Dr. Karsten Spiekermann, Dr. Klaus Metzeler |
| current number of patients included | 0 |

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

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| Verantwortlicher Studienleiter nach AMG | Prof. Dr. med. Andrea Tannapfel (molekulare Diagnostik/ Gewebebank)<br>Institut für Pathologie der Ruhr-Universität Bochum<br>Zentrale Gewebebank, Bürkle-de-la-Camp-Platz 1, 44789 Bochum<br>Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809<br>E-Mail: Andrea.tannapfel@rub.de |
| Projektkoordination | Prof. Dr. med. Anke Reinacher-Schick<br>(Leitung klinische Registerdaten)<br>Abteilung für Hämatologie, Onkologie und Palliativmedizin<br>St. Josef-Hospital Bochum, Klinikum der Ruhr-Universität<br>Tel.: 0234-509-3591, Fax:-Nr.: 0234-509-3592<br>E-Mail: onkologie@klinikum-bochum.de |
| Kontaktadresse/ Kontaktperson: | Institut für Pathologie der Ruhr-Universität Bochum<br>Bürkle-de-la-Camp-Platz 1, 44789 Bochum<br>Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809<br>Ansprechpartner:<br>Frau Westphal (0234-302-4924, stephanie.westphal@pathologie-bochum.de) |
| Das vollständige Kurzprotokoll finden Sie unter den Protokollen der AG Kolon-/Rektum-/Dünndarmtumoren | |

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

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

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| Verantwortlicher Studienleiter nach AMG / Kontaktadresse/ | PD Dr. med Michael Quante<br>Klinikum rechts der Isar<br>Technische Universität München<br>II. Medizinische Klinik, Ismaninger Straße 22, 81675 München<br>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**

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| Studiennummer/-Code: | AIO-STS-0415 - MEDISARC |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2018 - 2020 |
| Weitere Zentren: | sind leider nicht möglich |
| Letzte Aktualisierung | Oktober 2018 |

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| Study Type | Open label, randomized, ECOG stratified phase II study |
| Coordinating investigator (LKP) | Prof. Dr. med. Viktor Grünwald<br>Universitätsklinikum Essen<br>Innere Klinik (Tumorforschung) und Klinik für Urologie<br>Hufelandstr. 55<br>45147 Essen |
| Sponsor: | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431, info@aio-studien-ggmbh.de |
| Objectives | Primary objective:<br><br>To assess the efficacy of tremelimumab and durvalumab (MEDI4736) in comparison to doxorubicin in treatment-naïve STS patients<br>Secondary objectives:<br><br>Assessment of safety and tolerability of tremelimumab and durvalumab (MEDI4736) combination therapy<br><br>Exploratory objectives:<br><br>predictive biomarkers for ORR, PFS, OS |
| Endpoints | Primary endpoint:<br>• overall survival<br><br>Secondary endpoints:<br><br>• ORR according to conventional and modified RECIST 1.1<br>• criteria<br>• OS mile stone rate at 24 months<br>• PFS<br>• Duration of response<br>• AEs / SAEs and Treatment Emergent Adverse Events<br>• according to CTCAE 4.03<br>• Health related Quality of Life (HR-QoL - EORTC QLQ-C30) |
| Number of patients | **N=approx. 100 patients**<br>Currently recruited: 16 patients |
| Key inclusion criteria | 1. Histologically confirmed diagnosis of metastatic or advanced soft tissue sarcoma of intermediate or high grade [according to FNCLCC |

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| | score; intermediate=grade 2 score of 4-5 points, high grade = grade 3 score of 6-8 points] with disease progression within 6 months prior to study inclusion:<br>• Fibrosarcoma<br>• Pleomorphic high grade sarcoma (“malignant fibrous histiocytoma”)<br>• Leiomyosarcoma<br>• Liposarcoma (myxoid liposarcoma, dedifferentiated liposarcoma, pleomorphic liposarcoma)<br>• Malignant glomus tumor<br>• Rhabdomyosarcoma, alveolar or pleomorphic (excluding embryonal)<br>• Vascular sarcoma (angiosarcoma)<br>• Synovial sarcoma<br>• High-grade sarcoma, not otherwise specified (NOS)<br>• Malignant peripheral nerve sheath tumors<br>• Other types of sarcoma (not listed as ineligible), if approved by the coordinating investigator / study coordinator.<br>Excluding:<br>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).<br>2. Metastatic or locally advanced STS, not amendable to surgery with curative intention.<br>3. No prior treatment line for advanced or metastatic disease.<br>4. ECOG performance status 0-2<br>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.<br>6. Adequate blood count, liver-enzymes, and renal function:<br>• Haemoglobin ≥ 9.0 g/dL<br>• Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L (> 1500 per $mm^3$)<br>• Platelet count ≥ 100 x $10^9$/L (>100,000 per $mm^3$)<br>• Serum bilirubin ≤ 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 absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.<br>• AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN<br>• Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance<br>7. Adequate cardiac function (left ventricular ejection fraction ≥50% as assessed by ECHO) |
| Key exlusion criteria | 1. Patients who are suitable for anthracycline-based combination therapies<br>2. Cardiac events such as arrhythmias, myocardial infarction, CHF, apoplexy, lung embolism within 6 months prior to study treatment<br>3. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia’s correction<br>4. Uncontrolled severe hypertension (failure of diastolic blood pressure to fall below 100 mmHg and systolic blood pressure >160 mmHg)<br>5. Previous malignancy (other than STS) which either progresses or requires active treatment. |

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| | 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].<br>6. History or clinical evidence of CNS metastases<br>Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:<br>a) are asymptomatic and<br>b) have no requirement for steroids 6 weeks prior to start of study treament. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases<br>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.<br>8. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)<br>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)<br>10. Any previous treatment with a PD-1 or PD-L1 or CTLA-4 inhibitor, including durvalumab and tremelimunab<br>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<br>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) ≤ 21 days prior to the first dose of study drug or ≤4 half-lifes of the agent administered, which ever comes first. |
| Scheme of therapy | For all IMPs a flat dosing regimen will be implemented.<br><br>Cycles/courses 1-3:<br>Durvalumab 1.5g q4wks<br>Tremelimumab 75 mg q4wks<br><br>Cycles/courses ≥4:<br>Durvalumab 1.5g q4wks<br>Tremelimumab 75 mg q12wks<br><br>Active comparator for randomized part:<br>Doxorubicin 75 mg/m$^2$ q3wks for 6 courses<br><br>Treatment will be given until progression, intolerance/toxicity, death or end of treatment, whichever occurs first. |

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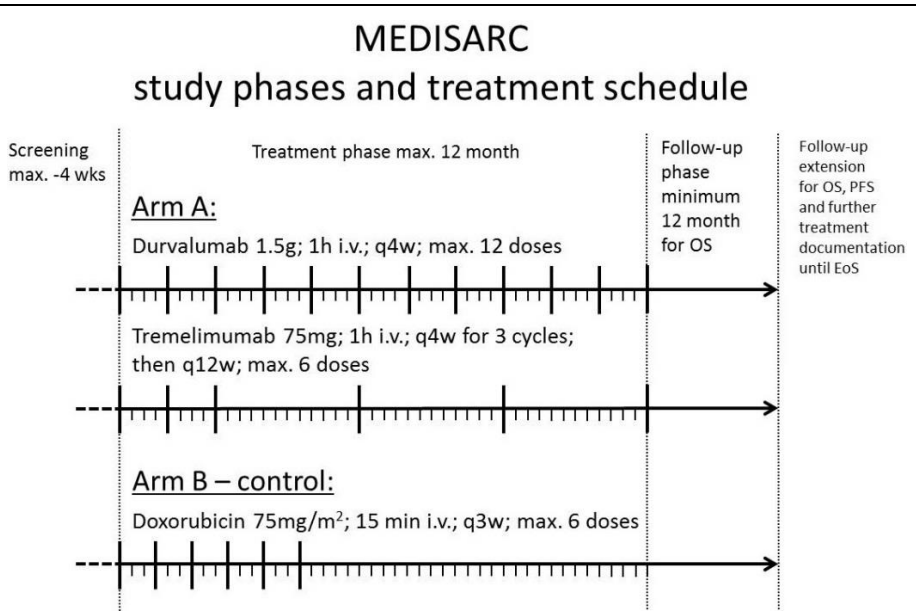
| |  |
| Criteria for tumor evaluation | RECIST 1.1 |
| Rationale | The mainstay of therapy of soft tissue sarcoma (STS) consists of anthracyclines, which achieved an overall survival of 1 year in previous trials (Santoro et al. 1995). This benchmark remains the current standard of therapy in 1st line, 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.<br><br>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.<br>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.<br>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 http://doi.org/10.1158/1078-0432.CCR-15-0491). Furthermore, durvalumab and tremelimumab have shown activity in ongoing early clinical trials. Single agent durvalumab achieved objectve remissions (ORR) in 2/20 (10%), while the combination of durvalumab and tremelimumab showed ORR |

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| | 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 clincial activity of immunotherapies.<br><br>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. |

*Gastrointestinal stromal tumor (GIST)*

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

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| Art der Studie<br>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 intolerability 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<br>Sarcoma Center, West German Cancer Center<br>Hufelandstr. 55, 45122 Essen, Germany<br>sebastian.bauer@uni-due.de, phone: +49-201-72385011<br>fax: +49-201-7235547 |
| Studienziele/<br>Objectives | Primäres Studienziel:<br>• 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 ≥16 weeks per modified response evaluation criteria in solid tumors (RECIST 1.1 [Demetri et al., 2012]) as a measure of disease control<br>• 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 |

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| | secondary resistance mutations in other exons or no resistance mutations (as measured by liquid biopsy in circulating DNA)<br>Sekundäre Studienziele:<br>• To assess progression-free survival (PFS) in each cohort and in the total patient population<br>• To assess objective response rate (ORR) in each cohort and in the total patient population<br>• To assess overall survival (OS) in each cohort and in the total patient population<br>• To evaluate the safety and tolerability of ponatinib in the total patient population<br>• To assess Quality of Life<br>• To assess limited elements of pharmacokinetics (PK) in the total patient population<br>Exploratory<br>• To explore the relationship between GIST genotype and CBR with ponatinib<br>• To explore the feasibility of detecting mutations in KIT and possibly other cancer-related genes using circulating nucleic acids derived from blood samples<br>To explore the usefulness of “liquid biopsies” to predict treatment response and development of resistance |
| Zielparameter/<br>Objectives | **Primary Endpoint**<br>• 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)<br>**Secondary Endpoints**<br>• PFS in each cohort and in the total patient population<br>• ORR (CR + PR) in each cohort and in the total patient population<br>• OS in each cohort and in the total patient population<br>• Safety and tolerability of ponatinib<br>• QoL<br>**Exploratory Endpoints**<br>• Molecular genetic features of GIST at baseline and after treatment with ponatinib<br>Monitoring of treatment response and resistance using “liquid biopsies” |
| Patientenzahl<br>Number of patients | Geplant: 60 Patienten<br>Bereits eingeschlossen: 9 |
| Rekrutierungzeitraum | Qu4/2016 – Qu4 2017 |
| Weitere teilnehmende Zentren erwünscht? | 4 Deutsche Zentren, 3 europäische Zentren |
| Haupt-Einschlusskriterien<br>/<br>Key inclusion criteria | 1. Male or female patients ≥18 years old<br>2. GIST with failure or intolerance to imatinib defined as:<br>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<br>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<br>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 |

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| | measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment<br>4. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2<br>5. Adequate hepatic function as defined by the following criteria:<br>a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome<br>b. ALT ≤2.5×ULN or ≤5.0xULN if liver metastases are present<br>c. AST ≤2.5×ULN or ≤5.0xULN if liver metastases are present<br>6. Adequate renal function as defined by the following criterion:<br>a. Serum creatinine <1.5×ULN<br>7. Adequate pancreatic function as defined by the following criterion:<br>a. Serum lipase and amylase ≤1.5×ULN<br>8. For patients of childbearing potential, a negative pregnancy test must be documented prior to enrollment<br>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<br>10. Provision of written informed consent<br>11. Willingness and ability to comply with scheduled visits and study procedures<br>12. Fully recovered (≤ Grade 1 or returned to baseline or deemed irreversible) from the <u>acute</u> effects of prior cancer therapy before initiation of study drug |
| Haupt-Ausschlusskriterien / Key exlusion criteria | 1. Major surgery within 28 days prior to initiating therapy<br>2. History of bleeding disorder<br>3. History of acute pancreatitis within 1 year of study or history of chronic pancreatitis<br>4. History of alcohol abuse<br>5. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL)<br>6. Clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:<br>a. Myocardial infarction within 6 months prior to enrollment<br>b. Unstable angina within 6 months prior to enrollment<br>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<br>d. History of clinically significant (as determined by the treating physician) atrial arrhythmia<br>e. Any history of ventricular arrhythmia<br>f. Cerebrovascular accident or transient ischemic attack within 6 months prior to enrollment<br>g. Any history of peripheral arterial occlusive disease requiring revascularization<br>h. Venous thromboembolism including deep venous thrombosis or pulmonary embolism within 6 months prior to enrollment<br>7. Uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic >140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control<br>8. Taking medications that are known to be associated with Torsades de Pointes (Appendix A)<br>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)<br>10. Ongoing or active infection. This includes but is not limited to the requirement for intravenous antibiotics<br>11. Known history of human immunodeficiency virus. Testing is not required in the absence of prior documentation or known history<br>12. Pregnant or breastfeeding<br>13. Malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drugs |

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| | 14. Individuals with a history of a different malignancy, other than cervical 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.<br>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<br>16. Any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the drug<br>17. History of apoplectic insult |
| Scheme of therapy | Ponatinib 30mg qd |
| Criteria for evaluation | RECIST |
| Rationale | 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-α (PDGFR-α) 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.<br><br>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.<br><br>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 ≥30% 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 ≥5% 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).<br><br>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 hematologic response (MaHR). Overall, 57% of patients with AP-CML (58% |

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| | 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.<br><br>Safety in the phase 2 trial was consistent with the phase 1 trial. The most commonly reported treatment-emergent AEs experienced by ≥30% of patients were the following: thrombocytopenia/platelet count decreased, rash, abdominal pain, headache, dry skin, and constipation. The most common SAEs in ≥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.<br><br>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 Iclusig-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.<br><br>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 ≥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 milde with most common (≥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 ≥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.<br><br>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.<br><br>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 ≥ 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.<br><br>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-assoziierte Studie**

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| Studiennummer/-Code: | AIO-STS-0317/ass |
| Status: | in Rekrutierung |
| Rekrutierungszeitraum: | 2017 – 2019 |
| Weitere Zentren: | sind derzeit leider nicht möglich |
| Letzte Aktualisierung | 23.10.2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | The Scandinavian Sarcoma Group (SSG)/<br>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) | **Primary:**<br>• Recurrence-free survival (RFS) after randomisation.<br>**Secondary:**<br>• Overall survival.<br>• GIST-specific survival.<br>• Adverse events (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).<br>• Quality of life<br>**Exploratory:**<br>• Effect of tumour site on RFS.<br>• Effect of tumour mutation type on RFS.<br>• Effect of imatinib dose at randomisation on RFS.<br>• To evaluate tumour tissue and blood molecular markers in prediction of GIST recurrence. |
| INTERVENTION(S) | **Arm A: Imatinib**<br>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.<br>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.<br>**Arm B: No imatinib**<br>No imatinib or other anti-cancer treatment will be administered in the adjuvant setting |
| KEY EXCLUSION CRITERIA | 1. Presence of distant metastases or local recurrence of GIST.<br>2. Not willing to donate tumour tissue and/or blood samples for the study molecular studies.<br>3. Presence of a substitution mutation at PDGFRA codon D842 (usually D842V).<br>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. |

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| | 5. Prior adjuvant (+ neoadjuvant) therapy with imatinib mesylate for at least 35 months has not been completed, or the total duration of prior adjuvant (+ neoadjuvant) imatinib administration exceeds the total duration of 38 months.<br>6. Neoadjuvant imatinib for a duration that exceeds 12 months.<br>7. Longer than 4-week break during adjuvant imatinib administration.<br>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.<br>9. Patient has received any investigational anti-cancer agents during adjuvant imatinib or between completion of adjuvant imatinib and the date of randomisation.<br>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, a small (2 cm or less in diameter) nodenegative<br>breast cancer (pT1N0M0), a low Gleason<br>score (<8) local (T1 or T2) prostate cancer. Recent existence of any other malignant disease is not allowed.<br>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).<br>12. Female patients who are pregnant or breast-feeding.<br>13. Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, severe chronic renal disease, or active uncontrolled infection).<br>14. Known diagnosis of human immunodeficiency virus (HIV) infection.<br>15. Patient with a significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.<br>16. Patients with chronic or active hepatitis B.<br>17. Patients that have been committed to an institution by official or judicial order.<br>18. Patients that are dependent upon the sponsor, the trial site or the investigator. |
| KEY INCLUSION CRITERIA | 1. Age ≥ 18 years.<br>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).<br>3. Macroscopically complete surgical resection of GIST (either R0 or R1 resection).<br>4. Mutation analysis of KIT and PDGFR genes has been carried out.<br>5. A high risk of GIST recurrence, either<br>1) gastric GIST with mitotic count >10/50 HPFs, or<br>2) non-gastric GIST with mitotic count >5/50 HPFs, or<br>3) non-gastric GIST treated with neoadjuvant<br>imatinib and initially larger than 10 cm<br>4) tumour rupture<br>Tumour rupture (spillage of the tumour contents into the abdominal cavity) may have occurred either before or at surgery.<br>6. ECOG performance status ≤ 2.<br>7. Adequate organ function, defined as serum total bilirubin <1.5 x ULN (upper limit of normal), serum AST (SGOT) and ALT (SGPT) <2.5 x ULN, creatinine <1.5 x ULN; blood ANC (neutrophil count) ≥1.0 x 109/L, platelet count ≥100 x 109/L.<br>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 |

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| | 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.<br>9. Patient willing to be followed up at the study site regardless of the result of randomisation.<br>10. Patient has provided a written, voluntary informed consent prior to study-specific screening procedures. |
| OUTCOME(S) | **Primary:**<br>• 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.<br>**Secondary:**<br>• Overall survival (the time period between the date of randomisation and the date of death).<br>• 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).<br>• Safety (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).<br>• Quality of Life (EQ-5D instrument).<br>**Exploratory:**<br>• Effect of the tumour mutation type on RFS.<br>• Effect of tumour site on RFS.<br>• Effect of the imatinib dose at randomisation on RFS.<br>• Tumour tissue and blood molecular markers in prediction of GIST recurrence. |
| STUDY TYPE | Open-label, 2-arm, prospective, randomised,<br>multicentre phase III trial.<br>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<br>imatinib will be randomly allocated to one of the following 2 arms in a 1:1 ratio:<br>**A.** to further 24 months of adjuvant imatinib (i.e. the planned total duration of adjuvant imatinib is 5 years)<br>**B.** to stop imatinib (i.e. the planned total duration of adjuvant imatinib is 3 years)<br>The study participants will be followed up for a minimum of 10 years post-randomisation or until death. |
| STATISTICAL ANALYSIS | 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). |
| SAMPLE SIZE | 300 patients to be randomised in 1:1 ratio, 150 to imatinib for further 24 months and 150 to stop imatinib |
| TRIAL DURATION | 2 years of recruitment followed by 10 years follow up after randomization |
| current number of patients included | 88 pts..recruited – 7 in Germany – Stand 23.10.2018 |

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| Number of sites | 9 German sites, 8 sites opened, 1 planned Q4/2018 |

*Chordome, Knochensarkome, fortgeschrittene Erkrankung*

**AIO-STS-0217/ass: CDK4/6 inhibition in locally advanced/metastatic chordoma - NCT-PMO-1601**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | AIO-STS-0217/ass - NCT-PMO-1601 |
| Status: | rekrutierend |
| Rekrutierungszeitraum: | 2018– 2020 |
| Weitere Zentren: | möglich |
| Letzte Aktualisierung | November 2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk<br>National Center of Tumor diseases, Heidelberg |
| CONDITION | locally advanced/metastatic chordoma |
| OBJECTIVE(S) | 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.<br>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.<br>Secondary Objectives include:<br>• Tumor Response (TR)<br>• Progression-free Survival (PFS)<br>• Overall Survival (OS)<br>• Safety/tolerability<br>• Quality of Life |
| INTERVENTION(S) | Palbociclib (CDK4/6-inhibition) |
| KEY EXCLUSION CRITERIA | • Prior treatment with palbociclib or known intolerance/allergy to the compound or any ingredient (acquired or hereditary).<br>• Co-therapy with strong/potent CYP3A inducers and/or inhibitors, (e.g., clarithromycin, indinavir, itraconazol, ketoconazol, lopinavir/ritonavir, nefazodon, nelfinavir, posaconazol, saquinavir, telaprevir, telithromycin, voriconazol, and St. John's Wort [Hypericum perforatum]))<br>• Co-therapy with corticosteroidsabove 7.5 mg prednisolone/prednisone or 30 mg hydrocortisone.<br>• Organ insufficiency: creatinine clearance <30ml/min; total bilirubin >1.5x upper normal serum level; AST > upper normal serum level; abnormal blood counts; heart failure (New York Heart Association (NYHA) III/IV); uncontrolled hypertension; unstable angina; serious cardiac arrhythmia; severe obstructive or restrictive ventilation disorder<br>• Uncontrolled infection<br>• 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.<br>• Severe neurologic or psychiatric disorder interfering with ability of giving informed consent<br>• Known or suspected active alcohol or drug abuse |

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| | • Known positivity for HIV, active HAV, HBV, or HCV infection<br>• Cytopenia: platelets <100 G/l, neutrophils <1.0 G/l, hemoglobin <10.0 g/dl<br>• corrected QT interval ($QTc_B$) >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 $QTc_B$ prolongation or Torsade de Pointes<br>• Uncontrolled electrolyte disorders that can aggravate the effects of a $QTc_B$-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia)<br>• Participation in other ongoing interventional clinical trials (according to AMG). |
| KEY INCLUSION CRITERIA | • 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.<br>• At least one measurable tumor lesion according to RECIST 1.1 criteria<br>• Loss of p16 determined immunohistochemically or CDKN2A/B genomically, presence of CDK4/6 and RB1 determined immunohistochemically or by RNA sequencing.<br>• Age ≥ 18 years, no upper age limit<br>• 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)<br>• No chemotherapy two weeks before study entry<br>• 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).<br>• Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or use a highly effective method of birth control (e.g. double barrier contraceptive method (IUD, condome), tubal ligation, or partner's vasectomy) while on therapy and for 14 weeks 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 14 weeks after end of treatment.<br>• 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 14 weeks after therapy is stopped, even if they have undergone successful vasectomy. Sperm donation is not permitted for the same time interval.<br>• Signed written informed consent<br>• Performance status ≤ 2 according to ECOG/WHO criteria<br>• Ability of patient to understand the character and individual consequences of clinical trial |
| 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 | The study is a phase II trial with standard palbociclib dose of 125 mg once daily for 21 days in a 28-day cycle.<br><br>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 $\alpha = 0.05$, the type II error at $\beta = 0.2$. Here, the null hypothesis that the true response rate is less or equal to $p_0 =$ |

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| | 0.1 will be tested against a one-sided alternative, where the desirable level of response is 0.25.<br><br>In the first stage, $n_1$ = 18 patients will be accrued. If there are $r_1$ = 2 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 n = 43 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. |
| SAMPLE SIZE | 18 in the first stage<br>25 in the second stage (only if first stage was positive)<br>Total sample size: minimum 18 patients; maximum 43 patients |
| TRIAL DURATION | Total trial duration: 48 months<br>Duration of the clinical phase: 36 months |
| PARTICIPATING CENTERS | 1. Universitätsklinikum Heidelberg, Prof. Dr. med. Stefan Fröhling<br>2. Universitätsklinikum Essen, Dr. med. Rainer Hamacher<br>3. Universitätsklinikum Ulm, Dr. Verena Gaidzik |
| CURRENT NUMBER OF PATIENTS INCLUDED | 7 (Okt. 2018) |

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

### AIO-STS/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-assoziierte Studie** | |
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| Studiennummer/-Code: | AIO-STS/TF-0117/ass - NCT-PMO-1603 |
| Status: | rekrutierend |
| Rekrutierungszeitraum: | 2018 – 2020 |
| Weitere Zentren: | sind möglich |
| Letzte Aktualisierung | November 2018 |

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| APPLICANT/ COORDINATING INVESTIGATOR | Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk<br>National Center of Tumor diseases, Heidelberg |
| CONDITION | • Advanced or recurrent solid tumors harboring DNA repair deficiencies<br>• Relapsed and metastatic solid tumors with homologous recombination DNA repair deficiency |
| Das vollständige Kurzprotokoll finden Sie unter den Studien der Arbeitsgruppe **Translationale Forschung**. | |

# Young Medical Oncologists

*Erstlinie Cholangiokarzinom*

**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)**

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| **AIO**-Studie | Eine Studie der Young-Medical-Oncologists (YMO) |
| Studiennummer/ - Code | AIO-YMO/HEP-0315 - NIFE |
| Status: | 22 Patienten rekrutiert, 22 randomisiert, 18 Zentren offen, Initiierungen laufen |
| Rekrutierungszeitraum: | 2017 - 2019 |
| Weitere Zentren: | 2 Plätze frei, bei Interesse bitte bei der AIO-Studien-gGmbH melden |
| Letzte Aktualisierung: | Oktober 2018 |

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| National Coordinating Investigator | Dr. med. Thomas J. Ettrich<br>Klinik für Innere Medizin I<br>Universitätsklinikum Ulm<br>Albert-Einstein-Allee 23, 89081 Ulm, Germany<br>Phone: +49 731 500 44501, Fax.: +49 731 500 44502<br>E-Mail: thomas.ettrich@uniklinik-ulm.de |
| Sponsor | AIO-Studien-gGmbH<br>Kuno-Fischer-Straße 8, 14057 Berlin, Germany<br>Phone: +49 30 814534435, Fax +49 30 322932926<br>E-Mail: info@aio-studien-ggmbh.de |
| Study design | Open label, non-comparative, randomized, multicenter phase II trial |
| Start date | FPI Januar 2018 |
| Duration of study | Enrollment: 18 months<br>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 1st-line treatments. |
| Total number of sites | 30 |
| Primary objective | To determine whether a combination of 5-FU and nal-IRI prolongs progression-free survival in patients with locally advanced or metastatic adenocarcinoma of the biliary tract |
| Secondary objectives | • Overall progression free survival according to RECIST 1.1<br>• Overall survival<br>• Disease control rate according to RECIST 1.1<br>• Proportion of patients with an objective response according to RECIST 1.1<br>• Toxicity/Safety according to CTC-AE-criteria (≥ Grade 3/4)<br>• Health related quality of life, anxiety and depression status (EORTC QLQ-BIL21, QLQ-C30 and HADS-D questionnaires)<br>• Retrospective correlation of resectability in accordance with a central surgical board compared to local surgical review<br>• Retrospective central radiological review |
| Planned | N=92 total (n=46 per treatment arm) |

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| sample size | |
| Inclusion criteria | 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<br>4. Age ≥ 18 years at time of study entry<br>5. Histologically confirmed, non-resectable, locally advanced or metastatic adenocarcinoma of the intrahepatic or extrahepatic biliary tract<br>6. Non-resectability has to be stated by local interdisciplinary tumor board<br>7. Measurable or assessable disease according to RECIST 1.1<br>8. ECOG performance status 0-1<br>9. Life expectancy of more than 3 months<br>10. If applicable, adequately treated biliary tract obstruction before study entry with total bilirubin concentration ≤ 2 x ULN<br>11. Adequate blood count, liver-enzymes, and renal function:<br>• White blood cell count ≥ 3.5 x 106/mL<br>• Platelet count ≥ 100 x 109/L (>100,000 per mm3)<br>• AST (SGOT)/ALT (SGPT) ≤ 5 x institutional upper limit of normal<br>• Serum Creatinine ≤ 1.5 x institutional ULN and a calculated glomerular filtration rate ≥ 30 mL per minute<br>12. Patients not receiving therapeutic anticoagulation must have an INR < 1.5 ULN and PTT < 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<br>13. No prior palliative chemotherapy for biliary tract cancer<br>14. No adjuvant treatment within 6 months prior to study entry<br>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. |
| Exclusion criteria | 1. Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes<br>2. Premalignant hematologic disorders, e.g. myelodysplastic syndrome<br>3. Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment<br>4. Prior (<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].<br>5. Pre-existing lung disease<br>6. History or clinical evidence of CNS metastases<br>Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria:<br>a) are asymptomatic and<br>b) have no requirement for steroids 6 weeks prior to start of study treament. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases<br>7. History of hypersensitivity to any of the study drugs or any of the constituents of the products<br>8. Known dihydropyrimidine dehydrogenase (DPD) deficiency<br>9. Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy<br>10. Severe non-healing wounds, ulcers or bone fractions<br>11. Evidence of bleeding diathesis or coagulopathy<br>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.<br>13. Medication that is known to interfere with any of the agents applied in the trial. |

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| | 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 β-HCG) at Screening.<br>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<br>16. Known Gilbert-Meulengracht syndrome<br>17. Known chronic hypoacusis, tinnitus or vertigo<br>18. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lifes of previously used trial medication, whichever is of longer duration.<br>19. Previous enrollment or randomization in the present study (does not include screening failure).<br>20. Any other chemotherapy at study start<br>21. Involvement in the planning and/or conduct of the study (applies to both Baxalta staff and/or staff of sponsor and study site)<br>22. Patient who might be dependent on the sponsor, site or the investigator<br>23. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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 and active comparators | • IRINOTECAN LIPOSOME (MM-398, nal-IRI)<br>• 5-Fluorouracil (5-FU)<br>• Leucovorin (calcium folinate)<br>• Cisplatin<br>• Gemcitabine |
| Treatment schedule | <u>Experimental intervention (Arm A):</u><br>• Nal-IRI 80 mg/m2 as a 1.5 hour infusion<br>• 5-FU 2400 mg/m2 as 46 hour infusion<br>• Leucovorin 400 mg/m2 as 0.5 hour infusion<br>• Cycle q2w<br><br><u>Control intervention – standard arm (Arm B):</u><br>• Cisplatin 25 mg/m$^2$ as 1 hour infusion on D1, D8<br>• Gemcitabine 1000 mg/m$^2$ as 0.5 hour infusion on D1, D8<br>• Cycle q3w<br>Treatment until progressive disease or intolerable toxicity.<br><br>Key study procedures (and routine procedures):<br>• Tumor assessment according to standard of care q8w<br>• QoL every new cycle; EORTC QLQ-BIL21, QLQ-C30 and HADS-D<br>• Core biopsy<br>• 2x 7.5 mL EDTA blood sample, 7.5 mL serum, 10 mL PaxGene-ccfDNA by Qiagen® |
| 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 | • Overall Progression-free survival<br>• 3-years overall survival<br>• Disease control rate according to RECIST 1.1 after 2 months<br>• Objective tumor response rate (ORR) according to RECIST 1.1<br>• Toxicity/Safety according to CTC-AE-criteria (≥ Grade 3/4) |

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| | • 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<br>• Tumor resectability in accordance with a retrospective central surgical board compared to local surgical review<br>• Radiological response according to RECIST 1.1 and volumetry determined by a retrospective central radiological review |
| Exploratory objectives and endpoints | • Exploratory biomarkers analysis (cfDNA exome sequencing, transcriptome, miRNA-arrays prior to and after start of treatment and upon progress)<br>• Establishment of Predictive/Prognostic biomarker profiles for advanced cholangiocarcioma<br>• Tumor Evolution under systemic therapy |
| Randomization procedure | 1:1<br>Stratified permutated block randomization will be applied to ensure balanced prognostic groups.<br><br>The stratification parameters will be:<br>• Primary site:<br>intrahepatic vs. extrahepatic biliary tract cancer<br>• Disease stage:<br>advanced vs. metastatic<br>• Age ≤ 70 vs. > 70 years<br>• Sex:<br>male vs. female<br>• WHO performance status:<br>ECOG 0 vs. ECOG 1 |
| Rationale Hypothesis | 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 todays 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 gemcitabin/cisplatin.<br>As the tumorbiology of CCC may seems 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.<br><br>Research hypothesis:<br>The combinational therapy of 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. |
| Safety data | • Treatment Emergent Adverse Events according to CTC 4.03<br>• Frequency of abnormal laboratory parameters |

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| Sample size estimation | Simon's optimal two-stage design: $H_0$: less than 40% of patients are progression-free by 4 months of NAL-IRI plus 5-FU/leucovorin. Alternative hypothesis: ≥60% 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, $H_0$ 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, $H_0$ 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 $H_0$ is alpha=10% (significance level) and the probability of falsely accepting $H_0$ - if in real $H_1$ is true - is beta=10% (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 n=46 per treatment arm and a toal N=92 enrolled and randomized patients is required.<br>It is assumed that approx. 120 patients need to be screened for eligibility. |
| Interim analysis | 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, $H_0$ 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. |
| Study plan / time lines | First Patient In (FPI): Q4/2017<br>Last Patient In (LPI): after approx. 18 months<br>Last Patient Last Visit (LPLV): after approx. 24-25 months<br>End of follow-up period after LPLV: after approx. 54 months<br>Study report: after approx. 63 months<br>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**

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| **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 |

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

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| | Sicherheit<br>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 Papillenkarzinome), die eine progrediente Erkrankung unter einer Erstlinienchemotherapie mit Gemcitabin- und platinhaltigen Chemotherapie zeigten. |
| Patientenzahl | Geplant: 56 Patienten<br>Bereits eingeschlossen: 5 (Stand Okt 2018) (in 4 Zentren) |
| Rekrutierungs-zeitraum | Erster Patient eingeschlossen: Mai 2016<br>Rekrutierungsdauer: 24 Monate<br>Therapiedauer: 12 Monate<br>Follow-up-Dauer: alle 6 Wochen bis Tod<br>Studienende: Mai 2019<br>Gesamtdauer: 3 Jahre |
| Haupt-Einschlusskriterien | Einschlusskriterien<br>• Vorherige Einwilligung nach erfolgter Aufklärung vor Einleitung einer studienspezifischen Maßnahme<br>• Patienten mit histologisch-gesichertem inoperablem oder metastasiertem Karzinom der Gallenwege und der Gallenblase.<br>• Progress unter systemischer Chemotherapie mit einem Platinderivat (Oxaliplatin, Cisplatin oder Carboplatin) und Gemcitabin oder Progress ≤ 3 Monate nach Beendigung einer Chemotherapie mit einem Platinderivat und Gemcitabin<br>• Alter ≥ 18 Jahre<br>• ECOG Performance-Status 0-2 (Appendix 21.2)<br>• Adäquate Knochenmarks, Leber- und Nierenfunktion:<br>Neutrophile > 1.500/mm³<br>Hämoglobin > 9 g/dl<br>Thrombozyten > 75 x $10^9$/l<br>INR ≤ 1,5<br>Gesamtbilirubin ≤ 2 mg/dl<br>ALT und AST < 5x ULN<br>Kreatinin < 1,5 x ULN<br>• Child-Pugh Stadium A bei Vorliegen einer Leberzirrhose<br>• Bei Frauen im gebärfähigen Alter ist ein negativer Serum-Schwangerschaftstest erforderlich, der innerhalb von 7 Tagen vor Randomisierung durchgeführt worden sein muss<br>• 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). |
| Haupt-Ausschlusskriterien | Ausschlusskriterien:<br>• Resektabler Primärtumor ohne Nachweis von Fernmetastasen<br>• Vorhergegangene Radiatio oder Radiochemotherapie, transarterielle Chemoembolisation (TACE), Radiofrequenzablation (RFA) oder selektive intraarterielle Radiotherapie (SIRT) innerhalb der letzten 3 Monate außer Radiatio von symptomatischen Knochenfiliae<br>• Begleitende photodynamische Therapie oder intraduktale Radiofrequenzablation innerhalb der letzten 8 Wochen<br>• Child Pugh Status B oder C (> 6 Punkte) bei Vorliegen einer Leberzirrhose (Appendix 21.3)<br>• Massiver, nicht kontrollierbarer Aszites<br>• Vorherige systemische Chemotherapie außer Gemcitabin und Platinderivat (Cisplatin, Carboplatin oder Oxaliplatin)<br>• Herzinsuffizienz > NYHA-Klasse 2 |

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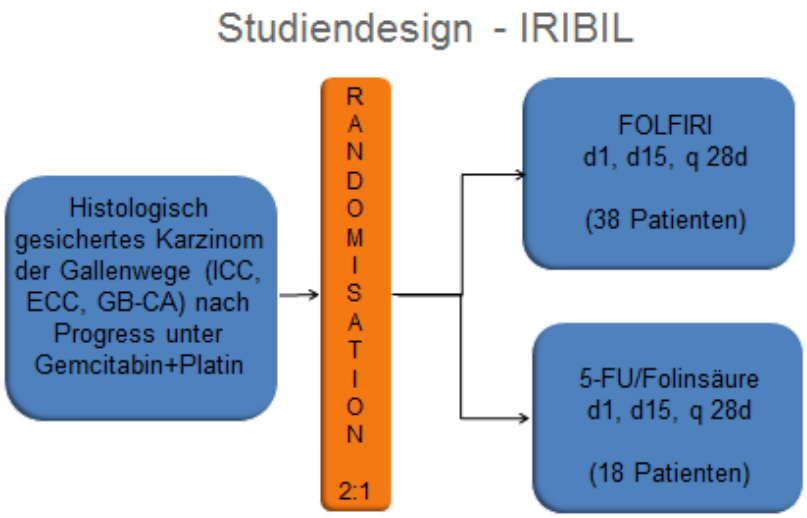
| | • Bekannte Hirnmetastasen, die nicht klinisch kontrolliert sind<br>• Vorhergegangene Organ- oder Stammzelltransplantation<br>• Aktive, unkontrollierte relevante Infektion > CTCAE Grad 2, ausgenommen einer chronischen Hepatitis C-Virusinfektion (Appendix 21.5)<br>• Größere chirurgische Eingriffe innerhalb der letzten 4 Wochen vor Beginn der Chemotherapie, Portimplantation ist erlaubt<br>• Bekannte oder vermutete Allergie gegen 5-FU, Folinsäure, Irinotecan<br>• Eine andere gleichzeitig oder innerhalb der letzten 3 Jahren bestehende Krebserkrankung (Ausnahmen: Zervixkarzinom in situ, behandeltes Basalzellkarzinom, oberflächliches Harnblasenkarzinom)<br>• Drogenmissbrauch, medizinische, psychologische oder soziale Einschränkungen, die die Studienteilnahme behindern können<br>• 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<br>• Schwangerschaft oder stillende Frau<br>• Unfähigkeit einer gültigen, schriftlichen Aufklärung über die Studie (dies trifft auch für Patienten zu, die in einem Abhängigkeitsverhältnis zum Sponsor oder Prüfarzt stehen) |
| Therapieschema |  |
| Tumorevaluierung | RECIST V1.1 |
| Rationale | 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 Analysen vereinzelt auch ein Ansprechen von Tumoren in der Zweitlinientherapie. Weiterhin werden Kombinationschemotherapie mit 5-FU und |

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| | 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. |
| Statistik | Exponentielle Verteilung<br>Medianes PFS 5-FU/folinic acid: 2 Monate<br>Medianes PFS FOLFIRI: 4 Monate<br>Überwachungsdauer: 12 Monate<br>Withdrawal rate: 0.03<br>Type I error (alpha): 0.10 (1-sided)<br>Type II error (beta = 1 – power): 0.20<br>Power: 80%<br>Patientenzahl FOLFIRI: 38<br>Patientenzahl 5-FU/folinic acid 18 |

*Metastatic adenocarcinoma of the lung (non-squamousNSCLC), second line and beyond*

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

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| **AIO-Studie** | 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 | Oktober 2018 |

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

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| Objectives | <u>Primary objective:</u><br>The primary objective is to investigate efficacy of a nivolumab-radiotherapy combination treatment in metastatic non-squamous NSCLC patients.<br><br><u>Secondary objectives:</u><br>• 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.<br>• To collect further efficacy data in patients without necessity of radiotherapy.<br>• To collect information on individual, patient reported and investigator-assessed quality of life.<br>• To explore immune related RECIST criteria as an evaluation method for clinical benefit of nivolumab and nivolumab/radiotherapy.<br><u>Exploratory objectives:</u><br>• Tissue collection and blood sampling whilst course of disease to explore potential predictors of response to nivolumab<br>The following exploratory objectives with regard to biomarkers will be investigated:<br>o PD-L1 assessment<br>o phenotypical analysis of lymphocytes<br>o functional analysis of T-cells<br>o analysis of T-cell receptor specificities<br>o biomarker assessment of tumor IHC beyond PD-L1<br>o soluble pro- and anti-inflammatory markers<br><br>• 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. |
| Endpoints | Primary endpoint:<br>• ORR according to RECIST 1.1 criteria<br><br>Secondary endpoints:<br>• PFS according to RECIST 1.1 criteria<br>• PFS and ORR using assessment according to irRECIST<br>• OS<br>• 1 year OS rate<br>• Descriptive sub-group analyses of efficacy in relation to PD-L1 expression levels (e.g. cut-off 1%, 5%, 10%)<br>• Treatment Emergent Adverse Events according to CTC 4.03<br>• Frequency of abnormal laboratory parameters<br>• QoL [FACT-L] |
| Number of patients | **N=130 total**<br>Currently recruited: 73 |
| Accrual period | Q4/2016 – Q2/2019 (30 months) |
| More centres? | No (Target number: 15) |
| Key inclusion criteria | 14. Age > 18 years at time of study entry.<br>15. ECOG performance status 0-1.<br>16. Patients with metastatic non-squamous non-small cell lung cancer after failure of platinum-based doublet chemotherapy and<br>a) no necessity of radiotherapy (group B) or |

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| | b) the necessity of radiotherapy of a metastatic bone lesion or soft tissue lesion (group A)<br>For details see protocol section 3.2.<br>17. Patients must have measurable disease by CT or MRI per RECIST 1.1 criteria. For details see protocol section 3.2.<br>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. |
| Key exlusion criteria | 1. Patients who require ongoing treatment with more than 10 mg of prednisone (or steroid equivalent, excluding inhaled or topical steroids) daily.<br>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).<br>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.)<br>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).<br>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.<br>6. Brain metastases mandating active treatment in terms of WBI (whole brain irradiation).<br>7. Subjects with brain metastases are eligible if metastases have been treated and treatment has been completed at least 12 weeks before inclusion in this study for group B and 2 weeks for group A. Moreover, there must be no magnetic resonance imaging (MRI) evidence of progression within 28 days prior to the first dose of nivolumab administrationThere must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.<br>8. Known activating EGFR mutation or a known ALK translocation. |
| Scheme of therapy | **Group A:**<br>Nivolumab 240 mg fixed dose (q2w). First dose followed by radiotherapy. Radiotherapy has to start at the latest 72 hours after nivolumab administration.<br>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)<br>**Group B:**<br>Nivolumab 240 mg fixed dose (q2w).<br>• 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. |

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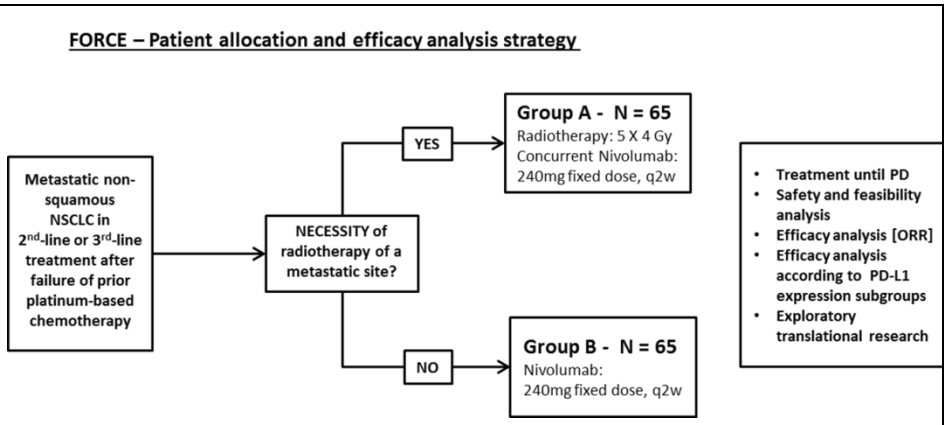
| |  |
| Criteria for tumor evaluation | RECIST 1.1 |
| Rationale | The rationale for the FORCE trial can be synthesized into three interconnected goals:<br>• to determine the safety and feasibility of the radio-immunological treatment approach with particular focus on potential differences between a concurrent and sequential immunological intervention with nivolumab;<br>• 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;<br>• 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.<br>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 ≥1% seemed to segregate patients who substantially benefit form 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.<br><br>**Hypothesis:**<br>The formal treatment-centered hypothesis of this trial is as follows:<br>It is hypothesized that radiotherapy combined with nivolumab is safe and feasible and will improve efficacy of nivolumab through the „abscopal effect”. |
| Statistical considerations | Based on the results of the Checkmate-057 study the following assumptions and hypothesis are formulated.<br><br>Patients treated with nivolumab (all-comer population) have an ORR of 19% during nivolumab treatment (historic control) and those with high PD-L1 expression (≥ 10%) an ORR of 37% (historic control).<br><br>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. |

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| | The study requires N=50 subjects (in Group A) to detect whether the 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 1-beta=0.8, 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.<br><br>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.<br><br>The readouts of the control arm will be used to verify historic data and for descriptive comparative analyses of safety and efficacy.<br><br>After 25 patients have been treated in Group A (nivolumab plus radiotherapy), a descriptive safety report will be done.<br><br>N=130 (N=65 per Arm) |

## *Metastatic non-small cell lung cancer (NSCLC)*

### AIO-YMO/TRK-0416: DURvalumab (MEDI4736) in frAil and elder PaTIents with metastatic Nsclc [DURATION]

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| **AIO-Studie** | Eine Studie der Young-Medical-Oncologists (YMO) |
| Studiennummer/-Code: | AIO-YMO/TRK-0416 - DURATION |
| Status: | In Rekrutierung |
| Rekrutierungszeitraum: | Q4 2017 – Q1 2020 |
| Weitere Zentren: | leider nicht möglich |
| Letzte Aktualisierung | Oktober 2018 |

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| Study design | Open label, treatment stratified and randomized phase II study |
| National Coordinating Investigator | Dr. med. Jonas Kuon<br>Internistische Onkologie der Thoraxtumoren<br>Thoraxklinik – Universität Heidelberg<br>Röntgenstrasse 1, 69126 Heidelberg<br>jonas.kuon@med.uni-heidelberg.de |
| Sponsor | AIO-Studien-gGmbH, Dr. Aysun Karatas<br>Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534431, Fax +49 30 322932926<br>info@aio-studien-ggmbh.de |
| Anticipated start date | Q4/2017 |
| Duration of study | Enrollment: 24 month<br>Treatment and follow-up: 24 month |
| Indication | metastatic non-small cell lung cancer (NSCLC) |

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| Target population | Frail or elderly patients with metastatic NSCLC with no targetable molecular alterations (EGFRwt; ALKtransl-) and not amenable to cisplatinum-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.<br>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 | **N=200 randomized patients in total**<br>Anticipated uninformative drop-outs: 15%<br><br>Currently randomized: 55 |
| Inclusion criteria | 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<br>2. Age ≥ 70 years at time of study entry and/or Charlson-Comorbidity-Index (CCI) >1 and/or Performance status ECOG >1<br>3. Histologically confirmed diagnosis of metastatic NSCLC and no targetable molecular alterations (EGFRwt; ALKtransl-) and not amenable to cisplatinum-based standard-combination chemotherapy.<br>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.<br>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 µm 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.<br>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 >6 months from last therapy.<br>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.<br>8. Adequate blood count, liver-enzymes, and renal function:<br>• Haemoglobin ≥ 9.0 g/dL<br>• Absolute neutrophil count (ANC) ≥ 1.5 x 109/L (> 1500 per mm3)<br>• Platelet count ≥ 100 x 109/L (>100,000 per mm3)<br>• Serum bilirubin ≤ 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 |

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| | absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.<br>• AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN<br>• Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance<br>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. |
| Exclusion criteria | 1. Mixed small-cell lung cancer and NSCLC histology<br>2. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's correction<br>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 >2 years befor 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)<br>4. Pre-existing peripheral neuropathy of Grade ≥ 2<br>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 treatement.<br>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.<br>7. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)<br>8. History of primary immunodeficiency<br>9. History of allogeneic organ transplant<br>10. History of hypersensitivity to durvalumab or any excipient<br>11. History of hypersensitivity to any of the comparator agents<br>12. Medication that is known to interfere with any of the agents applied in the trial.<br>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<br>14. Clinical diagnosis of active tuberculosis<br>15. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab<br>16. Male patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year)<br>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<br>18. Participation in another clinical study with an investigational product during the last 30 days before inclusion<br>19. Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab<br>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 |

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| | 21. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 21 days prior to the first dose of study drug or ≤4 half-lifes of the agent administered, which ever comes first.<br>22. Previous enrollment or randomization in the present study.<br>23. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff of sponsor and study site)<br>24. Patient who might be dependent on the sponsor, site or the investigator<br>25. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.<br>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].<br>27. |
| Investigational agent | • durvalumab (MEDI4736)<br>Comparators and standard chemotherapies:<br>• *nab*-Paclitaxel<br>• gemcitabine<br>• vinorelbine<br>• carboplatin |
| Treatment schedule | Dosage/Timepoints<br>Experimental arms:<br>• Induction: 2 cycles of mono-chemotherapy or combination chemotherapy followed by two cycles durvalumab 1125 mg Q3W<br>• Maintenance: durvalumab 1500 mg Q4W<br>Treatment will be given until progression, intolerance/toxicity, or withdrawel of consent, whichever occurs first.<br><br>Control arms -active comparators (SOC CTx):<br>Mono-chemotherapies:<br>• Vinorelbin 30 mg/m$^2$ D1 + D8 Q3W<br>• Gemcitabine 1000 mg/m$^2$ D1 + D8 Q3W<br><br>Combination chemotherapy:<br>• *nab*-Paclitaxel: 100mg/m$^2$ D1,D8 + Carboplatin AUC 5.0 D1; Q3W<br>Treatment will be given for a maximum of 4 cycles (chemotherapy) or until intolerance/toxicity, progressive disease or withdrawel of consent.<br>**Key study procedures (and routine procedures):**<br>• CARG-score for treatment (stratification) allocation<br>• geriatric assessments (G8-questionnaire, Timed up&go, 6MWT)<br>• HR-QOL (FACT-L)<br>• tumor response evaluation<br>• tumor tissue and blood biomarker assessments |
| Primary endpoint | Rate of treatment related Grade III/IV adverse events (CTCAE V4.03) |
| Secondary endpoints | • ORR according to RECIST 1.1 criteria<br>• Progression free survival (PFS)<br>• Overall survival (OS)<br>• AEs / SAEs according to CTCAE 4.03<br>• Health related Quality of Life (HR-QoL) |
| Stratification | 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:<br>• Total risk score ≤ 3 → combination chemotherapy<br>• Total risk score > 3 → mono-chemotherapy |
| Randomization procedure | 1:1 after CARG-score stratification |
| Rationale | Metastatic non-small cell lung cancer (NSCLC) bears a dismal prognosis with |

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| | 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/m2; 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/m2; 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.<br>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.<br>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.<br><br>Thus an appropriately defined patient population (EGFRwt; ALKtransl-), characterized by:<br>age ≥ 70 and / or<br>Charlson-Comorbidity-Index (CCI) > 1 (frailty) and / or<br>performance status ECOG > 1,<br>not amenable to cisplatinum-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).<br>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.<br>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 |

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| | combination) will serve as a comparator.<br><br>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.<br><br>**Hypothesis:**<br>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. |
| Safety data | • AEs, SAEs and Treatment Emergent Adverse Events according to CTC 4.03<br>• Frequency of abnormal laboratory parameters<br>• Immune related (ir)AEs of special interest will require additional reporting (colitis, hepatitis, hypophysitis, uveitis or pneumonitis, pancreatitis) |
| Sample size<br><br>and<br><br>statistical analysis considerations | Sample size calculation:<br>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 PB+C=0.18. 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 PA+D=0.35. With the planned number of patients of N=200, the assumed difference between these two groups can be detected using a Chi-square test at a two-sided significance level of α=10% with a probability of 1-β=0.80, also taking a dropout rate of 15% into account. Sample size calculation was performed using ADDPLAN v6.1.<br>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.<br><br>Statistical analysis considerations for the primary endpoint:<br>The null hypothesis for the primary (safety) endpoint of the trial is defined as H0: PB+C = PA+D (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 H1: PB+C ≠ PA+D (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 α=0.1 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. |
| Biomarker measurements | • PD-L1 expression and optionally other biomarkers in tumor tissue samples<br>Optional:<br>• phenotypical analysis of lymphocytes by FACS<br>• analysis of T-cell receptor specificities (T-cell receptor sequencing)<br>• mRNA profiling of T-cells<br>• soluble pro- and anti-inflammatory markers and Glycodelin<br>• Analysis of mutational load based on cfDNA |

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| QoL measurements | FACT-L |
| Study plan / time lines | First Patient In (FPI): Q4/2017<br>Last Patient In (LPI): after approx. 24 month<br>Last Patient Last Visit (LPLV): after approx. 48 month<br>End of follow-up period after LPLV: after approx. 48 month<br>Study report: after approx. 60 month<br>Publication: after approx. 63 month |

*AEG-Karzinome, 1st line palliativ*

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

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| **AIO**-Studie | 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 | Oktober 2018 |

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| Study design | Randomized, controlled, parallel-group, open-label, multicenter study |
| Principal Investigators | Dr. Georg Martin Haag<br>NCT- Med. Onkologie, Im Neuenheimer Feld 460, 69120 Heidelberg<br>GeorgMartin.Haag@med.uni-heidelberg.de |
| Sponsor | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>Tel.: 030-322932934, FAX:030-322932926<br>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**

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| **AIO-Studie** | 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 | Oktober 2018 |

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| 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<br>Klinikum rechts der Isar - Technische Universität München<br>II. Medizinische Klinik, Ismaninger Straße 22, 81675 München<br>michael.quante@tum.de |
| Studienziele/ Objectives | 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.<br>2. Bestimmung der Inzidenz der Entwicklung von LG-IEN, HG-IEN und AEG ausgehend von einem BE<br>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.<br>4. Korrelation von epidemiologischen und anamnestischen Faktoren mit der BE-Progression und möglichen Serumparametern. |
| 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<br>Bereits eingeschlossen:<br>Anzahl Studienpatienten: 567 (Stand 15.10.2018)<br>Anzahl Studienproben: 745 (Stand 15.10.2018) |
| Rekrutierungzeitraum | 01/2013 – 12/2023 |
| Weitere teilnehmende Zentren erwünscht? | Ja<br>Rekrutierung weiterer Studienzentren ist in Prozess |

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| | Stand zum 15.10.2018 : initiiert: 22, davon geschlossen: 4, geplante Initiierungen: 1 |
| Haupt-Einschlusskriterien<br>Key inclusion criteria | Alter zwischen 18 und 80 Jahren<br>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)<br>unterschriebene Einwilligungserklärung |
| Haupt-Ausschlusskriterien<br>Key exlusion criteria | andersartige Tumorerkrankung (unabhängig der Therapie)<br>fehlende Zustimmungsfähigkeit zur Studie<br>Kontraindikation zur Biopsie-Entnahme (Thrombozytopenie < 50.000/µl, Quick < 60%, pTT > 50 sec)<br>Patienten in reduziertem Allgemeinzustand |
| Therapieschema<br>Scheme of therapy | **Studienablauf:**<br>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 bioptisch 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<br>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.<br>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 (abhähing von der Definitionangenommen 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-bioptische Kontrollen (sogenannte Surveillance-Endoskopien) empfohlen wurden, um die Entartungssequenz möglichst in einem Frühstadium zu detektieren.<br>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 |

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| | 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 Biomarker, 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. |

*Registerstudie – Duktales Adenokarzinom des Pankreas*

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

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| **AIO-Studie** | Eine Studie der Young-Medical-Oncologists (YMO) |
| Studiennummer/-Code: | AIO-YMO/PAK-0215 - PDAC, PaCaReg |
| Status: | Eingeschlossene Patienten 2 |
| Rekrutierungszeitraum: | Rekrutierung gestartet 10/2018 |
| Weitere Zentren: | bitte wenden Sie sich ggfs. an die Studienleitung |
| Letzte Aktualisierung | Oktober 2018 |

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| **Studienleitung** | Dr. med. Thomas Ettrich<br>Universitätsklinikum Ulm, Klinik für Innere Med. I<br>89081 Ulm, Tel. 0731-500 44774,<br>thomas.ettrich@uniklinik-ulm.de<br>Mentoring Investigator:<br>Univ.-Prof. Dr. Thomas Seufferlein<br>Universitätsklinikum Ulm, Klinik für Innere Medizin I |
| **Studienkollektiv** | Patienten ab dem 18. Lebensjahr mit histologisch oder zytologisch gesichertem PDAC, resektabel (incl. *borderline* resektabel), lokal fortgeschritten oder metastasiert. |
| **Primäre Zielgröße** | • 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 QlQ30 Bogens) |

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| **Sekundäre Zielgrößen** | • Registrierung aller Patienten mit neu diagnostiziertem PDAC an den beteiligten Zentren<br>• Erfassung der definitiven Tumorstadien (TNM-Klassifikation, CRM, UICC-Stadium)<br>• Erfassung klinischer Parameter bei Erstdiagnose und im Verlauf (Tumoransprechen, krankheitsfreies Überleben, progressionsfreies Überleben, Gesamtüberleben, Überleben in Abhängigkeit vom Tumorstadium)<br>• Erfassung epidemiologischer, Patienten-bezogener Basisdaten<br>• Korrelation von Lebensqualität und Therapiekonzept<br>• 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 Univrsitätsklinikums Ulm sowie dem Institut für Pathologie der Universität Ulm/Biobank des Comprehensive Cancer Centers Ulm (CCCU) |
| **Einschlusskriterien** | • Zytologisch oder histologisch gesichertes duktales Adenokarzinom des Pankreas<br>• Alter ≥ 18 Jahre<br>• Schriftliches Einverständnis zur Teilnahme an der Studie |
| **Ausschlusskriterien** | • Papillenkarzinome<br>• Neuroendokrine Neoplasien des Pankreas<br>• PDAC-spezifische Vortherapie, außer Tumorresektion<br>• Schwere neurologische oder psychiatrische Störungen die eine Einwilligungsfähigkeit beeinträchtigen<br>• Kein Einverständnis für die Registrierung, Lagerung und Handhabung der personenbezogenen Krankheitsdaten |
| **Studiendesign** | Registerstudie zur Erfassung epidemiologischer und klinischer Eckdaten und Lebensqualität, sowie Etablierung biologischer Marker bei Patienten mit Erstdiagnose eines duktalen Adenokarzinoms des Pankreas |
| **Datenschutz** | 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. |
| **Zentren** | Kliniken und Praxen in Deutschland, die Patienten mit duktalem Adenokarzinom des Pankreas behandeln |

*Registerstudie – Seltene Maligne Tumoren der Schilddrüse*

**AIO-YMO/ENC-0216 - ThyCa: Multicenter registry study for patients with rare malignant tumors of the thyroid and parathyroid glands**

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| **AIO-Studie** | Eine Studie der Young-Medical-Oncologists (YMO) |
| Studiennummer/-Code: | AIO-YMO/ENC-0216 - ThyCa |
| Rekrutierungszeitraum: | retrospektiv 2000 – 2013, prospektiv seit 2014 |
| Weitere Zentren: | sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Art der Studie<br>Study Type | Retrospective and prospective registry study |
| Kontaktadresse/<br>Kontaktperson: | PD Dr. Dr. Matthias Kroiß<br>Tel.: 0931/201-39740<br>Email: Kroiss_M@ukw.de<br>Universitätsklinikum Würzburg<br>Medizinische Klinik und Poliklinik I<br>Schwerpunkt Endokrinologie/Diabetologie<br>Oberdürrbacher Str. 6<br>97080 Würzburg<br><br>Prof. Dr. Christine Spitzweg<br>Tel.: 089/44 00-73012<br>Email:<br>christine.spitzweg@med.uni-muenchen.de<br>Klinikum der Universität München<br>Medizinische Klinik und Poliklinik IV<br>Marchioninistraße 15<br>81377 München |
| Studienziele/<br>Objectives | Primary objectives:<br>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 (parathyrpod carcinoma). The aim is to improve diagnosis and treatment of patients by definition of<br>- Parameters and biomarkers for diagnosis.<br>- Parameters and biomarkers of treatment response and side effects<br>- Parameters for risk stratification.<br>- Parameters and biomarkers for follow-up<br><br>Secondary objectives:<br>Establishment of<br>- cooperative structures for rare malignant tumors of the thyroid.<br>- a clinical cancer registry for rare malignant tumors of the thyroid at the natio European centers.<br>- Structures to facilitate translational research.<br>- Structures to enable future prospective clinical trials.<br><br>Collaborative evaluation of data collected retrospectively in individual centers. |
| Zielparameter/<br>Objectives | overall survival, disease free survival, time to progression, time to recurrence |
| Patientenzahl<br>Number of patients | not restricted; current recruitment status:<br>MTC: 1060; ATC: 128; PDTC (incl Hürthle-Zellkarzinom): 56; radiojodrefraktäres Schilddrüsenkarzinom: 74; Nebenschilddrüsenkarzinom: 70 |

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| Rekrutierungzeitraum<br>von/bis<br>period of | retrospective: 2000 – 2013<br>prospective: 2014 bis (derzeit geplant) 2028 |
| Weitere teilnehmende Zentren erwünscht?<br>More centres? | Studiengruppe für seltene Tumoren der Schilddrüse und Nebenschilddrüsen - current centers (10/2018):<br>- Klinikum Augsburg<br>- Universitätsspital Basel<br>- Universitätsklinikum Düsseldorf<br>- Gemeinschaftspraxis für Endokrinologie Heidelberg<br>- Universitätsklinikum Halle<br>- Universitätsklinikum Greifswald<br>- Universitätsklinikum Leipzig<br>- Universitätsklinikum Magdeburg<br>- Universitätsklinikum Gießen/Marburg, Standort Marburg<br>- Universitätsklinikum Schleswig-Holstein, Standort Lübeck<br>- Klinikum der Universität München<br>- Diakonie-Klinikum Stuttgart<br>- Helios-Klinik Schwerin<br>- Universitätsklinikum Würzburg<br>- Universitätsklinik Wien<br>- Universitätsspital Zürich<br><br>additional centers are invited to participate |
| Haupt-Einschlusskriterien<br>Key inclusion criteria | Histologically confirmed medullary, poorly differentiated and anaplastic thyroid carcinoma; histologically confirmed differentiated thyroid carcinoma documented to be refractory to radioiodine |
| Haupt-Ausschlusskriterien /<br>Key exlusion criteria | inability to provide informed consent |
| Therapieschema<br>Scheme of therapy | standard of care; investigational therapies |
| Tumorevaluierung<br>Criteria for evaluation | standard of care; per protocol for investigational therapies |
| Rationale | 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.<br>Treatment of parathyroid carcinoma beyond surgery is not established. |
| Statistik<br>(optional) | 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. |

# Arbeitsgruppe ZNS-Tumoren/Meningeosis

*Registerstudie*

**Prospektive Beobachtungsstudie zur Behandlungspraxis des ZNS-Befalls maligner Lymphome in der klinischen Routine (SZNSL Register)**

**AIO-assoziierte Studie**

| | |
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| Studiennummer/-Code: | |
| Status: | In Rekrutierung |
| Rekrutierungszeitraum: | Seit 2011, unbegrenzt |
| Weitere Zentren: | Sind sehr erwünscht |
| Letzte Aktualisierung | Oktober 2018 |

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| Art der Studie | Registerstudie |
| Projektleiter, wiss. Leiter: | Dr. med. Felicitas Strehlow<br>PD Dr. med. Agnieszka Korfel<br>Studienleitung der Deutschen Studiengruppe Primäre ZNS Lymphome (G-PCNSL-SG) - Im Kompetenznetz Maligne Lymphome (KML)<br>Charité Universitätsmedizin Berlin, Campus Benjamin Franklin<br>Medizinische Klinik mit Schwerpunkt Hämatologie und Onkologie<br>Hindenburgdamm 30, 12203 Berlin<br>Tel: 030 450 513447, Fax: 030 8445 2896<br>E-Mail: felicitas.strehlow@charite.de; E-Mail: agnieszka.korfel@charite.de |
| Datenmanagement: | Frau Brigitta Niemer<br>Charité Universitätsmedizin Berlin, Campus Benjamin Franklin<br>Medizinische Klinik mit Schwerpunkt Hämatologie und Onkologie<br>Hindenburgdamm 30, 12203 Berlin<br>Tel: 030 450 513447, Fax: 030 8445 2896<br>E-Mail: brigitta.niemer@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 *et al*, 2000; Colocci *et al*, 2004; Feugier *et al*, 2004; Kasamon *et al*, 2005; van Besien *et al*, 1998; Williams *et al*, 1994a; Hollender *et al*, 2002; Keldsen *et al*, 1996; Bishop *et al*, 1999; Liang *et al*, 1990; Montserrat *et al*, 1996). ZNS-Rezidive aggressiver Lymphome treten überwiegend im ersten Jahr nach Diagnosestellung auf und manifestieren sich zumeist in einem meningealen oder parenchymalen Befall (Kasamon *et al*, 2005; van Besien *et al*, 1998), während ein kombinierter Befall beider Kompartimente eher seltener ist (Haioun *et al*, 2000; Hollender *et al*, 2002; Tilly *et al*, 2003; van Besien *et al*, 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 *et al*, 2000; Bokstein *et al*, 2002; Bollen *et al*, 1997; Colocci *et al*, 2004; van Besien *et al*, 1998; Feugier *et al*, 2004; Johnson *et al*, 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:<br>• Bestrahlung<br>• intrathekale Therapie<br>• systemische Chemotherapie.<br>Abgesehen von 3 prospektiven Studien (Phase II Methotrexat/ Procarbacin/ Cytarabin, Vergleich von MTX und Thiotepa intrathekal sowie von Cytarabin und liposomalem Cytarabin intrathekal) (Bokstein *et al*, 2002; Glantz *et al*, 1999; |

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| | Grossman *et al*, 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 *et al*, 1991; Bokstein *et al*, 2002; Bollen *et al*, 1997; Hoerni-Simon *et al*, 1987; Recht *et al*, 1988; van Besien *et al*, 1998; Zinzani *et al*, 1999; Colocci *et al*, 2004). In der eigenen retrospektiven Analyse konnte ein Langzeitüberleben nur bei intensiv systemisch behandelten Patienten beobachtet werden (Jahnke *et al*, 2005).<br>Prospektive Studien zur Therapie der SZNSL, die über den palliativen Ansatz hinausgehen, fehlen weitgehend. Vor wenigen Jahren wurde eine deutsche Phase II Studie der G-PCNSL-SG beendet (siehe unten). |
| | **Lokale Strahlentherapie** 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 Hämatotoxizität. Eine Ganzhirnbestrahlung zusammen mit einer Hochdosischemotherapie führte zu einem medianen Gesamtüberleben von 10 Monaten und einem 2-Jahres 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). |
| | Eine **intrathekale Therapie** 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 *et al*, 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 *et al*, 1999).<br>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). |
| | **Hochdosischemotherapie mit autologer Stammzelltransplantation**<br>Bei rezidiviertem aggressivem Lymphom ist für das Erreichen einer langanhaltenden Remission eine Hochdosischemotherapie mit Stammzelltransplantation nötig (Philip *et al*, 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, Thiotepa oder Busulfan nur eine geringe ZNS-Gängigkeit besitzen (Busulfan aud Thiotepa |

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| | 80% des Serumspiegels, Carmustin 50–80%, Etoposid 5%, AraC 6–22%, Melphalan 10%; Wiebe 1992).<br>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 *et al*, 2000; Kasamon *et al*, 2005; Williams *et al*, 1994b). In der retrospektiven Auswertung der EBMT fand sich ein entscheidender Einfluss des Remissionsstatus vor der Hochdosischemotherapie für das *outcome* der Patienten mit einem 5-Jahres 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 *et al*, 2013).<br>In der kürzlich abgeschlossenen Phase II Studie der G-PCNSL-SG wurden Patienten <=65J. mit ZNS-Rezidiven aggressiver Lymphome mit folgendem Schema behandelt: |
| | 1-2 Zyklen<br>HDMTX 4 g/m$^2$ (Tag 1)<br>Ifosfamid 2 g/m$^2$ (Tag 3-5)<br>Depocyte 50 mg ith. (Tag 6)<br>Dexamethason 2x4 mg (Tag 6-10)<br>1-2 Zyklen<br>HDAraC 3 g/m$^2$ (Tag 1-2)<br>Thiotepa 40 mg/m$^2$ (Tag 2)<br>Depocyte 50 mg ith. (Tag 3)<br>Dexamethason 2x4 mg (Tag 3-7)<br>gefolgt von einer Hochdosischemotherapie mit:<br>BCNU 400 mg/m$^2$ (Tag -5)<br>Thiotepa 2x5 mg/kg (Tag -4 bis -3)<br>Etoposid 150 mg/m$^2$ (Tag -5 bis -3)<br>und autologer Stammzelltransplantation.<br>Ein Ansprechen wurde mit der gesamten Therapie bei 71% der Patienten erreicht. Die Therapieversagensrate nach 2 Jahren betrug 49% für alle 30 Patienten und 58% für die 24, die tatsächlich transplantiert wurden (Korfel *et al*, Hematologica 2013). Ein kuratives Potential des verwendeten Protokolls wird vermutet. |
| | Diese Therapiebeobachtung ist eine prospektive Studie (prospektives Register). Aus diesem Grund werden weder diagnostische noch therapeutische Maßnahmen vorgeschrieben.<br>Zur besonderen Beachtung: Entsprechend Amendment 1 wird die Frist für die Meldung schwerer unerwünschter Ereignisse komplett aufgehoben. |
| Beobachtungsziel | 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:<br>• Welche Therapieansätze werden verfolgt?<br>• Wie ist das klinische Ergebnis der verschiedenen Behandlungsoptionen?<br>• Wie ist die Frequenz schwerer unerwünschter Ereignisse bei den jeweiligen Therapieansätzen?<br>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, Tumorgewebe und ggf. daraus entnommenem genetischen Material), sofern für |

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| | die Diagnosestellung nicht mehr benötigt, gebeten. |
| Auswahl der Prüfärzte | Die Beobachtungsstudie soll in Kliniken, Ambulanzen und bei niedergelassenen onkologisch tätigen Ärzten durchgeführt werden. Die Prüfärzte 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 bis 2017 ca. 200 Patienten, in den darauffolgenden Jahren ca. 30 Patienten pro Jahr prospektiv eingeschlossen werden. Aktuell sind 226 Pat. eingeschlossen (Stand Okt. 2018). |
| Beobachtungsdauer | Es wird eine Nachbeobachtung des individuellen Patienten von mind. 3 Jahren angestrebt. |
| Rekrutierungszeitraum | Seit Juli 2011. Der Rekrutierungszeitraum ist unbegrenzt. |
| Weitere teilnehmende Zentren erwünscht? | Weitere teilnehmende Zentren sind erwünscht. Es handelt sich um eine Registerstudie, damit kann jedes Zentrum Patienten einbringen. |

# Kontaktadressen der Arbeitsgruppensprecher (alphabetisch)

**CUP-Syndrom**
*Arbeitsgruppensprecher*
Dr. Gerdt Hübner
Sana-Kliniken Ostholstein
Hämatologie und Internistische Onkologie
Mühlenkamp 5, 23758 Oldenburg
Telefon 04361 513632
huebner@aio-portal.de

**Endokrine Tumoren**
*Arbeitsgruppensprecher*
Prof. Dr. Martin Fassnacht
Universitätsklinikum Würzburg
Medizinische Klinik und Poliklinik I
Oberduerrbacher Str. 6, 97080 Würzburg
Tel 0931 201 39021
fassnacht@aio-portal.de

*Arbeitsgruppensprecherin*
Prof. Dr. Christine Spitzweg
Klinikum der Ludwig-Maximilians-Universität München
Medizinische Klinik II
Marchioninistraße 15, 81377 München
Telefon 089 4400 0
spitzweg@aio-portal.de

**Geriatrische Onkologie (gemeinsame AG der DGHO, AIO, DGG)**
*Sprecher für die AIO*
Priv.-Doz. Dr. Ulrich Wedding
Universitätsklinikum Jena
Klinik für Innere Medizin II
Erlanger Allee 101, 07740 Jena
Telefon 03641 9392203
wedding@aio-portal.de

**Hepatobiliäre Tumoren**
*Arbeitsgruppensprecher*
Prof. Dr. Arndt Vogel
Medizinische Hochschule Hannover
Klinik für Gastroenterologie, Hepatologie & Endokrinologie
Carl-Neuberg-Str. 1, 30625 Hannover
Telefon 0511 5329590
vogel@aio-portal.de

**Interdisziplinäre AG Hodentumoren**
*Sprecher für die AIO*
Prof. Dr. Carsten Bokemeyer
Universitätsklinikum Hamburg-Eppendorf
Medizinische Klinik II
Martinistraße 52, 20246 Hamburg
Telefon 040 7410 0
bokemeyer@aio-portal.de

**IAG-N – Interdisziplinäre AG Nierenzellkarzinom**

*Sprecher für die AIO*
Prof. Dr. Viktor Grünwald
Universitätsklinikum Essen
Innere Klinik (Tumorforschung) und Klinik für Urologie
Hufelandtsr. 55, 45147 Essen
Telefon 0201 723 85584
gruenwald@aio-portal.de

**Mammakarzinom und Gynäkologische Tumoren**

*Arbeitsgruppensprecher*
Prof. Dr. Thomas Decker
Onkologische Praxis
Elisabethenstraße 19
88212 Ravensburg
Tel.: 0751 366197-0
decker@aio-portal.de

*Arbeitsgruppensprecherin*
Dr. Anja Welt
Innere Klinik (Tumorforschung)
Hufelandstraße 55
45122 Essen
Telefon 0201 723 3101
welt@aio-portal.de

**Kolon-/Rektum-/Dünndarmkarzinom**

*Arbeitsgruppensprecher*
Prof. Dr. Dirk Arnold
Asklepios Klinik Altona
Hämatologie, internistische Onkologie
und Palliativmedizin
Paul-Ehrlich-Straße 1, 22763 Hamburg
Telefon 040 1818- 810
arnold@aio-portal.de

*Arbeitsgruppensprecherin*
Prof. Dr. Anke Reinacher-Schick
St. Josef-Hospital
Klinikum der Ruhr-Universität Bochum
Abt. für Hämatologie und Onkologie
Gudrunstr. 56, 44791 Bochum
Telefon 0234 509 - 0
reinacher@aio-portal.de

**Kopf-Hals-Tumoren**

*Arbeitsgruppensprecher*
Prof. Dr. Viktor Grünwald
Universitätsklinikum Essen
Innere Klinik (Tumorforschung) und Klinik für Urologie
Hufelandtsr. 55, 45147 Essen
Telefon 0201 723 85584
gruenwald@aio-portal.de

**Lebensqualität und PRO**

*Arbeitsgruppensprecher*
Dr. med. Deniz Gencer, M.Sc.
Universitätsklinikum Mannheim
III. Medizinische Klinik
Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
Telefon 0621 383-4115
deniz.gencer@umm.de

*Arbeitsgruppensprecherin*
Ulli Simone Bankstahl M.Sc.
Krankenhaus Nordwest GmbH
Institut für Klinisch-Onkologische Forschung (IKF)
Steinbacher Hohl 2-26
60488 Frankfurt am Main
bankstahl@aio-portal.de

**Neuroendokrine Tumoren/ Karzinoide im Rahmen der NETWORKs-Arbeitsgruppe**

*Sprecherin*
Prof. Dr. Marianne Pavel
Leitung Endokrinologie
Medizinische Klinik 1
Ulmenweg 18, 91054 Erlangen
0 9131-85 34651
pavel@aio-portal.de

*Arbeitsgruppensprecher*
Prof. Dr. Dieter Hörsch
Zentralklinik Bad Berka GmbH
Zentrum für Neuroendokrine Tumoren Bad Berka
Robert-Koch-Allee 9, 99437 Bad Berka
Telefon 0 36458 5 2601
hoersch@aio-portal.de

**Onkologische Rehabilitation**

*Arbeitsgruppensprecher*
Prof. Dr. Oliver Rick
Klinik Reinhardshöhe
Quellenstr. 8-12, 34537 Bad Wildungen
Telefon 05621 705 154
rick@aio-portal.de

**Onkologische Therapieprotokolle im Internet**

*Arbeitsgruppensprecher*
Prof. Dr. Hartmut Link
Westpfalz-Klinikum, Medizinische Klinik I
Hellmut-Hartert-Straße 1, 67655 Kaiserslautern
Telefon 0631 2031260
link@aio-portal.de

**Ösophagus-/Magenkarzinom**

*Arbeitsgruppensprecherin*
Prof. Dr. Sylvie Lorenzen
III. Medizinischen Klinik
des Klinikums rechts der Isar
Ismaninger Str 22, 81675 München
Telelefon 089 41407706
lorenzen@aio-portal.de

*Stellv. Arbeitsgruppensprecher*
Priv.-Doz. Dr. Peter Thuss-Patience
Charité Campus Virchow-Klinikum
Med. Klinik m.S. Hämatologie und Onkologie (CC14)
Augustenburger Platz 1, 13353 Berlin
Telelefon 030 450653193
thuss@aio-portal.de

**Pankreaskarzinom**

*Arbeitsgruppensprecher*
Prof. Dr. Volker Heinemann
Klinikum der Universität München
Medizinische Klinik III
Marchioninistraße 15, 81377 München
Telefon 089 4400 - 0
heinemann@aio-portal.de

*Arbeitsgruppensprecher*
Prof. Dr. Michael Geißler
Klinikum Esslingen GmbH
Klinik für Allgemeine Innere Medizin, Onkologie/Hämatologie, Gastroenterologie und Infektiologie
Hirschlandstraße 97, 73730 Esslingen
Telefon 0711 3103 2451
geissler@aio-portal.de

**Supportive Therapie**

*Arbeitsgruppensprecherin*
Prof. Dr. med. Karin Jordan
Universitätsklinikum Heidelberg
Innere Medizin V
Im Neuenheimer Feld 410, 69120 Heidelberg
Telefon 06221 56 8030/8001
jordan@aio-portal.de

*Arbeitsgruppensprecher*
Prof. Dr. Hartmut Link
Westpfalz-Klinikum
Medizinische Klinik I, 67655 Kaiserslautern
Telefon 0631 2031260
link@aio-portal.de

**Forum Young Medical Oncologist**

*Sprecherin*
Dr. Farastuk Bozorgmehr
Thoraxklinik Heidelberg
Abt. Interne Onkologie
Röntgenstraße 1, 69126 Heidelberg
bozorgmehr@aio-portal.de

*Sprecher*
Dr. Stephan Kruger
Klinikum der Universität München
Medizinische Klinik III
Hämatologie und Onkologie
Marchioninistraße 15, 81377 München
kruger@aio-portal.de

**Thorakale Onkologie**

*Arbeitsgruppensprecher*
Prof. Dr. Rudolf M. Huber
Ludwig-Maximilians-Universitätsklinikum
Abt. Pneumologie
Ziemssenstraße 1, 80336 München
Telefon 089 5160 2590
huber@aio-portal.de

*Stellv. Arbeitsgruppensprecher*
Prof. Dr. Frank Griesinger
Pius-Hospital - Medizinischer Campus
Universität Oldenburg
Klinik für Hämatologie und Onkologie
Georgstr. 12, D-26121 Oldenburg
griesinger@aio-portal.de

**Translationale Forschung**

*Arbeitsgruppensprecher*
Prof. Dr. Matthias Ebert
Universitätsklinikum Mannheim GmbH
II. Medizinischen Klinik
Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
Telefon 0621 383-3284
matthias.ebert@umm.de

*Arbeitsgruppensprecher*
Prof. Dr. Sebastian Stintzing
Klinikum der Universität München
Medizinische Klinik III
Marchioninistraße 15, 81377 München
Telefon 089 4400 0
stintzing@aio-portal.de

**Wirkstoffentwicklung/Phase-I-Studien/frühe Phase-II-Studien**

*Arbeitsgruppensprecher*
Prof. Dr. Nisar P. Malek
Universitätsklinikum Tübingen
Innere Medizin I
Otfried-Müller-Str. 10, 72076 Tübingen
Telefon 07071 29 82722
malek@aio-portal.de

**Weichteilsarkom/Knochentumoren**

*Arbeitsgruppensprecher*
Prof. Dr. Sebastian Bauer
Universitätsklinikum Essen, Innere Klinik und Poliklinik
Hufelandstraße, 55, 45147 Essen
Telefon 0201 723 2112
bauer@aio-portal.de

**ZNS-Tumoren / Meningeosis**

*Arbeitsgruppensprecher*
Prof. Dr. Meinolf Karthaus
Krankenhaus Neuperlach
Onkologie und Hämatologie
Oskar-Maria-Graf-Ring 51, 81737 München
Telefon 089 6210 2731
karthaus@aio-portal.de