STUDIENKURZPROTOKOLLE

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Impressum

Arbeitsgemeinschaft
Internistische Onkologie (AIO)
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Die Veröffentlichung eines Kurzprotokolls erfolgt erst nach Konsentierung und Bewertung der klinischen Studie innerhalb der zuständigen Leitgruppe nach Vergabe der AIO-Studiennummer (siehe Seite 2!)

Alle Studienkurzprotokolle sind online zu finden unter:
www.aio-portal.de

Anmerkung zu den Ein- und Ausschlußkriterien / Gewährleistung

Dieses Studienhandbuch dient der Information zu den unmittelbar vor dem Start stehenden und laufenden Studien.
Studien, die sich im Follow up befinden, sind nicht mehr aufgefürt. Diese Studien finden Sie auf der AIO-Website unter der jeweiligen Arbeitsgruppe, dort unter der Rubrik „geschlossenen Studien“. Die AIO übernimmt keine Gewähr für die Richtigkeit der Angaben. Im Allgemeinen sind in diesem Handbuch nur die wichtigsten Ein- und Ausschlußkriterien aufgeführt. **Bitte konsultieren Sie in jedem Fall den vollständigen Prüfplan.**

Auszug aus den Standardarbeitsanweisungen (SOP’s) der AIO

Registrierung von Studienprotokollen
→ ab 01.07.2013 verbindlich für jede Arbeitsgruppe

Die Antragstellung erfolgt mittels Antragsformulars, das auf der AIO-Website hinterlegt ist.

Eingehende **Studienanträge** werden von der AIO-Geschäftsstelle entgegengenommen und registriert. Voraussetzung für die Registrierung ist die vorherige Diskussion des Studienkonzeptes in der Leitgruppe und der Arbeitsgruppe, die anschließende Übermittlung des schriftlichen positiven Votums der Leitgruppe an die AIO-Geschäftsstelle sowie die Vorlage einer Synopse. Danach erhält jede eingereichte Studie eine Chiffre (bzw. eine AIO-Studiennummer).

Als **AIO-Studie** gilt eine Studie, die von einer Arbeitsgruppe der AIO als Studie der Gruppe initiiert und entwickelt worden ist, und die durch die AIO-Geschäftsstelle organisatorische Unterstützung erhält und falls gewünscht, über die AIO-Studien-gGmbH als Sponsor durchgeführt werden kann. Die Studienidee muss zuvor in der zuständigen Arbeitsgruppe diskutiert, durch die Leitgruppe genehmigt und als in die aktuelle Studienlage passend bewertet worden sein. Zur Einleitung des Verfahrens zur Anerkennung als AIO-Studie ist die Vorlage einer Studiensynopse ausreichend.

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Die kompletten SOPs und das Studien-Antragsformular finden Sie unter dem folgenden Link:
http://www.aio-portal.de/index.php/standard-operating-procedures-sop.html

Ausführliches Inhaltsverzeichnis

Arbeitsgruppe CUP-Syndrom

CUP – palliative Therapie,1st-line

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

AIO-assoziierte-Studie	
Studiennummer:	**AIO-CUP-0117/ass - CUPISCO**
Status:	in Rekrutierung
Rekrutierungszeitraum	2018 – 2022
Anzahl Zentren:	geplant: 156 (34 Länder, 15 Zentren in D) initiiert: 134
Weitere Zentren:	sind leider nicht möglich
Anzahl Patienten:	geplant: 790 aktuell eingeschlossen: 480 (international), davon 59 in Deutschland
Letzte Aktualisierung	Oktober 2021

Art der Studie:	randomisierte Phase-II-Studie
Verantwortlicher Studienleiter nach AMG / Kontakt	Prof. Dr. Alwin Krämer Klinische Kooperationseinheit Molekulare Hämatologie/Onkologie Deutsches Krebsforschungszentrum und Medizinische Klinik V, Universität Heidelberg Im Neuenheimer Feld 581, 69120 Heidelberg Tel: +49-6221-42-1440, Fax +49-6221-42-1444
Studienziele	Primary Endpoint: PFS - Progression Free Survival (from randomization to first occurrence of disease progression) Secondary Endpoints: Overall survival (OS), Overall Response Rate (ORR), Duration of Clinical Benefit (DCB)
Rekrutierung	Rekrutierungsbeginn international Mai 2018, Deutschland November 2018
Zentren	134 Zentren in 34 Ländern, 13 Zentren in Deutschland
Einschlusskriterien	• Histologic or cytologic proven, non-resectable carcinoma of unknown primary (adenocarcinoma or poorly differentiated carcinoma or squamous cell carcinoma) • Measurable tumor lesion(s) according to RECIST criteria • WHO PS 0 to 1 • Signed written informed consent • ≥18 years of age • Sufficient tumor tissue sample (for NGS-testing) • No prior lines of chemotherapy • Life expectancy >= 12 weeks • Effective contraception for both male and female subjects if the risk of conception exists • Adequate hematologic and organ function
Ausschlusskriterien	• CNS-metastases or leptomeningal disease • Spinal cord compression not definitely treated • Non epithelial cancer • Patients belonging to subsets of CUP with good prognosis:

	○ Women with axillary node metastasis as predominant tumor site ○ Women with papillary adenocarcinoma of the peritoneal cavity ○ Men with poorly diff. ca. with midline distribution ○ Squamous cell carcinoma in cervical lymph nodes ○ Poorly diff. neuroendocrine tumors ○ Men with blastic bone metastases and elevated PSA ○ Isolated inguinal adenopathy ○ Single, potentially resectable tumor site • Investigational agents or participation in clinical trials within 28 days before treatment start in this study • 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) • If CR, PR, SD: randomize 3:1: molecular guided therapy or inv. choice vs. platinum doublet continuation • If PD: molecular guided therapy or inv. choice
Tumorevaluierung	According to RECIST-criteria 1.0

Arbeitsgruppe Digitalisierung

DEfenseCOVID-19 – Ein deutschlandweites Register für alle Krebspatientinnen und Krebspatienten zur Erfassung der Auswirkungen der COVID 19 Pandemie

AIO-assoziierte-Studie

Studiennummer/-Code:	**AIO-DIG-MAM-0221/ass - DEfenseCOVID-19**	
Status:	in Rekrutierung	
Rekrutierungszeit:	von: 12/2020	bis: 12/2021
Anzahl Zentren:	monozentrisch; Einschluss deutschlandweit über e-consent	
Weitere Zentren:	keine, Unterstützer machen Patient*innen auf die Studie aufmerksam, weitere Unterstützer sind erwünscht	
Anzahl Patienten:	aktuell eingeschlossen: 332	
Letzte Aktualisierung	05.10.2021	

Projektleiter	Prof. Dr. Peter A. Fasching Universitätsklinikum Erlangen Frauenklinik Universitätsstraße 21/23 91054 Erlangen
Leitung Projekt-management	Dr. Lena A. Wurmthaler Universitätsklinikum Erlangen Frauenklinik Universitätsstraße 21/23 91054 Erlangen
Kontaktperson	Prof. Dr. Peter A. Fasching: peter.fasching@uk-erlangen.de Stellvertretend: Dr. Lena A. Wurmthaler: lena.wurmthaler@uk-erlangen.de
Scientific Board	Prof. Dr. Matthias W. Beckmann, Erlangen Prof. Dr. Sara Brucker, Tübingen Prof. Dr. Peter A. Fasching, Erlangen PD Dr. Alexander Hein, Erlangen Prof. Dr. Wolfgang Janni, Ulm Prof. Dr. Diana Lüftner, Berlin Prof. Dr. Volkmar Müller, Hamburg Prof. Dr. Anton Scharl, Amberg Prof. Dr. Michael Untch, Berlin Prof. Dr. Andreas Schneeweiss, Heidelberg Prof. Dr. Hans Tesch, Frankfurt
Projektpartner	Diese Studie wird unterstützt durch die Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e. V. (DGGG), die Deutsche Gesellschaft für Senologie e.V. (DGS), die Arbeitsgemeinschaft für Gynäkologische Onkologie e.V. (AGO), AGO-B Breast Study Group e. V., den Brustkrebs Deutschland e.V. – Prognose Leben (BKD), das PRAEGNANT-Breast Cancer-Register, AIO- Arbeitsgemeinschaft

	Internistische Onkologie in der Deutschen Krebsgesellschaft e.V. u.a.
Rationale	Im Rahmen der aktuellen COVID-19-Pandemie sind zahlreiche Infektionen auch bei Krebspatientinnen und Krebspatienten zu erwarten. Durch ein fehlendes Register kann die Information über den Krankheitsverlauf dieser Patientengruppen nur sehr ungenau erfasst werden. Darüber hinaus hat die Pandemie unterschiedliche Einflüsse auf Krebspatientinnen und Krebspatienten, deren Versorgung und Wohlbefinden. Daher sollen in diese prospektive Registerstudie alle Krebspatientinnen und Krebspatienten unterschiedlicher Kohorten eingeschlossen werden. Im Rahmen dieser Registerstudie dezidierte Gesundheitsdaten über Krebspatientinnen und Krebspatienten unter verschiedenen Therapien gesammelt werden. Um große Datenmengen in kurzer Zeit sammeln zu können bedarf es einer besonders flexiblen Datenstruktur, aber auch einer besonderen Infrastruktur, um den Datenschutz gewährleisten zu können. Deswegen berichten die Patientinnen und Patienten selbst Ihre Daten durch eine *Progressive Web Applikation* (PWA). Hierbei werden Daten durch strukturierte Fragebögen erhoben und vorerst nur auf dem Smartphone der Teilnehmenden in verschlüsselter Form gesammelt. Die Patientinnen und Patienten übertragen dann anonymisiert die Daten auf einen zentralen Server zu Auswertungszwecken. Angaben über die Identität der Patientinnen und Patienten werden nicht gesammelt. Von den teilnehmenden Patientinnen und Patienten kann eine weitere Vertrauensperson in die Dokumentation einbezogen werden, welche über intensivmedizinische Behandlungen oder schwerwiegende medizinische Ereignisse berichten könnte. Somit soll von Krebspatientinnen und Krebspatienten sowie von einer durch diese benannte Vertrauensperson mit einer *PWA-App* Daten gesammelt werden. Diese sollen primär hinsichtlich Morbidität und Mortalität nach einer SARS-CoV-2 Infektion analysiert werden. Durch die Erkenntnis besonderer Risiken könnten Therapieentscheidungen neu überdacht werden und eine Einschätzung des Nutzen-Risiko-Verhältnisses unter Einbeziehung eines bestehenden Infektionsrisikos vorgenommen werden. Darüber hinaus soll die Stimmung der teilnehmenden Krebspatientinnen und Krebspatienten zur Versorgung und Impfung während der COVID-19-Pandemie sowie die Stressbelastung und Verunsicherungen im Zusammenhang mit der Versorgung, Therapie und privaten Leben analysiert werden.
Primäres Studienziel	Mortalität bei Krebspatientinnen und Krebspatienten unter verschiedenen Therapien innerhalb von 6 Monaten
Sekundäre Studienziele	• Stimmung zur Versorgungslage in der COVID-19-Pandemie • Stimmung zur Impfsituation in der COVID-19-Pandemie • Verlauf der Stressbelastung im Zusammenhang mit der Versorgung, Therapie und privaten Leben • Verlauf von Verunsicherungen im Zusammenhang mit der Krebstherapie während der COVID-19-Pandemie • Rate an Pneumonie • Notwendigkeit und Dauer einer Hospitalisierung

	• Notwendigkeit und Dauer des Aufenthalts auf einer Intensivstation • Notwendigkeit und Dauer einer maschinellen Beatmung
Einschlusskriterien	• Patientinnen und Krebspatienten ≥ 18 Jahre • Patient(inn)en die die online Einverständniserklärung akzeptiert haben • (**optional**) Aktuell oder in der Vergangenheit nachgewiesene SARS-CoV-2-Infektion (entweder durch Direkttest oder Serumtest) **Einschlusskriterien für die Krebspatientinnen/Krebspatienten** • Bekannte Diagnose einer Krebserkrankung • Eine der folgenden Gruppen ○ **Gruppe 1**: Patient(inn)en mit vergangener Krebsdiagnose ohne aktuelle Therapie ○ **Gruppe 2**: Patient(inn)en mit einer Krebsdiagnose unter einer aktuellen Therapie **Einschlusskriterien für die Vertrauensperson** • Vertrauensperson muss einen Zugangscode zur App von der Patientin/dem Patienten erhalten haben • Vertrauensperson muss die online Einverständniserklärung akzeptiert haben
Ausschlusskriterien	• Krebspatient(inn)en oder Vertrauenspersonen, die nicht die online Einverständniserklärung akzeptieren
Studienablauf	Die unterstützenden Fachgesellschaften informieren ihre Mitglieder über die Registerstudie, die Mitglieder erhalten ein Informationsblatt, welches sie ausdrucken können und Patientinnen und Krebspatienten mit einer Krebserkrankung aushändigen sollen. Ärztinnen, Ärzte, Patientinnen, Patienten und Patient(inn)envertreter teilen den Inhalt über soziale Medien. Die Patientinnen und Patienten registrieren sich selbst durch die PWA und erhalten nach Registrierung einen QR-Code auf ihrem Smartphone, mit welchem sich der Partner/die Vertrauensperson registrieren kann. Durch die Registrierung werden keine personenbezogenen Daten übermittelt oder zentral gespeichert. Alle Teilnehmenden bleiben anonym. Patient(inn)en sowie Vertrauenspersonen sollen von dort an unabhängig voneinander Fragebögen über den Gesundheitszustand und den Therapieverlauf der Patientin/des Patienten ausfüllen bis das Ende der Beobachtungszeitraums erreicht ist oder der Patient/die Patientin verstorben ist.
Fallzahlkalkulation	In Bezug auf das primäre Studienziel (Tod) ist anzunehmen, dass die Todesrate für SARS-CoV-2 Infizierte (alle Gruppen) ca. 4% ist (globaler Stand 25.3.2019). Es soll ausgeschlossen werden, dass die Todesrate in einer der beschriebenen Krebs-Gruppen über 10% ist. Die Nullhypothese, dass die Todesrate größer als 10% ist, wird mit einem einseitigen exakten Binomialtest mit Signifikanzniveau alpha = 5% (Fehler 1. Art) getestet. Es wird angenommen, dass die tatsächliche Todesrate 4% beträgt. Eine Fallzahlplanung ergibt, dass 142 Patienten notwendig sind, um eine Testgüte von 80% (Fehler 2. Art: 20%) zu erreichen. Es wird eine Ausfallrate von 10% erwartet, was zu einer finalen Fallzahl von 158 Patienten führt.

Teilnehmende Zentren	Frauenklinik des Universitätsklinikums Erlangen. Beworben wird die Studie aber in multiplen Kliniken und Praxen über die kooperierenden Fachgesellschaften.
Studiendauer	Patientinnen und Patienten können sich von 22. Dezember 2020 bis Dezember 2021 in die Studie registrieren. Die letzte Beobachtung soll ebenfalls im Dezember 2022 stattfinden.
Protokoll-version	DEfenseCOVID19 Studienprotokoll zur Synopse: V2.0, 21.01.2021

Arbeitsgruppe Endokrine Tumoren

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

Studiennummer/-Code:	AIO-ENC-0118/ass - CaboACC
Status:	Rekrutierend
Rekrutierungszeitraum:	2019 – 2021
Patienten:	geplant: 37 (min. 29) aktuell eingeschlossen: 17
Weitere Zentren:	Nicht geplant (single center trial)
Letzte Aktualisierung	10/2021

Art der Studie Study Type	Prospective multicenter open label phase-II
Kontaktadresse/ Kontaktperson:	Verantwortlicher Studienleiter nach AMG: Prof. Dr. Dr. Matthias Kroiß Tel.: 0931/201-39740 Email: Kroiss_M@ukw.de Universitätsklinikum Würzburg Medizinische Klinik und Poliklinik I Schwerpunkt Endokrinologie/Diabetologie Oberdürrbacher Str. 6 97080 Würzburg
Studienziele/ Objectives	To determine the efficacy and safety of cabozantinib as a treatment for unresectable/advanced adrenocortical carcinoma. To explore the relationship between cabozantinib pharmacokinetics and treatment response and tolerability To study steroid hormone biomarkers and targeted metabolomics as markers of disease response. To study the effect of cabozantinib on immune markers by obtaining blood samples collection at baseline, during therapy and at time of progression. To explore the relation between pharmacogenetic variants and cabozantinib pharmacokinetics. 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 To characterise pre-defined populations of immune cells, immune cell differentiation status and functionality in available fresh/fresh frozen tumor specimens
Zielparameter/ Objectives	Primary end point: - progression free survival at 4 months Secondary end points: - overall survival - Best Objective Response Rate (ORR) - duration of response (DR) - progression-free survival - best percentage change in size of target lesions

	- incidence and severity of adverse events possibly related to cabozantinib graded according to CTC-AE 4.03 - quality of life by EORTC QLQ-C30 Exploratory - steady-state trough plasma concentration of cabozantinib by quantile - 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). - 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) - change from baseline of pre-specified immune cell markers at during treatment - correlation of steady state trough cabozantinib plasma concentration with pre-specified variants of enzymes of drug metabolism and disposition - descriptive analysis of expression of tissue markers and response
Patientenzahl Number of patients	Planned: 37 Already included: 17
period of trial	2019 – 2022, extension planned
More centres?	single center trial, expansion to additional center(s) planned for 2021
Haupt-Einschlusskriterien / Key inclusion criteria	1. ≥ 18 years old on the day of consent 2. histological confirmation of ACC 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 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 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 6. Life expectancy of at least 3 months 7. Organ and bone marrow function and laboratory values within pre- 8. Capable of understanding and complying with the protocol requirements. 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. 10. Able to give written informed consent
Haupt- Ausschlusskriterien 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. 2. Treatment with mitotane <28 days prior study inclusion OR mitotane serum/plasma con-centration documented of ≥2 mg/L. 3. Prior treatment with cabozantinib or other cMET inhibitors 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. 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. 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 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. 7. The use of strong CYP3A4 inhibitors (with the exception of ketoconazole). 8. The subject has experienced any of the clinical conditions defined in the full protocol 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. 10. Uncontrolled, significant concurrent or recent illness or disorders as specified in the protocol. 11. Any of the following within 6 months before the first dose of study treatment: • abdominal fistula • gastrointestinal perforation • bowel obstruction or gastric outlet obstruction • intra-abdominal abscess 12. Unable to swallow tablets 13. QTcF>500 milliseconds within 28 days before first dose of study 17. Pregnancy or breastfeeding. 18. A previously identified allergy or hypersensitivity to components of the study treatment formulation. 19. Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee. 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 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 Scheme of therapy	Cabozantinib tablets 60 mg qd.
Tumorevaluierung 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. 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.

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). Sample size calculation according to the algorithm of Simon for two-stage phase II trials: 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. 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. 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). 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 – Seltene Maligne Tumore der Schilddrüse

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

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/ENC-0216 - ThyCa
Rekrutierungszeitraum:	retrospektiv 2000 – 2013, prospektiv seit 2014
Zentren:	sind sehr erwünscht
Letzte Aktualisierung	Oktober 2021

Art der Studie Study Type	Retrospective and prospective registry study
Kontaktadresse/ Kontaktperson:	Prof. Dr. Dr. Matthias Kroiß LMU Klinikum Medizinische Klinik und Poliklinik IV Endokrinologie/Diabetologie Ziemssenstr. 1 80336 München

	Tel.: 089/4040-52221 Email: matthias.kroiss@med.lmu.de Prof. Dr. C. Spitzweg Medizinische Klinik und Poliklinik IV Endokrinologie/Diabetologie Marchioninistr. 15 81377 München Tel.: 089/4040-73012 Email: christine.spitzweg@med.lmu.de Studiensekretariat: J. Putz Tel.: 089/4400-52414 Email: jacqueline.putz@med.lmu.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Young-Medial-Oncologists	

Europäisches Nebennierentumor-Register (ENSAT adrenal tumor registry and biobank)

AIO-assoziierte Studie

Studiennummer/-Code:	ENSAT
Status:	in Rekrutierung
Rekrutierungszeitraum	seit 2011 fortlaufend
Weitere Zentren:	sind erwünscht
Letzte Aktualisierung	Oktober 2021

Studienleiter	Prof. Dr. Martin Fassnacht Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie Universitätsklinikum Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg Tel 0931-201-39021, Fassnacht_m@ukw.de
Kontaktadresse/ Kontaktperson:	Frau Michaela Haaf (Study Nurse) Schwerpunkt Endokrinologie und Diabetologie, Medizinische Klinik I, Universtitätsklinik Würzburg, Oberdürrbacher Str. 6, 97080 Würzburg Tel.: 0931 – 201 39717, Fax: 0931 – 201 639716 haaf_m@medizin.uni-wuerzburg.de
Studienziele	Maligne Nebennierentumoren (Nebennierenkarzinom= NN-Ca und Maligne Phäochromozytome=mPhäo) sind seltene Tumoren mit meist schlechter Prognose. Für beide Tumoren gibt es zu vielen Aspekten der Diagnostik und Therapie keine guten prospektiven oder gar randomisierten Studien. Ziel dieses europäischen Registers ist es, strukturelle Verbesserung in der Betreuung von Patienten mit Nebennieren-Tumoren herbeizuführen. Durch die bundesweite Erfassung möglichst vieler Patienten werden Daten zur Prognose und zu den Erfolgsaussichten unterschiedlicher Therapieregime gewonnen. 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-Tumor-Register werden europaweit Patienten mit histologisch gesichertem Nebennierenkarzinom und Phäochromozytom aufgenommen. Die Daten werden zentral in einer digitalen

	Datenbank gesammelt und ausgewertet. Das Register wird durch das europäische Nebennierentumornetzwerk ENSAT koordiniert. Die Daten aus Deutschland können weiterhin vom behandelnden Arzt an die Studienzentrale nach Würzburg übermittelt werden und werden dann von hier zentral eingegeben. Die weitere Auswertung erfolgt pseudonymisiert. Anfangs werden die Patienten retrospektiv analysiert. Mit dem Zeitpunkt der Erstaufnahme in das Register erfolgt eine prospektive Beobachtung. Parallel zu den klinischen Daten werden Bioproben (Tumor, Blut und Urin) von den Patienten gesammelt und ausgewertet.
Erfasste Patienten	Nebennierenkarzinom: Oktober 2021: 4322 (davon > 1550 aus Deutschland) Phäochromozytom: Oktober 2021: 4634 (davon ca. 650 aus Deutschland)
Fragestellungen	In den letzten Jahren konnten auf Basis der Daten dieses Registers viele klinische drängende Fragen beantwortet werde; u.a. zur Diagnostik (Eisenhofer Clin Chem 2018, Bancos Lancet Diab & Endocrinol 2020), adjuvanten Therapie (Fassnacht JCEM 2006, Terzolo NEJM 2007), zu Operationonsverfahren (Brix Eur Urol 2010; Reibetanz Ann Surg 2012) oder zur Therapie beim Rezidiv (Erdogan JCEM 2013) oder Behandlung bei fortgeschrittener Erkrankung (Quinkler JCEM 2008, Weismann EJE 2009, Kroiss Horm Cancer 2016, Megerle JCEM 2018, Kroiss JCEM 2020). Zusätzlich wurde eine neue TNM-Klassifikation vorgeschlagen, die inzwischen allgemein akzeptiert wird (Fassnacht et al. Cancer 2009). Weitere Informationen und bisherige Publikationen unter: www.nebennierenkarzinom.de; www.ensat.org
Förderung	Initial über die Deutsche Krebshilfe 2011-2017 Förderung durch die Europäische Union im Rahmen des FP-7 Programms Seit 2017 durch die DFG (TR-SFB 205 Nebenniere)

Arbeitsgruppe Hepatobiliäre Tumoren

HCC – frühes Stadium

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

AIO-Studie

Studiennummer/-Code:	AIO-HEP-0417/ass	
Status:	In Rekrutierung	
Rekrutierungszeitraum:	Seit Q3/2019, 24 Monate Rekrutierung	
Zentren	geplant: 10	aktuell initiiert: 13
Patienten	geplant: 30	aktuell rekrutiert: 28
Weitere Zentren:	sind leider nicht mehr möglich	
Letzte Aktualisierung	Oktober 2021	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover E-Mail: Vogel.Arndt@mh-hannover.de
SPONSOR / PROJECT MANAGER	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt Dr. Regina Eickhoff E-Mail: eickhoff.regina@ikf-khnw.de
CONDITION	Early stage hepatocellular carcinoma (HCC)
OBJECTIVE(S)	Primary: Overall response rate (ORR) before local ablation Secondary: Time to recurrence (TTR), recurrence free survival, and overall survival (OS) Safety and tolerability Identification of predictive molecular biomarkers
INTERVENTION(S)	pembrolizumab 200mg IV Q3W on D1C1 and D1C2 RFA, MWA, brachytherapy or combination of TACE with RFA, MWA or brachytherapy will be performed on D1C3 pembrolizumab 200mg IV administration on D3C3 pembrolizumab 200mg IV Q3W for up to one year total treatment duration
KEY EXCLUSION CRITERIA	• Extrahepatic disease • Fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC • Tumor thrombus involving main trunk of portal vein • Prior history of Grade ≥ 2 hepatic encephalopathy • Pericardial effusion, uncontrollable pleural effusion, or clinically significant ascites • Autoimmune autoimmune disease that has required systemic treatment in the past 2 years

KEY INCLUSION CRITERIA	• Histologically confirmed diagnosis of HCC • Child-Pugh Classification score ≤ 6 • Candidate for local ablation • Patients (including high risk patients) with: Presence of ≤ 5 tumor nodules with diameters ≤ 7cm [longest axis] each OR Vascular infiltration • No prior systemic therapy for HCC (TACE >8 weeks before study allocation permitted) • Measurable disease based on RECIST • Archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion • ECOG performance status 0 to 1
OUTCOME(S)	Efficacy : • We hypothesize that treatment with pembrolizumab before local ablation will allow conversion / downstaging of borderline candidates for local ablation. This will be displayed by an ORR of 30% (measured before local ablation, compared to baseline). • We hypothesize that peri-interventional treatment with pembrolizumab will increase TTR, recurrence free survival and overall survival after local ablation. Safety: • We hypothesize that combination of local ablation 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. 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. 54 months from FPI to LPO (consisting of 24 months recruitment, 12 months treatment after LPI, and 18 months FU for OS after LPLT)
PARTICIPATING CENTERS	10 sites planned

HCC, intermediäres Stadium

AIO-HEP-0321/ass - The ABC-HCC Trial: A Phase IIIb, randomized, multicenter, open-label trial of Atezolizumab plus Bevacizumab versus transarterial Chemoembolization (TACE) in intermediate-stage HepatoCellular Carcinoma

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-HEP-0321/ass
Status:	in set-up
Rekrutierungszeitraum	2021-2023 (geplant)
Weitere Zentren:	in Deutschland gesucht
Zentren:	geplant: 60 in Europa und Asien (17 in DE geplant), aktuell 8 Zentren initiiert
Patienten:	geplant: 434
Letzte Aktualisierung	Okt 2021

Trial type	Randomized, multicenter, open label, phase IIIb study
Coordinating investigator	Prof. Dr. med. Peter R. Galle Universitätsmedizin Mainz I. Medizinische Klinik Langenbeckstr. 1 55131 Mainz
Sponsor Project Management Sponsor	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Dr. Johanna Riedel Tel: +49 69 / 76 01-4635 Email: Riedel.johanna@ikf-khnw.de
Medical condition	intermediate hepatocellular carcinoma (HCC)
Objectives/Endpoints (efficacy, safety)	The main purpose of this phase IIIb study is to test the efficacy and safety of atezolizumab in combination with bevacizumab compared to TACE in patients with intermediate stage liver cancer. <u>Primary Efficacy Objective</u> To assess the efficacy of atezolizumab in combination with bevacizumab compared to Transarterial Chemoembolization (TACE) in patients with intermediate stage liver cancer. Corresponding Endpoint • Time to failure of treatment strategy (TTFS [assessed every 8 weeks (±7days)]): <u>Secondary Efficacy Objectives</u> a) To further characterize the responses obtained with the respective therapeutic strategy Corresponding Endpoints • Overall Survival (OS): • Overall Survival Rate at 24 months (OS@24 • Objective Response Rate (ORR): • Time to Progression (TTP): • Time to loss of systemic treatment options (TTSYS) • Progression free survival (PFS)

	• Duration of Treatment • Duration of Response (DOR): b) To assess the impact of each therapeutic strategy on liver function over time Corresponding Endpoint • Time to deterioration of liver function: c) To evaluate the safety and tolerability of each therapeutic strategy and their respective impact on Quality of Life. Corresponding Endpoints • Safety: • QoL (Patient Reported Outcome; PRO) <u>Exploratory Biomarker Objectives</u> a) To identify prognostic and predictive angiogenic and immune related biomarkers (tissue and circulating) for study endpoints. b) To assess expression of Programmed Death-Ligand 1 (PD-L1) protein expression by immunohistochemistry on available FFPE biopsy tissue samples collected. Corresponding explorative endpoint for PD-L1 expression Baseline PD-L1 protein expression in FFPE tumor tissue
Intervention(s)	Arm A (experimental arm): • Atezolizumab 1200 mg intravenous (IV) infusions Q3W (dosed in 3-week cycles) plus • Bevacizumab 15 mg/kg IV Q3W (dosed in 3-week cycles) Arm B (standard arm): • Transarterial Chemoembolization (using conventional TACE [cTACE] or drug-eluting bead TACE [DEB-TACE]) Following randomization, study patients will enter the study treatment period which will last approximately 36 to 52 weeks (estimated mean values) depending on treatment arm. The active treatment period is limited to a maximum of 24 months.
Inclusion/exclusion criteria	<u>Patients must meet all of the following criteria to be **eligible** for the study:</u> 1. Signed Informed Consent Form available 2. Patients* ≥ 18 years of age at time of signing Informed Consent Form (for Taiwan: ≥ 20 years) 3. Confirmed hepatocellular carcinoma diagnosis based on histopathological findings from tumor tissue or typical diagnostic imaging on dynamic CT or MRI according to AASLD criteria. 4. Disease not amenable to curative surgery or transplantation or curative ablation BUT disease amenable to TACE 5. Extent of disease according to the following parameters: • Multifocal HCC beyond Milan criteria (i.e. >3 lesions of any size OR ≥2 lesions with at least one of them being ≥ 3cm) • More than one untreated HCC untreated nodule > 10 mm showing arterial hyperenhancement • No massive multinodular pattern preventing adequate TACE • No tumor of a diffuse infiltrative HCC type • Patent portal vein flow • No portal vein invasion/thrombosis (even segmental) on baseline/eligibility imaging • No extrahepatic disease 6. Patients with recurrence after resection/ablation are eligible if initially having achieved complete response AND recurrence developed within 2 years (i.e. ≤730 days) before trial inclusion AND if ≥ 2 untreated nodules with > 10 mm with arterial enhancement are present at timepoint of trial inclusion. 7. Child-Pugh score class A without ascites requiring more than 100 mg of spironolactone/day (see exclusion criteria) at enrollment.

	8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 at enrollment. 9. Adequate organ and bone marrow function 10. Life expectancy of ≥ 3 months 11. The following laboratory values obtained less than or equal to 7 days prior to randomization. • Platelet count ≥ 75,000 per µL (75x109/L) • Hemoglobin ≥ 9.0 g per dL [transfusion allowed] • Total bilirubin ≤ 2.0 x the upper limit of normal (ULN) • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 x ULN • Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCL) ≥ 50mL/min (calculated using the Cockcroft-Gault formula) • Urine dipstick for proteinuria ≤ 2+ (within 7 days prior to initiation of study treatment) Patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate <1 g of protein in 24 hours • INR or aPTT ≤ 1.5 x ULN (therapeutic anticoagulation prohibited – see exclusion criterion #13; prophylactic anticoagulation permitted, e.g. LMW heparin, ASS up to 250mg/qd) • Alkaline phosphatase ≤ 2.5 x ULN • Absolute neutrophil count (ANC) ≥ 1.500 per µL (1.5x109/L) without granulocyte colony-stimulating factor support • Serum albumin ≥ 2.8 g per dL (28g/L) 12. Pre-treatment tumor tissue sample (if available) • If tumor tissue is available, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or approximately 10 to 15 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report. • If FFPE specimens described above are not available, any type of specimens (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion], and lavage samples) are also acceptable. This specimen should be accompanied by the associated pathology report. • If tumor tissue is not available (e.g., patient has never undergone biopsy or tissue depleted because of prior diagnostic testing), patients are still eligible. 13. Negative serum pregnancy test done lesser than or equal to 7 days prior to randomization, for females of childbearing potential only. 14. No presence of untreated or incompletely treated varices with bleeding or high-risk for bleeding: Availability of esophagogastroduodenoscopy (not older than 6 months) in which all size of varices (small to large) had been assessed and varices were treated per local standard of care prior to enrollment. 15. Absence of other severe comorbidities 16. Resolution of any acute, clinically significant treatment-related adverse events from prior therapy/procedure to Grade ≤ 1 prior to study entry, with the exception of alopecia. 17. For patients with active hepatitis B virus (HBV): • HBV DNA ≤500 IU/mL obtained within 28 days prior to initiation of study treatment, AND • Anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study. 18. For patients with active hepatitis C virus (HCV): • Patients positive for hepatitis C virus (HCV) antibody are eligible, also if polymerase chain reaction testing is positive for HCV ribonucleic acid (RNA). • However, anti-viral therapy against HCV is only allowed prior to trial but not during the trial. 19. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 1 month after the last TACE procedure.

	• A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥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 contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper 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. 20. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below: • With female partners of childbearing potential, 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 6 months after the last dose of bevacizumab or 1 month after the last TACE procedure. Men must refrain from donating sperm during this same period. • With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of bevacizumab or 1 month after the last TACE procedure to avoid exposing the embryo. • 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. *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. <u>Patients who meet any of the following criteria will be **excluded** from study entry</u>: 1. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC. 2. Disease still amenable to curative surgery or transplantation or curative ablation. 3. Previous treatment with atezolizumab or bevacizumab. 4. Previous treatment with a programmed death 1 (PD1), programmed death-ligand (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, or any form of cancer immunotherapy for HCC. 5. Previous TACE or any other transarterial treatment for HCC • Previous RFA / MWA allowed (refer to inclusion criterion #6) • Other local therapies are prohibited (e.g. cryoablation, high-intensity focused ultrasound, irreversible electroporation) 6. Extent of disease too advanced: • Evidence of macrovascular invasion (even segmental) on baseline / eligibility imaging • Massive multinodular pattern preventing adequate TACE • Extrahepatic disease 7. Tumor of diffuse infiltrative HCC type (hypovascular infiltrative tumors with ill-defined borders) 8. Clinically meaningful ascites, defined as ascites requiring non-pharmacologic intervention (e.g. paracentesis) to maintain symptomatic control, within 6 months prior to the first scheduled dose. • Patients with ascites requiring pharmacologic intervention (e.g. diuretics) and stable for ≥2 months on low doses of diuretics (spironolactone 100 mg/d or equivalent) for ascites are eligible. Of note, diuretics for other indications such as congestive heart failure are not considered in this regard. 9. Previous radiotherapy for HCC 10. Major surgical procedure, open biopsy, or significant traumatic injury ≤28 days prior to randomization or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure.

	11. Significant cardiovascular disease, such as cardiac disease (New York Heart Association Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to randomization, as well as unstable arrhythmias (note: beta blockers or digoxin are permitted), unstable angina, new-onset angina (begun within the last 3 months). 12. Uncontrolled hypertension defined by a systolic blood pressure (BP) ≥150 mmHg or diastolic blood pressure (BP) ≥100 mmHg, with or without antihypertensive medication. Patients with initial blood pressure (BP) elevations are eligible if initiation or adjustment of antihypertensive medication lowers pressure to meet entry criteria. 13. Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose. 14. History of or current pheochromocytoma. 15. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism ≤6 months prior to randomization. 16. With regards to eligibility for adequate TACE, patients presenting with either of the following conditions are excluded: • Past history of bilioenteric anastomosis or biliary procedure (e.g., endoscopic papillotomy or biliary stenting) or patients with aerobilia • Central biliary obstruction (right or left intrahepatic duct, common hepatic duct, common bile duct) • Celiac occlusion 17. Ongoing infection > grade 2 NCI-CTCAE version 5.0. 18. Patients with seizure disorder requiring medication. 19. Prior allogeneic bone marrow transplantation or prior solid organ transplantation. 20. Evidence or history of bleeding diathesis or any hemorrhage or bleeding event >CTCAE grade 3 within 4 weeks prior to randomization. 21. Non-healing wound, ulcer, or bone fracture. 22. Renal failure requiring hemo- or peritoneal dialysis. 23. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results. 24. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation including a history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion protein; known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulation. 25. Positive test for human immunodeficiency virus (HIV) 26. Active tuberculosis 27. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent. 28. 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 Note: History of radiation pneumonitis within the radiation field (fibrosis) is permitted. 29. Persistent proteinuria of CTC Grade 3 or higher (> 3.5 g/24 hrs, measured by urine protein: creatinine ratio on a random urine sample). Any malabsorption conditions. 31. Pregnant or nursing women 32. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens. 33. Active or 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

	syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Note: History of autoimmune-mediated 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: • Rash must cover < 10% of body surface area • Disease is well controlled at baseline and requires only low-potency topical corticosteroids • 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, 34. Pleural effusion or (thoracal/abdominal) ascites causing respiratory compromise (≥CTCAE version 5.0 Grade 2 dyspnea). 35. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions: • Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study. • Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study. 36. Use of any herbal remedies known to interfere with the liver or other major organ functions. Patients must notify the investigator of all herbal remedies used during the study. 37. 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. 38. History of malignancy other than HCC within 3 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g. 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer 39. Receipt of an investigational drug within 28 days prior to initiation of study drug 40. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.
Number of patients, and location	Total number of patients: 434 global Location of sites: Germany, Austria, Switzerland, Spain, France, UK, Italy, Taiwan, South-Korea, Japan
Trial duration	The estimated study duration at the trial sites is 48 months (24 months recruitment, 24 months follow-up after last patient in). The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, i.e. when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for 24 months since the last study patient has been enrolled (LPI), whichever occurs first.
Number of enrolled pts.	0, trial in set-up
Participating centers	60 in total (ca. 17 in DE)

AIO-HEP-0220/ass: Transarterial chemoembolization (TACE) with Irinotecan and Mitomycin C versus TACE with Doxorubicin in patients with Hepatocellular carcinoma not amenable to curative treatment - IRITACE- a randomized multicenter phase 2 trial. A trial of the German Alliance for Liver Cancer (GALC). (IRITACE)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-HEP-0220/ass - IRITACE		
Status:	in Rekrutierung		
Rekrutierungszeit:	36 Monate		
Anzahl Zentren:	geplant: 15	aktuell initiiert: 6	aktiv rekrutierend: 3
Weitere Zentren:	sind erwünscht		
Anzahl Patienten:	geplant: 104	aktuell eingeschlossen: 14	
Letzte Aktualisierung	07.10.2021		

National Coordinating Investigator (LKP)	Prof. Dr. Oliver Waidmann Medizinische Klinik 1 Universitätsklinikum Frankfurt Theodor-Stern-Kai 7 60590 Frankfurt
Sponsor	Dekan des Fachbereiches Medizin der Johann Wolfgang Goethe-Universität Theodor-Stern-Kai 7 60590 Frankfurt
Indication	Hepatocellular carcinoma not amenable to curative treatment
Study design	Multi-center, randomized, open-label phase II study
Duration of study	Enrollment: 36 months Total study duration: 54 months
Treatment schedule	Patients will receive TACE with 200 mg Irinotecan and 10 mg Mitomycin C (Arm A) or TACE with 150 mg Doxorubicin (Arm B) every 8 weeks +- 7 days.
Primary Objective/Endpoint	The primary endpoint is progression free survival (PFS) time.
Secondary Objectives/Endpoints	The secondary endpoints are: - overall survival (OS) - response/disease control rate (DCR) (either complete response, CR, or partial response, as measured by mRECIST for HCC) - time to progression - time to macrovascular invasion/extrahepatic spread (MVI/EHS) - time to unTACEable progression - safety profile - quality of life (as measured by FACT-Hep and FACT-G7 questionnaires)
Translational Research	In order to define prognostic as well as predictive biomarkers of patients responding to treatment with TACE, blood samples (6 mL EDTA-blood and 10 mL serum at baseline, and 10 mL serum every 56 days, and 10mL serum at the end of treatment) will be analyzed. Furthermore, tumor tissue from the liver will be analyzed for mutations and expression of DNA and mRNA. DNA, RNA and serum proteins from the blood samples will be extracted and further processed for analysis.
Rationale Hypothesis	For patients with advanced HCC not suitable for resection or liver transplantation but without extrahepatic manifestations or portal vein thrombosis, namely BCLC B stage patients, local therapy with TACE is regarded as standard treatment [Greten et al., 2013]. However, there is no standard chemotherapeutic agent. Doxorubicin is widely used. However, the evidence for its use is scarce. An extensive work-up including bioinformatic, biochemical, pharmacological and cell culture models as well as in vivo mouse HCC models has shown that Irinotecan, which is currently not used

	for HCC treatment, improves the therapeutic efficacy of Mitomycin C in HCC [Hosseini et al., 2017]. The pre-clinical data demonstrates that SN-38, the active metabolite of Irinotecan, inactivates the oncoprotein FUBP1 which is overexpressed in 90% of all HCC patients, while it is not expressed in normal hepatocytes, and whose expression is required for HCC tumorigenesis [Rabenhorst et al., 2009, Jessica Zucman-Rossi, personal communication]. Inhibition of FUBP1 sensitizes HCC tumor cells for the cytotoxic impact of Mitomycin C, leading to a synergistic induction of HCC tumor cell death upon combinatorial treatment with Irinotecan and Mitomycin C. Evaluation of twelve HCC patients treated with TACE plus Irinotecan and Mitomycin C indicates that Irinotecan plus Mitomycin C may represent a superior therapeutic option for non-resectable HCCs. As indicated by several clinical trials [Wu et al. 2014; Chen et al. 2005; Takeba et al. 2007] Irinotecan might prolong survival time of HCC patients. In addition, TACE in combination with Mitomycin and Irinotecan showed a significant better local tumor control and prolonged PFS in comparison to TACE with Mitomycin alone [Gruber-Rouh et al. 2018]. In general, no major complications were observed in patients treated with TACE in combination with chemotherapy [Wu et al. 2014]. During the treatment with TACE combined with Mitomycin and Irinotecan 7 out of 28 patients developed symptoms in form of abdominal pain, nausea and vomiting for 2–7 days. However, most patients tolerated the therapy well and no major toxicities were observed [Gruber-Rouh et al. 2018]. These data strongly support the attempt to perform a hypothesis-driven clinical trial in HCC patients comparing TACE with Mitomycin C and Irinotecan (both agents already approved for clinical application) to Doxorubicin-based TACE which is regarded a current standard. Hypothesis The hypothesis is that median PFS with TACE using Mitomycin C and Irinotecan is 9 months compared to 5 months with TACE using Doxorubicin only.
Key Inclusion Criteria	1. Written informed consent granted prior to initiation of any study specific screening procedures 2. Patients with histologically confirmed HCC primarily not suitable for resection, ablation or liver transplantation , a combined therapy of TACE and subsequent ablation is possible 3. Availability of Biopsy for translational research, if patients give their consent 4. Absence of extrahepatic spread 5. Age ≥ 18 years 6. Patients with measurable disease according to mRECIST 7. Performance status ECOG 0 and 1 (Appendix 20) 8. Normal organ and bone marrow function defined as: – Hematopoetic: absolute neutrophil count ≥ 1,500/mm3, platelet count ≥ 60 x 109/l, hemoglobin ≥ 9 g/dL – INR ≤ 1.5 x ULN – Hepatic: AST and ALT < 5 x ULN, bilirubin ≤ 2 mg/dl – Renal: serum creatinine ≤ 1.5 x ULN 9. Child-Pugh stage A 10. Women of childbearing potential must have a negative pregnancy test performed within 7 days prior to enrolment 11. Male or female patients of child-bearing potential must agree to use oral contraception, intrauterine device, bilateral tubal occlusion, vasectomized partner or avoidance of intercourse during the study and for 180 days after last investigational drug dose received
Key Exclusion Criteria	1. Extrahepatic tumor manifestation 2. Tumor infiltration of more than 50% of the whole liver mass 3. Infiltration or thrombosis of the main portal vein or the main left or right intrahepatic branches 4. Child Pugh status B or C > 6 points according to Child Pugh classification (Appendix 20) 5. Prior TACE or selective intraarterial Radiotherapy (SIRT) 6. Prior systemic anticancer therapy for HCC 7. Life expectancy of less than 12 weeks

	8. Esophageal varices grade III (any) or esophageal varices grade II with increased risk for bleeding (red wale signs, cherry spots, red coloration, hematocystic spots) without prophylactic band ligation 9. Known or suspected manifest hyperthyroidism 10. Congestive heart failure > class II NYHA (Appendix 20) 11. Cardiac ventricular arrhythmias requiring antiarrhythmic therapy, acute myocardial infarction, myocardial infarction, acute inflammatory heart disease > CTCAE grade 2 within the past 6 months (Appendix 20) 12. Previous treatment with doxorubicin up to the maximum lifetime dose of 550mg/m2 13. History of organ allograft or bone marrow transplantation 14. Active uncontrolled clinically serious infections > CTCAE grade 2 except chronic hepatitis C infection (Appendix 20) 15. Severe restrictive or obstructive lung disease 16. Clinically apparent chronic inflammatory bowel disease and/or ileus 17. Hemorrhage/bleeding event or variceal bleeding > CTCAE grade 2 within 4 weeks of first dose of study drug (Appendix 20) 18. Major surgery, open biopsy or significant traumatic injury within 4 weeks of first dose of study drug 19. Known or suspected allergies to Iodine-containing or Gadolinum-containing contrast medium, Irinotecan, Mitomycin C, Doxorubicin or other inactive ingredients of the drugs 20. Previous cancer that is distinct in primary site or histology from HCC except cervical cancer in situ, treated basal cell carcinoma, superficial bladder tumors or any cancer curatively treated 3 years prior to study entry 21. Concomitant treatment with St. John's wort 22. Substance abuse, medical, psychological or social condition that may interfere with the patient´s participation in the study 23. Participation in another clinical trial with any investigational study drug (whatever the use, curative, prophylactic or diagnostic intent) within 30 days prior to enrollment 24. Incapability to give valid informed consent (including patients who are dependent on the sponsor or the investigator) 25. Pregnancy or breast-feeding women
SAMPLE SIZE	The required sample size was calculated using the program PASS 13 using the following assumptions: Exponential distribution Median PFS for Doxorubicin: 5 months (corresponding to a hazard of 1.66) Median TTP for Mitomycin C + Irinotean: 9 months (resulting in a hazard ratio of 0.56) Study time: 18 months Accrual time: 36 months Withdrawal rate: 0.03 Type I error (alpha): 0.10 (2-sided) Type II error (beta = 1 – power): 0.20 Sample size: 52 treated patients per group Sample size screened: 136 screened patients with a failure rate of 30% With these assumptions, the statistically necessary sample size to demonstrate that PFS for TACE with Mitomycin C and Irinotecan is at least 9 months compared to 5 months for TACE with Doxorubicin is 104 patients (1:1 randomization; 52:52 patients, power 80 %).

AIO-HEP-0418: A randomized, 2-arm non-comparative phase II study on the effects of atezolizumab and Roche bevacizumab (atezo/bev) followed by on-demand selective TACE (sdTACE) upon detection of disease progression or of initial synchronous treatment with TACE and atezo/bev on 24-Months survival rate in the treatment of BCLC B hepatocellular carcinoma patients. (DEMAND)

AIO-Studie

Studiennummer/-Code:	AIO-HEP-0418 – DEMAND www.demand-study.com	
Status:	Recruiting	
Rekrutierungszeitraum:	Studienstart Q2 2020 – Q3 2022	
Zentren:	geplant: 15	initiiert: 15
Patienten:	geplant: 106	eingeschlossen: 24
Weitere Zentren:	Interessierte Zentren können sich auf die Wartliste setzen lassen	
Letzte Aktualisierung	Oktober 2021	

STUDY TYPE	Open label, multicenter phase II trial
PRINCIPAL INVESTIGATOR	PD Dr. med. Enrico De Toni CO-PI: Prof. Jens Ricke and Prof. Julia Mayerle Medizinische Klinik und Poliklinik 2 and Department of Clinical Radiology Klinikum der Universität München Marchioninistr. 15 81377 München Phone: +49 89-4400-0 Fax.: +49-89-4400-5571 E-Mail: enrico.detoni@med.uni-muenchen.de
DATA MANAGEMENT	ClinAssess, Gesellschaft für klinische Forschung mbH Werkstättenstraße 39b 51379 Leverkusen Phone: +49 2171 36 33 6-0 Fax: +49 2171 36 33 6-55 E-Mail: info@clinassess.de
CONDITION	Hepatocellular carcinoma
DESIGN	Open label, multicenter phase II trial
INDICATION	Unresectable hepatocellular carcinoma
OBJECTIVE(S)	**Primary objective**: Assessment of the effect of up-front atezolizumab/Roche bevacizumab (Atezo/Bev) followed by on-demand selective Trans Arterial Chemo Embolization (sdTACE) and of initial synchronous treatment with TACE or Atezo/Bev on 24-months survival rate in the treatment of BCLC B HCC patients. **Secondary objectives:** to determine OS, PFS, CRR, DCR, ORR, Progression rate (both according to Recist 1.1. and mRECIST), time to deterioration of liver function, time to stage progression, time to first TACE (Arm A), time to untreatable progression (TTuP), safety and tolerability of atezo/bev in combination with sdTACE or standard TACE, Quality of Life (EORTC QLQ-C30, EORTC QLQ-HCC18). Objective response as determined by the investigator according to RECIST v 1.1 and OS based on the following biomarkers in tumor tissue: CD8, CD3, CD4 protein expression level or TREG, MDSC, CD8+ CD3+ and CD4+ T cell localization in tumor samples; Immune-related and tumor-related biomarkers profiling in plasma and serum (miRNA-122, AFP, AFP-L3, IL-6, PIVKA II)
INTERVENTION(S)	Arm A: Up-front Atezo/Bev followed by sdTACE: Patients will receive atezolizumab at the fixed dose of 1200mg IV and Roche Bevacizumab at the dose of 15 mg/Kg IV on day 1 and every three weeks. Upon detection of

	radiological progression according to RECIST 1.1., selective TACE directed against progressive lesions (sdTACE) will be performed within a week. Atezo/Bev will be administered on day 0-2 and every three weeks for up to two years. Arm B: Synchronous Atezo/Bev+TACE: TACE will be performed on day 0 as selectively as possible against all viable tumor lesions. Atezo/Bev will be administered on day 0-2 and every three weeks for up to two years. Randomization will be stratified according to the following stratification factors: 1. Baseline AFP ($<$ 400 vs. $\geq$ 400 ng/mL) 2. Child-Pugh (A vs.B7) 3. Localization of lesions (unilobar vs. multilobar) TACE In order to standardize treatment and avoid TACE-related differences in efficacy and treatment tolerability, DEB-TACE will be used as a standard method for TACE in the DEMAND study. TACE will be performed as selectively as possible until criteria for discontinuation of local treatment are met. Each lesion can be treated only once by TACE within the study. However, treatment with radiofrequency ablation (RFA) or microwave ablation (MWA) within the study is permitted to treat progression. Study assessments Patients will be assessed weekly after the first application of therapy and thereafter every 3 weeks in alignment with drug administration. Efficacy will be evaluated by CT or MRI abdomen and CT thorax 6 weeks after treatment initiation and every 8 weeks thereafter (**Table 1**). Since these intervals correspond to the accepted standard of care, no BfS approval will be needed.
BACKROUND/RATIONALE	Phase II trials with nivolumab and pembrolizumab showed promising results in terms of objective response and overall survival (1-3) which led to the approval of these agents by the FDA for treatment of advanced HCC. The ORR in patients treated with nivolumab amounted to 15% and the median overall survival of sorafenib-naïve patients to 28.6 months (4). The reported OS for nivolumab compares favorably with the median OS reported for HCC patients undergoing TACE in the real-life setting (19 months (5)) and in recent randomized trials (6-10) on the use of TACE for patients with intermediate-stage HCC. The recent phase I trials of combined treatment with pembrolizumab/lenvatinib or atezolizumab/bevacizumab (11, 12) have shown that the efficacy of Check Point Inhibitors may be enhanced by their combination with substances with antiangiogenic potential. ORR in patients treated with atezolizumab and bevacizumab was 34% (acc. to mRECIST) with a complete response rate of 11% and a disease control rate of 77% (12). These promising data suggest that systemic treatment with atezolizumab/bevacizumab might be combined with TACE for the treatment of patients with intermediate-stage HCC. In fact, due to the potential sensitizing effect of TACE to the action of CPI inhibitors, a more than additive effect of the two treatment modalities might be expected (13). Although TACE is usually performed selectively in order to prevent unintended collateral damage to the liver parenchyma, significant deterioration of liver function may occur due to TACE treatment (14). Combining CPI and TACE might contribute to preserve liver function during treatment by reducing the extent and the number of TACE cycles needed to achieve tumor control.

	Rationale for sdTACE In arm A, treatment will be initiated with Atezo/Bev. TACE will be performed only upon detection of radiological progression, and will be directed against progressive lesions only. This has several potential advantages: − a CPI-first approach would select a group of responders benefitting from the potential long-term tumor control associated to treatment with Atezo/Bev (12) hereby limiting the use of TACE only to patients with progressive disease. The fact that response to CPI translates into excellent survival is exemplified by the fact that responders to Nivolumab had OS rates of 100% after 18 months (El-Khoueiry et al., ASCO GI-cancer symposium 2018). Of note, almost all responders to Atezo/Bev showed an objective response within 8 weeks from treatment initiation (12) which allows for early selection of responders to treatment. − TACE directed against progressive lesions only (i.e. non reponsive to the effect of CPI) will cause a reduction of the proportion of liver parenchyma exposed to the potential collateral damage caused by TACE. However, release of tumor-specific antigen caused by treatment of these lesions might enhance the effect of Atezo/Bev in all tumor lesions (13). Since liver function is a major determinant of prognosis in HCC patients, restriction of the use of TACE to progressive lesions is expected to reflect into a survival advantage. − up-front administration of CPI before TACE is also relevant to the concern that the disruption of tumour vascularization caused by TACE might impair the delivery of CPI and, possibly, prevent the access of circulating lymphocytes to the tumor lesions. IN SUMMARY. An increase of effectiveness and a decrease of treatment-related impairment of liver function are expected owing to: 1) the combined effect of the treatment modalities, 2) the potential sensitizing effect of TACE to the action of Atezo/Bev (both study arms), 3) the smaller proportion of liver parenchyma exposed to the potential collateral damage caused by TACE allowed by the up-front selection of tumor lesions responsive to CPI and the selective treatment of progressive lesions (arm A). Safety considerations Life-threatening septic and vascular complications were described in earlier trials of combined TACE and bevacizumab. The most important concerns were raised by a report of high incidence of severe vascular and septic complications with fatal outcomes (15). Instead, no fatalities and an altogether lower number of severe events were reported by two other studies with comparable design, although in these studies higher doses of bevacizumab (10 mg/kg vs. 5 mg/Kg every 2 weeks) were used in combination to TACE (16, 17). Although baseline differences in patients' history and characteristics represent a possible explanation for these different outcomes, it is likely that the frequency of TACE (median: 3 TACE cycles, range 1 to 6 (15) vs. median 2, range: 1-3 (17)) might have affected the incidence of adverse events in the different studies. To minimize the possible detrimental effect of repeated TACE, only one TACE of each lesion will be allowed as study-specific treatment. In addition, the need for repeated local or locoregional treatment is expected to be markedly delayed by the combined effect of Atezo/Bev on disease progression (DCR amounting to 77%). The potential negative impact of TACE on liver function will be further decreased by employment of sdTACE in study arm A. To reduce the likelihood of septic complications related to extensive tumor necrosis and abscess formation, patients with tumors exceeding 7 cm

	in diameter (vs. up to 15 cm in previous trials (15) will be excluded from the study.
KEY INCLUSION CRITERIA	Patients must meet the following criteria for study entry: Signed Informed Consent Form Age ≥ 18 years at time of signing Informed Consent Form Ability to comply with the study protocol, in the investigator's judgment HCC with diagnosis confirmed by histology Disease which is not amenable to curative surgical and/or local ablation treatment but eligible for TACE, with tumor burden below 50% of liver volume. No prior systemic therapy for HCC At least one measurable (per RECIST 1.1) untreated lesion Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound) are eligible provided the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field of local therapy have subsequently progressed in accordance with RECIST version 1.1. ECOG Performance Status of 0 or 1 Child-Pugh class A or B7 Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment Negative HIV test at screening
KEY EXCLUSION CRITERIA	Patients who meet any of the following criteria will be excluded from study entry: Diffuse HCC or presence of vascular invasion or extrahepatic spread, more than 7 lesions or at least one lesion >= 7 cm Prior treatment with TACE, prior radiation treatment of liver lesions Patients on a liver transplantation list or with advanced disease as defined by the presence of encephalopathy and/or untreatable ascites. Any condition representing a contraindication to TACE Active or history of autoimmune disease or immune deficiency Active tuberculosis Significant cardiovascular disease Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study History of malignancy other than HCC within 5 years prior to screening Severe infection within 4 weeks prior to initiation of study treatment Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment Pregnancy or breastfeeding Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC Patients with untreated or incompletely treated varices with bleeding or high-risk for bleeding Moderate or severe ascites History of hepatic encephalopathy Co-infection of HBV and HCV Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) Patients with indwelling catheters (e.g., PleurX®) are allowed.

	Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment Inadequately controlled arterial hypertension, prior history of hypertensive crisis or hypertensive encephalopathy, significant vascular disease Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of bevacizumab History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment, or history of intestinal obstruction Radiotherapy within 28 days and abdominal/ pelvic radiotherapy within 60 days prior to initiation of study treatment, except palliative radiotherapy to bone lesions within 7 days prior to initiation of study treatment Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure Chronic daily treatment with a nonsteroidal anti-inflammatory drug (NSAID)
STATISTICAL ANALYSIS	Basing on historical data from previous randomized studies (including the TACE-2 (7) the BRISK (8) the SPACE (9) and the ORIENTAL (10) trials), the sample size has been calculated assuming a survival rate of 55% at 20 months for treatment with TACE (null hypothesis). An exact binomial test with a nominal significance level 0.05 will have 80% power to detect a significant difference when the sample size amounts to 44 patients assuming as alternative hypothesis a 20-months survival rate of 75%. Due to 10-15% non-informative drop-outs, the sample size is increased to 50 patients. Secondary parameters will be analyzed in a descriptive manner.
SAMPLE SIZE	N=100 patients randomized into 2 arms, each of 50 patients
TRIAL DURATION AND TIMELINE	Enrolment: 18 Months, Maximal duration: 48 Months including follow-up
COUNTRY	GERMANY
SAFETY ASSESSMENT	A safety analysis will be conducted by an independent safety monitoring once 20 patients in each arm will have completed study treatment. This independent Data Monitoring Committee (iDMC) will also evaluate safety data during the study on a periodic basis. In addition to the planned safety review, additional unscheduled meetings may take place at request of the iDMC or the study team.

AIO-HEP-0319/ass - A Phase II study of immunotherapy with durvalumab (MEDI4736) and tremelimumab in combination with either Y-90 SIRT or TACE for intermediate stage HCC with pick-the-winner design - IMMUWIN

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-HEP-0319/ass - IMMUWIN	
Status:	rekrutierend	
Rekrutierungszeitraum:	Q3 2020 – Q3 2022	
Weitere Zentren:	sind sehr erwünscht	
Zentren:	geplant: 25	initiiert: 6
Patienten:	geplant: 84	aktuell eingeschlossen: 5
Letzte Aktualisierung	18.10.2021	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover
CONDITION	Multinodular or large, solitary HCC, not eligible for resection or local ablation.
OBJECTIVE(S)	Primary objective: To assess the anti-tumor activity of the combination of durvalumab and tremelimumab with either Y-90 SIRT or TACE by objective response rate (ORR) after 6 months. Secondary objectives To assess the efficacy by progression free survival (PFS) and overall survival (OS); to assess safety of the combination treatments (AEs, impact on liver function, use of subsequent therapies); to additionally assess ORR as best overall response (BOR) during therapy; to assess quality of life (QoL). Exploratory objective: To perform correlation analysis between selected molecular parameters and clinical data to identify molecular biomarkers predictive for ORR, PFS and OS
INTERVENTION(S)	Treatment Arm A: Y-90 SIRT + Durvalumab + Tremelimumab Treatment Arm B : TACE + Durvalumab + Tremelimumab
KEY EXCLUSION CRITERIA	1. Diffuse HCC or presence of vascular invasion or extrahepatic spread with the following exception: ○ Invasion of a segmental portal vein or hepatic veins. 2. Patients with advanced liver disease as defined below: ○ Encephalopathy; ○ Untreatable Ascites. 3. Any contraindications for hepatic embolization procedures: ○ Known hepatofugal blood flow; ○ Known porto-systemic shunt; ○ Impaired clotting test (platelet count < 70 Thsd/L, INR > 1.25); ○ Renal failure/insufficiency requiring hemo-or peritoneal dialysis; ○ Known severe atheromatosis; ○ Total thrombosis or total invasion of the main branch of the portal vein. 4. Locoregional therapies ongoing or completed < 4 weeks prior to the baseline scan. 5. History of cardiac disease: ○ Congestive heart failure > New York Heart Association (NYHA) class 2; ○ Active coronary artery disease (CAD) (myocardial infarction ≥ 6 months prior to study entry is allowed); ○ Cardiac arrhythmias (Grade > 2 NCI-CTCAE Version 5.0) which are poorly controlled with anti-arrhythmic therapy or requiring pace maker;

	○ Uncontrolled hypertension; ○ Clinically significant gastrointestinal bleeding within 4 weeks prior to start of study drug 6. 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. 7. Prior, systemic anti-cancer therapy, radiotherapy administered > 4 weeks prior to study entry, endocrine- or immunotherapy or use of other investigational agents. 8. 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: ○ Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) ○ Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent ○ Steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication) 9. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP. 10. Major surgery within 4 weeks of starting the study and patients must have recovered from effects of major surgery. 11. Patients with second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix, unless curatively treated and disease-free for 3 years or longer. 12. 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. 13. 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, history of non-infectious pneumonitis requiring steroids, or patients with Grade ≥2 pneumonitis, 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 14. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice) 15. History of allogenic organ transplantation. 16. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or compliance with the study protocol. 17. Symptomatic brain metastases. A scan to confirm the absence of brain metastases is required in the presence of corresponding symptoms. 18. Pregnant or breast-feeding women. 19. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV). 20. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g. colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], 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: ○ Patients with vitiligo or alopecia ○ Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement ○ Any chronic skin condition that does not require systemic therapy ○ Patients without active disease in the last 5 years may be included but only after consultation with the study physician

	○ Patients with celiac disease controlled by diet alone 21. Known allergy or hypersensitivity to any of the IMPs or any of the constituents of the product. 22. Is currently participating or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. 23. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
KEY INCLUSION CRITERIA	1. Capable of giving written informed consent, including participation in optional translational research if applicable, 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. 2. Age ≥ 18 years at time of study entry. 3. Body weight > 30 kg. 4. Multinodular or large, solitary HCC, not eligible for resection or local ablation. 5. Histologically confirmed diagnosis of HCC. 6. Scheduled to receive locoregional therapy as standard of care. 7. At least one measurable site of disease as defined by RECIST 1.1criteria with spiral CT scan or MRI. 8. No prior systemic anti-cancer therapy. 9. Child-Pugh A. 10. Performance status (PS) ≤ 1 (ECOG scale). 11. Life expectancy of at least 12 weeks. 12. Adequate blood count, liver-enzymes, and renal function: ○ Hemoglobin ≥ 9.0 g/dL, absolute neutrophil count ANC ≥1.5 x 10^9/L (> 1500 per mm^3), platelets ≥ 75 x 10^9/L (>75,000 per mm^3); ○ Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN); ○ AST (SGOT), ALT (SGPT) ≤ 2.5 x institutional ULN unless liver metastases are present, in which case it must be ≤5x ULN; ○ International normalized ratio (INR) ≤ 1.25. 13. Albumin ≥ 31 g/dL. 14. Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance. 15. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial and must use at least 1 **highly** effective form of contraception if sexually active. 16. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving IMP 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 (durvalumab and tremelimumab). Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception). 17. If patient has concurrent Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection, meets the following criteria: ○ Patients with HBV or HCV infection should be monitored for viral levels during study participation; ○ Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA should have HBV DNA < 100 IU/ml and should be managed per local treatment guidelines. Controlled (treated) hepatitis B subjects will be allowed if they started treatment at the time point of enrollment into the study by the latest and treatment is continued during study participation and for ≥ 6 months after end of study treatment; ○ HCV patients with advanced HCC are mostly not treated for their HCV infection. However, patients treated for HCV are considered

	suitable for inclusion if antiviral therapy has been completed prior to first administration of study drug. 18. 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.
OUTCOME(S)	Primary endpoint: ORR at 6 months. Secondary endpoints: • PFS • OS • Safety (AEs, impact of liver function, use of subsequent therapies) • ORR as BOR during therapy • ORR at 6 months for patients who received single treatment of TACE/SIRT • ORR at 6 months for patients who received additional treatment of TACE/SIRT • QoL Exploratory endpoints: Collection of tissue and blood samples for future evaluation of predictive biomarkers for ORR, PFS, OS.
STUDY TYPE	Randomized two arm phase II study
STATISTICAL ANALYSIS	The trial design is based on the Simon, Wittes and Ellenberg's Pick-the-winner design [Simon et al., 1985]. The trial requires 36 patients per arm to detect 10% difference in ORR between arms with an 80% power, considering an ORR of 40% for anti-PD-L1 antibodies combined with TACE. If no difference in response rate is detected, the least toxic regimen will be selected. Only eligible patients who received at least one cycle of IMP treatment with at least one subsequent tumor response assessment will be considered for the primary endpoint. The dropout rate is set at 15%. Therefore, the total population is 84 patients (42 patients per arm). Primary endpoint can be analyzed as soon as events are available.
SAMPLE SIZE	84 patients to be randomized (42 patients per treatment arm).
TRIAL DURATION	Considering an enrollment of 4 patients/month from 25 participating centers, a total of 24 months is estimated for enrollment. The follow-up time for primary endpoint after last patient in is at 6 months.
PARTICIPATING CENTERS	25 participating centers planned.

HCC, fortgeschrittenes Stadium, 2nd-line

AIO-HEP-0121/ass – A phase-II open-label study of pembrolizumab and lenvatinib in patients with advanced stage hepatocellular carcinoma who are refractory to atezolizumab and bevacizumab/ IO-based therapy - SOLARIS

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-HEP-0121/ass - SOLARIS**
Status:	in Vorbereitung
Rekrutierungszeitraum	2021-2024 (geplant)
Weitere Zentren:	Nicht benötigt
Zentren:	geplant: 10
Patienten:	geplant: 32
Letzte Aktualisierung	Oktober 2021

Trial type	Interventional, single-arm, open-label, multicenter phase II trial
Coordinating investigator	Prof. Dr. med. Arndt Vogel Medizinische Hochschule Hannover Klinik für Gastroenterologie, Hepatologie and Endokrinologie Carl-Neuberg-Str. 1 30625 Hannover
Sponsor Project Management Sponsor	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Sabine Junge Tel: +49 69 / 76 01-4186 Email: junge.sabine@ikf-khnw.de
Medical condition	Advanced hepatocellular carcinoma (HCC)
Objectives/Endpoints (efficacy, safety)	The primary objective of this phase II trial is to assess the objective response rate (ORR) according to RECIST 1.1 criteria. Secondary objectives are assessment of progression free survival (PFS), overall survival (OS) and safety and toxicity. <u>Primary endpoint:</u> • Objective response rate (ORR), defined as the percentage of patients with complete response (CR) or partial response (PR) according to RECIST 1.1 <u>Secondary endpoints:</u> • Progression-free survival, defined as time from first dose of study treatment to disease progression according to RECIST 1.1 or death • Overall survival, defined as time from first dose of study treatment to the date of death of any cause • Safety and toxicity: Adverse events will be recorded and graded according to version 5.0 of National Cancer Institute Common Toxicity Criteria (NCI-CTC). Exploratory Objective: • Identification of molecular biomarkers predictive for ORR, PFS and OS in tumor and serum.

<table>
<tr><td>Intervention(s)</td><td>All patients will be treated as follows:
Pembrolizumab 200 mg IV Q3W
Lenvatinib 8 mg for BW < 60 kg / 12 mg for BW ≥ 60 kg p.o. QD
Treatment will be performed until disease progression, unacceptable toxicity, patients' request or end of protocol treatment (maximum of 24 months).</td></tr>
<tr><td>Inclusion/exclusion criteria</td><td>Patients must meet all of the following <u>Inclusion Criteria</u> for trial participation:
Histologically confirmed diagnosis of HCC.
Have a tumor, not eligible for resection or local ablation.
Have experienced disease progression under previous ≥ 4 cycles/12 weeks atezolizumab and bevacizumab therapy.
Have a Child-Pugh Classification score ≤ 6 for assessed liver function within 7 days before allocation
Have at least one measurable site of disease based on RECIST 1.1 with spiral CT scan or MRI. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
Male/female participants who are at least 18 years of age on the day of signing informed consent will be enrolled in this study.
A female participant is eligible to participate if she is not pregnant not breastfeeding, and at least one of the following conditions applies:
a.) Not a woman of childbearing potential (WOCBP) as defined in OR
b.) A WOCBP who agrees to follow the contraceptive guidance in during the treatment period and for at least 120 days after the last dose of study treatment.
A male participant with female partner of childbearing potential is eligible to participate if he agrees to follow the contraceptive guidance in during the treatment period and for at least 120 days after the last dose of study treatment.
A male participant must agree to use a contraception as detailed in of this protocol during the treatment period and for at least 210 days after the last dose of study treatment and refrain from donating sperm during this period.
The participant provides written informed consent for the trial.
Either pre-treatment tumor tissue available
Newly obtained biopsies are preferred to archived tissue (archived specimen ≤ 6 months may be acceptable).
Core or excisional biopsies mandatory (fine needle aspiration and bone metastasis samples are not acceptable).
Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides.
If submitting 15 unstained cut slides, newly cut slides should be submitted to the IKF GmbH lab within 14 days from the date slides are cut.
OR
tumor tissue is not available as e.g., patient has never undergone biopsy or tissue depleted because of prior diagnostic testing
Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of allocation.
Have a life expectancy of ≥ 12 weeks.
Have adequate organ function as defined in the following table. Specimens must be collected within 7 days prior to the start of study intervention.
<table><tr><th>System</th><th>Laboratory Value</th></tr><tr><td>Hematological</td><td></td></tr></table></td></tr>
</table>

Absolute neutrophil count (ANC)	≥ 1500/µL
Platelets	≥ 75000/µL
Hemoglobin	≥ 8.0 g/dL[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 × ULN OR ≥ 40 mL/min for participant with creatinine levels > 1.5 × institutional ULN
Hepatic	
Total bilirubin	≤ 2 mg/dL OR direct bilirubin ≤ ULN for participants with total bilirubin levels > 2 mg/dL
AST (SGOT) and ALT (SGPT)	≤ 5 × ULN
Albumin	≥ 3.0 g/dL
Pancreatic	
Amylase	≤ 1.5 × ULN
Lipase	≤ 1.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Transfusion are permitted to meet criteria.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

14. Participants with past or ongoing HCV infection will be eligible for the study. The treated participants must have completed their treatment at least 1 month prior to starting study intervention and HCV viral load must be below the limit of quantification.

    Participants with controlled hepatitis B will be eligible if they meet the following criteria:

    - Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be less than 500 IU/mL prior to first dose of study drug. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study intervention.
    - Participants who are positive for anti-hepatitis B core antibody HBc, negative for HBsAg, and negative or positive for anti-hepatitis B surface antibody (HBs), and who have an HBV viral load under 100 IU/mL, do not require HBV antiviral prophylaxis.
    - Has adequately controlled blood pressure with or without antihypertensive medications, defined as BP ≤ 150/90 mm Hg at Screening and no change in antihypertensive medications within 1 week before Cycle 1 Day 1.

	Participants are excluded from the study if any of the following criteria apply: 1. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC. 2. Have received prior therapy with any TKI and/ or anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137) other than atezolizumab and bevacizumab. 3. A WOCBP who has a positive urine pregnancy test within 72 hours prior to allocation (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: in the event that 24 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication. 4. Have received prior systemic anti-cancer therapy including investigational agents within 4 weeks or at least 5 half-lives of the respective drug/IMP (whichever is longer) prior to allocation. Note: Participants must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy may be eligible. Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study intervention. 5. Have received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease. 6. Have received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed. 7. Are currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks or for a period of at least 5 half-lives of the respective drug/IMP (whichever is longer) before Screening and during Screening for this trial. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks or at least 5 half-lives of the respective drug/IMP (whichever is longer) after the last dose of the previous investigational agent. 8. Have a diagnosis of immunodeficiency or are receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. 9. Have a known additional malignancy that is progressing or has required active treatment within the past 2 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. 10. Have known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. 11. Have severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients. 12. Have a history of congestive heart failure NYHA > Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose

	of study treatment, or cardiac arrhythmia requiring medical treatment at Screening 13. Have bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. Note: The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy 14. Have active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. 15. Have a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. 16. Have an active infection requiring systemic therapy (exception: HBV infection – see inclusion criteria). 17. Have a history of Human Immunodeficiency Virus (HIV) (mandatory testing for HIV during screening is required). 18. Have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating Investigator. 19. Have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 20. Are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment. 21. Are unable to swallow orally administered medication or have gastrointestinal disorders likely to interfere with absorption of the study medication. 22. Legal incapacity or limited legal capacity.
Number of patients, and location	Total number of patients: 32 Location of sites: Germany
Trial duration	First patient in to last patient out (months): 36 Duration of the entire trial (months): 36 Recruitment period (months): 12
Number of enrolled pts.	0, trial in preparation
Participating centers	10 in total

AIO-HEP-0320/ass: A phase II study evaluating reduced starting dose and dose escalation of Cabozantinib as second-line therapy for advanced HCC in patients with compensated liver cirrhosis (CaboRISE)

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-HEP-0320/ass_CaboRISE**
Status:	aktiv
Rekrutierungszeit:	Studienstart Q4 2020, Rekrutierungszeit 12 Monate
Anzahl Zentren:	geplant: 10 aktuell initiiert: 8 aktiv rekrutierend: 4
Weitere Zentren:	sind sehr erwünscht
Anzahl Patienten:	geplant: 40 aktuell eingeschlossen: 7 (FPI 12.10.2020)
Letzte Aktualisierung	10/2021

APPLICANT/ COORDINATING INVESTIGATO	Prof. Dr. med. Jörg Trojan Universitätsklinikum Frankfurt Goethe-Universität Medizinische Klinik 1 Theodor-Stern-Kai 7 60590 Frankfurt/Main
CONDITION	Advanced stage hepatocellular carcinoma (HCC) patients with compensated liver cirrhosis in second line therapy
OBJECTIVE(S)	The primary objective is to assess the tolerability of a reduced starting dose of 40 mg cabozantinib once-daily for 4 weeks and subsequent dose escalation to 60 mg cabozantinib once-daily to be maintained until disease progression or intolerable toxicities in patients with advanced stage hepatocellular carcinoma (HCC) with compensated liver cirrhosis in second line therapy.
INTERVENTION(S)	Cabozantinib 20 mg/day // Cabozantinib 40 mg/day // Cabozantinib 60 mg/day
KEY EXCLUSION CRITERIA	1. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within at least 4 months. 2. Significant portal hypertension (moderate or severe ascites). Significant hypertension, defined as blood pressure ≥ 140 mmHg (systolic) or ≥ 90 mmHg (diastolic) in repeated measurements. 3. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC. 4. Liver cirrhosis Child-Pugh B or C. 5. Severely impaired kidney function. 6. Elevations of AST/ALT > 5 x ULN at baseline. 7. History of encephalopathy in past 12 months. 8. Significant cardiovascular disease (such as NYHA Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina. 9. Baseline QTcF > 500 ms. 10. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study. 11. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. 12. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational

	drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications. 13. Treatment with investigational systemic therapy within 28 days or five times the elimination half-life of the investigational product, whichever is longer, prior to initiation of study treatment. 14. Prior cabozantinib use. 15. Known or suspected hypersensitivity to cabozantinib or any other excipients of the IMP. 16. Rare hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption. 17. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. 18. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 19. 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].
KEY INCLUSION CRITERIA	1. Fully informed written consent. 2. Males and females ≥ 18 years of age. *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. Patients with HCC who have been previously treated with sorafenib or lenvatinib in first line. 4. Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/ cytology or clinically by guideline criteria in cirrhotic patients. 5. Disease that is not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and /or locoregional therapies. 6. Resolution of any acute, clinically significant treatment-related toxicity from prior therapy to Grade 1 prior to study entry, with the exception of alopecia. 7. ECOG performance status ≤ 2. 8. Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment. 9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods from the time of signing the informed consent through at least 4 months after the last dose of study drug or agree to completely abstain from heterosexual intercourse. Male patients, even if surgically sterilized (i.e. status post-vasectomy) must agree to practice effective barrier contraception (e.g. condom) and to refrain from sperm donation during the entire study treatment period and through at least 4 months after the last dose of study drug or agree to completely abstain from heterosexual intercourse.
OUTCOME(S)	<u>Primary endpoint</u>: Treatment discontinuation rate due to treatment-related adverse events. <u>Secondary endpoints:</u> • Overall survival (OS) • Progression free survival (PFS) at 10 weeks • Objective response rate (ORR) • Time on treatment • Treatment exposure (dose intensity/dose reductions) • Toxicity • QoL (QLQ-C30)

	• Correlation of biomarkers potentially associated with clinical efficacy (OS, PFS and ORR) Translational Research: FFPE tissue for future translational research projects are being collected upon the patient's consent only. Translational research projects are not per-determined by this protocol and will be defined taking latest research data into account. The TR might include the assessment of the following: • FFPE tissue for IHC staining; • FFPE tissue for nucleic isolation to assess the expression of biomarkers, determination of genetic alterations in HCC (panel sequencing) or to determine the mutational load.
STUDY TYPE	Open-label, single-arm, multicenter phase II trial
STATISTICAL ANALYSIS	Based on the study by Abou-Alfa [Abou-Alfa et al., 2018], the rate of Cabozantinib treatment discontinuation for toxicity is 16%. Our hypothesis is that therapy optimization using a lower starting dose would reduce the rate of treatment discontinuation or toxicity to 10% or lower, which is a reasonable aim, and is considered to be a clinically relevant advantage. On the other hand, efficacy will not be impaired as more patients will be able to maintain the planed doses. The study is exploratory and has no formal, power-based sample size calculation. The primary endpoint is the rate of treatment discontinuation for toxicity. Because only the highest rate of discontinuation for toxicity is of interest, the tests are one-sided. Enrolling 40 patients would result in an upper 90% confidence interval (CI) limit of 16.3% for the expected discontinuation rate, which is similar to mean rate seen with the standard dose regimen and is considered acceptable for an exploratory trial. Secondary endpoints are overall survival, progression-free survival, and dose reductions. The primary population for the analyses consists of all registered patients (intention-to-treat). A per-protocol population will be prospectively defined for sensitivity analyses, based on the amount of treatment actually received according to protocol. The primary endpoint is defined as the number of patients with treatment discontinuation for toxicity divided by the number of all patients enrolled. The secondary endpoints PFS and OS will be analyzed using the Kaplan-Meier method.
SAMPLE SIZE	40 patients
TRIAL DURATION	Overall study duration: 27 months
PARTICIPATING CENTERS	10 centers

AIO- HEP-0419/ass: A Phase II, non-randomized, single arm, translational study of CAbozantinib for Patients with HepatocellUlaR CarcinOma (HCC) Refractory to first line TreAtment - AURORA

AIO-assoziierte Studie		
Studiennummer/-Code:	**AIO- HEP-0419/ass - AURORA**	
Status:	rekrutierend	
Rekrutierungszeitraum:	Q3 2020 – Q2 2021	
Weitere Zentren:	Vorerst nicht geplant	
Zentren:	geplant: 10	initiiert: 9
Patienten:	geplant: 45	aktuell eingeschlossen: 6
Letzte Aktualisierung	18.10.2021	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover
CONDITION	Locally Advanced and/or metastatic and/or unresectable Hepatocellular Carcinoma (HCC)
OBJECTIVE(S)	The primary objective is to assess the Time-to-Treatment-Failure with cabozantinib in lenvatinib pre-treated patients with locally advanced and/or metastatic and/or unresectable Hepatocellular Carcinoma (HCC).
INTERVENTION(S)	Cabozantinib 60 mg/day
KEY EXCLUSION CRITERIA	1. Unwillingness to give informed consent for participation in the study. 2. Prior sorafenib treatment. 3. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within at least 5 months. 4. Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment. 5. Significant portal hypertension (moderate or severe ascites). 6. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC. 7. Liver cirrhosis Child-Pugh B with > 7 points and Child-Pugh C. 8. Severely impaired kidney function. 9. History of encephalopathy in past 12 monthsmonths, if not completely regressive or more than one episode within the last 6 months. 10. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina. 11. Baseline QTcF >500 ms. 12. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study. 13. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. 14. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational

	drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications. 15. Elevations of AST/ALT exceeding 5 X ULN. 16.Treatment with investigational systemic therapy within 28 days prior to initiation of study treatment. 17. Prior cabozantinib use. 18.Is currently participating or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. 19.Patients who have been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 20.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].
KEY INCLUSION CRITERIA	1. Fully-informed written consent. 2. Males and females ≥ 18 years of age. *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/ cytology or clinically by guideline criteria in cirrhotic patients 4. Disease that is not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and /or locoregional therapies. 5. Patients who have shown progressive disease during or after first line therapy OR patients must have had their treatment interrupted due to the level of toxicities AND cabozantinib therapy is intended as second line therapy. 6. ECOG performance status ≤ 2. 7. Resolution of any acute, clinically significant treatment-related toxicity from prior therapy to Grade 1 prior to study entry, with the exception of alopecia. 8. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods.
OUTCOME(S)	<u>Primary Endpoint</u> The primary efficacy endpoint is: • Time-on-Treatment <u>Secondary Endpoints</u> The secondary endpoints will include: • Overall survival (OS) • Progression free survival (PFS) • Objective response rate (ORR) according to RECIST 1.1 • Duration of response (DOR) • Treatment exposure (time on treatment/dose intensity/dose reductions) • Toxicity: o Treatment-related adverse events (TRAEs) o TRAE related treatment interruptions o TRAE related treatment modifications o TRAE related treatment discontinuations • Change in ECOG Performance Status during treatment • Change in ALBI Grade during treatment • Change in Child Pugh Score during treatment • Translational research: correlation of biomarkers potentially associated with clinical efficacy (OS, PFS and ORR) of cabozantinib by o NGS Oncopanel analysis o VEGF module expression analysis.

STUDY TYPE	Open-label, single-arm, multicenter phase II trial
STATISTICAL ANALYSIS	The present trial aims to estimate the therapeutic efficacy of the experimental regimen after prior first line therapy with time on treatment as primary endpoint. Since the efficacy of Cabozantinib after first line therapy other than sorafenib has not yet been studied, this study is hypothesis generating. It is intended to include 45 patients. The patients will be enrolled in 10 centers. All analyses are of purely descriptive character. OS, PFS and time on treatment be analyzed using Kaplan-Meier methods. Binary, categorical and ordinal parameters will be summarized by means of absolute and percentage numbers within the various groups (including 'missing data' as valid category). Numerical data will be summarized by means of standard statistics (i.e. number of available data, number of missing data, mean, standard deviation, minimum, median, maximum, lower and upper quartile).
TRIAL DURATION	Overall study duration: 30 months

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 (DKN-01)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-HEP-0318/ass	
Status:	rekrutierend	
Rekrutierungszeitraum:	Studienstart August 2018 – antizipiert bis August 2021	
Weitere Zentren:	ggfs. im Verlauf möglich	
Zentren:	geplant: 6-7	initiiert: 6
Patienten:	geplant: 70	aktuell eingeschlossen: 5 (Part A)
Letzte Aktualisierung	12.10.2020	

PRINCIPAL INVESTIGATOR	Jun. Prof. Dr. J. U. Marquardt Prof. Dr. Markus Möhler
TRIAL OFFICE	I. Medizinische Klinik und Poliklinik Universitätsmedizin Mainz 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. - New York Heart Association Class III or IV cardiac disease, myocardial infarction within the past 6 months, or unstable arrhythmia. - 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. - Active, uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry requiring systemic therapy. - human immunodeficiency virus (HIV) positive, - History of major organ transplant (i.e., heart, lungs, liver, or kidney). - History of autologous/allogenic bone marrow transplant. - Serious non-malignant disease that could compromise protocol objectives in the opinion of the Investigator and/or Sponsor. - Pregnancy or nursing. - Major surgical procedures, open biopsy or significant traumatic injury within 4 weeks prior to treatment start (minor procedures within 1 week) - History of osteonecrosis of the hip or evidence of structural bone abnormalities in the proximal femur on magnetic resonance imaging (MRI) scan that are symptomatic and clinically significant. Degenerative changes of the hip joint are not exclusionary. Screening of asymptomatic patients is not required. - 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. - Known osteoblastic bone metastasis. Screening of asymptomatic patients without a history of metastatic bone lesions is not required. - Medical or psychological conditions that would jeopardise an adequate and orderly completion of the trial. - Thrombotic or embolic events (except HCC tumor thrombus <pVT4) within the past 6 months (including cerebrovascular accidents) - Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 6 months - Patients with portal thrombosis = pVT4 Medication Related - Prior locoregional therapy or radiation therapy within 28 days prior to first dose. - prior systemic therapy for HCC - Currently receiving any other investigational agent or received an investigational agent within last 30 days prior to first dose or within 5 times the half-life of this agent before the first dose of study treatment. - Previously treated with an anti-DKK1 therapy.

	- Treatment with strong inducers of CYP3A4 within 7 days prior to first dose (including Cyclosporin, Erythromycin, Ketoconazole, Itraconazole, Quinidine, Phenobarbital salt with Quinidine, Ritonavir, Valspodar, Verapamil, St John's wort, rifampicin). - Significant allergy to a pharmaceutical therapy that, in the opinion of the Investigator, poses an increased risk to the patient. - 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. Lifestyle-Related - Active substance abuse (including active alcohol abuse). - Involuntary incarcerated patients
KEY INCLUSION CRITERIA	- Ambulatory male or female patients ≥ 18 years - 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. - Tumor tissue is **mandatory** for pre-treatment evaluation (baseline) (fresh biopsy during 4-weeks screening time preferred. Archived specimen is only acceptable, if ≤ 6 months old. Baseline tumor biopsy samples must be available prior to the first dose of DKN-01. - Tumor tissue (FFPE) must be received by central histopathology laboratory for correlative studies (fine needle aspiration and bone metastasis samples are not acceptable). - 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. - Child-Pugh score <7 (Child-Pugh Class A). - Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease not amenable to resection, locoregional therapy or refractory to locoregional therapy. - At least one tumor lesion measurable on radiographic imaging as defined by mRECIST for HCC **that has not been previously** treated by locoregional therapies. - Locoregional therapies or radiation therapy must be completed at least 4 weeks prior to baseline scan. All toxic effects > grade 1 (NCI CTCAE v5.0) 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). - ECOG performance status (PS) of 0 or 1. - Estimated life expectancy of at least 3 months, in the judgment of the Investigator. - 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. - Patients are eligible to enroll if they have non-viral-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows: 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). Patients with chronic HBV infection must have HBV DNA < 2000 IU/mL and must be on antiviral therapy. o HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody - Acceptable liver function: o Total bilirubin ≤2.0 × upper limit of normal (ULN). o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN. - Acceptable renal function: o Calculated creatinine clearance ≥50 mL/min using the Cockcroft and Gault Method (Cockcroft and Gault 1976). - Acceptable hematologic status: o Neutrophil Granulocyte ≥1500 cells/µl. o Hemoglobin ≥ 8,5 g/dL (= 5,28 mmol/l) (transfusion permitted within 30 days of study entry). o Platelet count ≥75,000 cells/µl. - Acceptable coagulation status:

	○ INR ≤ 1.7 and no active bleeding, (i.e., no clinically significant bleeding within 14 days prior to first dose of study therapy) - Female subjects who are post-menopausal (defined as spontaneous amenorrhea for at least a year) or permanently sterilized (e.g. bilateral oophorectomy, hysterectomy, bilateral salpingectomy) can participate in the trial and are not required to use any contraception. - Women of child bearing potential (WOCBP, a woman is considered of childbearing potential i.e. fertile, following menarche and until becoming post-menopausal) 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 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. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as: ○ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: ▪ oral ▪ intravaginal ▪ transdermal ○ progestogen-only hormonal contraception associated with inhibition of ovulation: ▪ oral ▪ injectable ▪ implantable ○ intrauterine device (IUD) ○ intrauterine hormone-releasing system (IUS) ○ bilateral tubal occlusion ○ vasectomised partner (medical assessment must be present and done) ○ sexual abstinence when this is in line with the preferred and usual lifestyle of the subject - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together. Sexually-active male subjects must be willing to use contraception (condom, contraception for non-pregnant WOCBP partner) with their partners throughout the study and for 18 months after last dose of study drug and agree to inform the
OUTCOME(S)	Part A: 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. Part B: To assess the time to progression (TTP1, TTP2) in treatment naïve patients with advanced HCC after treatment with DKN-01 monotherapy until PD1 and in combination with sorafenib until PD2. TTP1 and TTP2 will be determined according to mRECIST.
STATISTICAL ANALYSIS	Definition: PD1: Progressive Disease according to mRECIST with DKN-01 monotherapy. 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. Primary analysis variable: 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. Secondary analysis variables: - 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. - For duration of response (time from first to the last disease control (CR, PR, or SD)) will be displayed by descriptive statistics. - 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 Interim analysis: 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, Lübeck

CCA –1st-line / 2nd-line

AIO-HEP-0221/ass: A phase II single-arm, open-label study of Atezolizumab and Derazantinib for patients with advanced intrahepatic cholangiocarcinoma with FGFR2 fusions/rearrangements - ADVANCE

AIO-assoziierte-Studie

Studiennummer/-Code:	**AIO-HEP-0221/ass**		
Status:	in Vorbereitung		
Rekrutierungszeit:	von: Jul-2021	bis: Jul-2023 (Rekrutierung 2 Jahren)	
Anzahl Zentren:	geplant: 20	aktuell initiiert: 0	aktiv rekrutierend: 0
Weitere Zentren:	sind erwünscht (Details siehe unten)		
Anzahl Patienten:	geplant: 37	aktuell eingeschlossen: 0	
Letzte Aktualisierung	26.03.2021		

STUDY TYPE	Multicenter, single-arm, open-label, phase II
PRINCIPAL INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover

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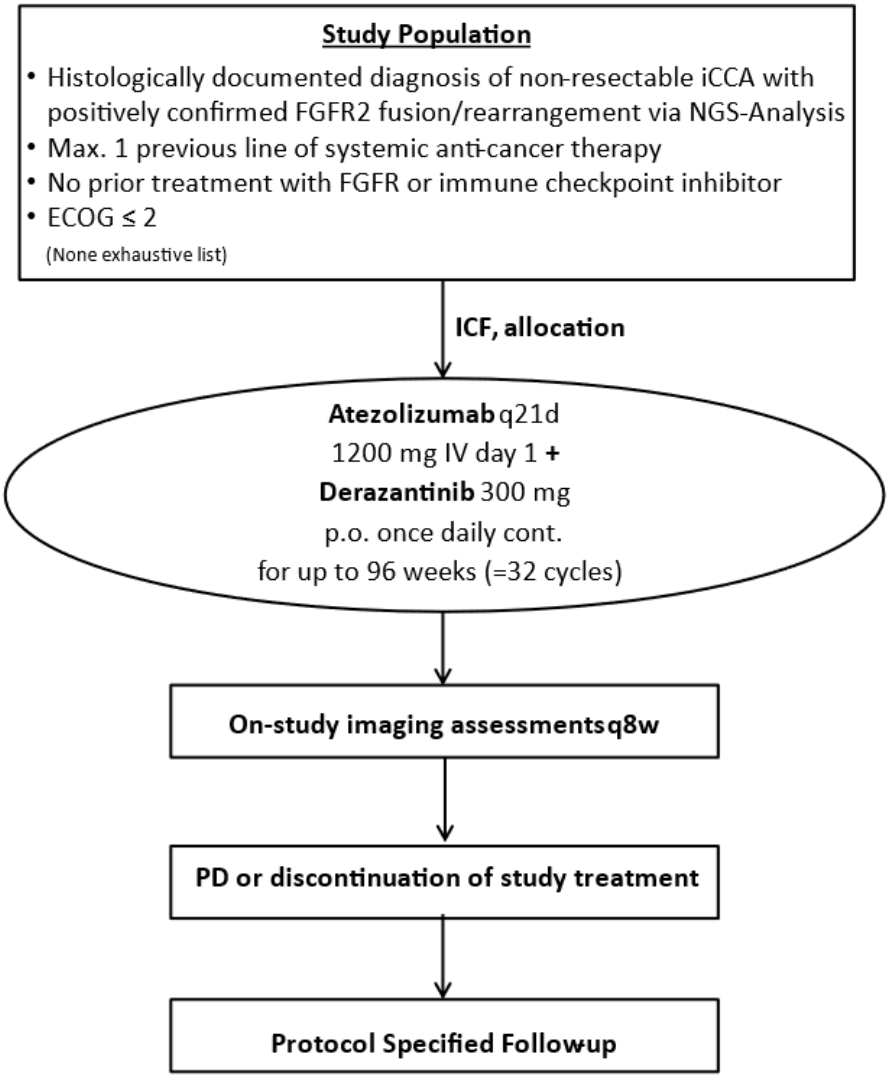
TRIAL OFFICE	IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
SPONSOR	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main, Germany Tel.: +49 69 7601-4420, Fax -3655 info@ikf-khnw.de
CONDITION	Advanced Intrahepatic Cholangiocarcinoma (iCCA) with FGFR2 fusions/rearrangements
DESIGN	This is a Phase II study, which investigates as a prospective, exploratory, single-arm, open-label study the efficacy of atezolizumab and derazantinib for patients with advanced intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements 37 patients will be enrolled to receive atezolizumab 1.200mg i.v. Q3W and derazantinib 300mg p.o. once daily until disease progression or unacceptable toxicity or a maximum of 96 weeks (32 cycles). Tumor imaging (CT/MRI scans) will be performed Q8W according to current SOC.
INDICATION	Advanced Intrahepatic Cholangiocarcinoma (iCCA) with FGFR2 fusions/rearrangements
OBJECTIVE(S)	The aim of this phase II study is to explore the safety and anti-tumor efficacy of the combination of atezolizumab and derazantinib in patients with advanced intrahepatic cholangiocarcinoma, with ORR as the primary endpoint. **Primary Objective** To assess the efficacy by ORR after 9 months of study treatment according to RECIST 1.1 criteria. Corresponding Endpoint • **Objective Response Rate (ORR [assessed every 8 weeks (±7 days)]):** Objective response rate (ORR) according to investigator-based RECIST 1.1 assessment, defined as the proportion of allocated subjects with best response of complete or partial response within 9 months after the date of first administration of study treatment **Secondary Objectives** a) To assess safety. Corresponding Endpoints • Incidence, treatment relationship, seriousness, and severity of all AEs, SAEs, AESIs according to CTCAE V5.0 b) To assess efficacy further. Corresponding Endpoints • **ORR@EOT:** Objective response rate (ORR) according to investigator-based RECIST 1.1 assessment, defined as the proportion of allocated subjects with best response of complete or partial response within study treatment. • **PFSR@6, 8 and 10 months:** The proportion of patients known to be alive and without confirmed objective disease progression at 6, 8 and 10 months after first administration of study treatment, respectively.

	• **PFS:** Time from first administration of study treatment until the date of first objective disease progression or death. • **OS:** Time from first administration of study treatment until death of a patient due to any cause.
INTERVENTION(S)	Patients will receive atezolizumab 1.200mg i.v. on day 1 every 3 weeks (Q3W). Derazantinib will be given in its recommended phase 2 dose of 300 mg p.o. once daily (q.d.). Treatment will be divided into 3-week cycles according to the i.v. component and will be administered until disease progression or unacceptable toxicity or a maximum of 96 weeks (32 cycles). Tumor imaging (CT/MRI scans) will be performed every 8 weeks (Q8W) according to current SOC. 
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Details on the accompanying translational research will be provided in a separate translational research manual. Examples: • to identify biomarkers • to monitor immune cell population before and during therapy • to analyse immune cell infiltration before therapy
BACKROUND/RATIONALE	At advanced stage, cholangiocarcinoma (CCA) has a devastating prognosis. For patients with advanced or unresectable cholangiocarcinoma, the available systemic therapies are of limited effectiveness: the median overall survival with the current standard-of-care chemotherapy regimen

	(gemcitabine and cisplatin) is <1 year (Rizvi S et al., 2018). The desmoplastic stroma and genetic heterogeneity both contribute to the resistance of cholangiocarcinoma to therapy; the rich tumor microenvironment fosters potent survival signals and might pose a barrier to the delivery of chemotherapy to the tumor. The combination of cisplatin with gemcitabine is the standard first-line chemotherapy for patients with unresectable CCA. So far, no standardized second-line therapy has been established due to the lack of prospective, randomized controlled trials. Atezolizumab (Tecentriq®) is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma or metastatic non-small cell lung cancer. The role of adding immune-checkpoint blockade to the treatment armamentarium of iCCA is currently the subject of clinical research. With regard to derazantinib and from data obtained in comparative kinase screens of known FGFR inhibitors, CSF1R kinase inhibition seems to be a unique characteristic of derazantinib (Basilea, data on file, 2019). In the context of the putative role of CSF1R inhibition to bypass tumor-induced immunosuppression, restore T cell activity, downregulate immunosuppressive macrophage activity and improve susceptibility to therapeutic immune checkpoint blockade using anti-programmed cell death receptor-1 (PD-1)/PD-L1 antibodies (Fleming et al., 2018, Kim et al., 2015, Ries et al., 2014), the dual targeting of immunosuppressive stromal cells via CSF1R and PD-L1 to revert immune escape of tumor cells plus the target therapy of FGFR-driven tumor cells form a rationale to explore the potential benefit of derazantinib-atezolizumab in combination, which is investigated in Substudy 3 under this protocol. Of note, derazantinib may provide clinically meaningful inhibition of CSF1R signaling based on both its low IC50 of 16.2 nM for CSF1R (with a CSF1R-to-FGFR2 ratio of 3) and the derazantinib-related reduction of phospho-CSF1R in a concentration-dependent manner observed in vitro, which are hypothesized to augment the treatment effect of the immune-checkpoint blockade. Atezolizumab is generally well tolerated, with reported AEs with potentially immune related causes being consistent with an immunotherapeutic agent. These include rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, which have been observed in ongoing studies, and which to date have been monitorable and treatable. Detailed guidance on the management of immune-related AEs is available in the US Prescribing Information (PI), and the EU Summary of Product Characteristics (SmPC) for Tecentriq® (atezolizumab). No PK interactions are expected between a small molecule kinase inhibitor such as derazantinib and an antibody, such as atezolizumab. The combination of derazantinib and atezolizumab has been studied in 26 patients with advanced solid tumors in a dedicated Phase 1b substudy of an ongoing Phase 2 study (NCT04045613) and has shown an acceptable safety profile, and the RP2D has been determined as 300 mg of daily oral derazantinib and 1200 mg atezolizumab, administered intravenously once every three weeks. The overall outcome of BTC (Biliary Tract Cancer), although relevantly improving during the last decades, remains poor with a median progression free survival limited to 7-8 months and a median overall survival of less than 15 months with current standard doublet chemotherapy regimen. Intensification of standard doublet regimen resulted so far in limited improvement in survival but added relevant toxicities in all- comer populations. Thus, the development of an efficacious and tolerable combination regimen is urgently required particularly in the first line treatment. The experimental regimen evaluated in this trial combines atezolizumab with derazantinib in patients with FGFR2

	fusions/rearrangements, which have not been previously treated with FGFR and/or immune-checkpoint inhibitors. The assessments and evaluations performed in this study are in line with those usually used in the treatment of patients with iCCA in routine clinical practice. The combination of PD-1/PD-L1 antibodies and FGFR2 inhibitors is relatively new, but the safety, feasibility, and efficacy as monotherapies have been proven and also first clinical trials on combination treatment point out to an acceptable safety profile. Taken together, the risks emerging from participation in this clinical trial are acceptable, considering an anticipated direct benefit for a subset of patients and the impact of the study results on the future treatment of patients in the given indication. This leads to a favorable overall risk benefit ratio of the trial.
KEY EXCLUSION CRITERIA	Patients who meet any of the following criteria will be excluded from study entry: 1. Mixed cholangiocarcinoma and HCC. 2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) study or a study without a medical intervention (specifically the PLATON registry [ClinicalTrials.gov identifier: NCT04484636] is allowed). *Note: After the Safety Follow-up (28 days post treatment discontinuation) participation in another clinical study is allowed.* 3. Major surgery (as defined by the Investigator) within 4 weeks prior to enrollment into the study; patients must have recovered from effects of any major surgery. *Note: Local non-major surgery for palliative intent (e.g. surgery of isolated lesions, per-cutaneous biliary drainage or biliary stenting) is acceptable.* 4. 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 active, uncontrolled, 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. 5. History of another primary malignancy except for: o Malignancy treated with curative intent and with no known active disease ≥ 3 years before the first dose of IMP and of low potential risk for recurrence; o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; o Adequately treated carcinoma in situ without evidence of disease. 6. 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 5 months after the last dose of combination therapy or for a period of at least 5 half-lives of the respective drug/IMP after the last dose of combination therapy (whichever is longer). 7. Known allergy or hypersensitivity to any of the IMPs or any of the constituents of the product. 8. 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. 9. Active or 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.

	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. 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 following conditions are met: *o Rash must cover < 10% of body surface area;* *o Disease is well controlled at baseline and requires only low-potency topical corticosteroids;* *o 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.* 10. History of non-infectious pneumonitis requiring steroids, or patients with Grade ≥ 2 pneumonitis. 11. History of active primary immunodeficiency. 12. History of allogeneic bone marrow transplantation or prior solid organ transplantation. 13. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions: • Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study. Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study. 14. Administration of a live, attenuated vaccine within four weeks or for a period of at least 5 half-lives of the respective drug/IMP (whichever is longer) 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. 15. Significant cardiovascular disease, such as cardiac disease (New York Heart Association Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmias, unstable angina, and/or concurrent and clinically significant abnormalities on electrocardiogram (ECG) at Screening, including QTcF > 450 ms for males or > 460 ms for females. 16. Clinically significant valvular defect. 17. Unable or unwilling to swallow the complete daily dose of derazantinib capsules. 18. Clinically unstable central nervous system (CNS) metastases (to be eligible, subjects must have stable disease > 3 months, confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan, and/or have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications). 19. Current evidence of clinically significant corneal or retinal disorder, including but not limited to bullous/band keratopathy, keratoconjunctivitis (except for keratoconjunctivits sicca), corneal abrasion (except if related to trauma), inflammation/ulceration, confirmed by ophthalmologic examination. 20. Significant gastrointestinal disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of

	derazantinib and/or atezolizumab (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection). 21. Active tuberculosis. 22. Co-infection with hepatitis B and hepatitis C. Patients who are negative for HCV RNA will be considered non-infected for HCV. 23. Severe bacterial, fungal, viral and/or parasitic infections on therapeutic oral or IV medication at the time of first dose of study drug administration. 24. Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogues) or St. John's wort. 25. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 26. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot make a rational/informed decision after receiving the study information [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
KEY INCLUSION CRITERIA	Patients must meet all of the following criteria to be eligible for the study: 1. Fully informed written consent and locally required authorization (European Union [EU] Data Privacy Directive in the EU) obtained from the patient prior to performing any protocol-related procedures, including screening evaluations. 2. Patients*, age ≥ 18 years at the time of signing the Informed Consent Form. 3. Histologically documented diagnosis of non-resectable iCCA with positively confirmed FGFR2 fusion/rearrangement via NGS-Analysis. *Note: Only CE-IVD marked NGS-tests are applicable which cover FGFR2 fusions and rearrangements.* 4. Performance status (PS) ≤ 2 (ECOG scale). 5. At maximum one previous line of systemic anti-cancer therapy, (chemotherapy, hormonal, targeted therapy, experimental therapy) for which treatment was discontinued at least 4 weeks before the first dose of study treatment, or five half-lives of the respective anti-cancer therapy, whichever is the longer period. *Note: For mABs in previous therapy the restriction to five half-lives does not apply.* 6. No prior treatment with any FGFR or immune checkpoint inhibitor (including but not limited to antiCTLA-4, antiPD-1, and antiPD-L1 therapeutic antibodies). 7. Body weight > 30 kg AND BMI ≥ 15. 8. At least one measurable site of disease as defined by RECIST 1.1 criteria. 9. Adequate bone marrow and renal function including the following: o Hemoglobin ≥ 9.0 g/dL (previous transfusion permitted); o Absolute neutrophil count (ANC) ≥ 1.500 per µL (1.5×10^9/L); o Platelet count ≥ 75,000 per µL (75×10^9/L); o International normalized ratio (INR) between 0.8 × ULN to 1.0 × ULN OR ≤ 3 × ULN for subjects receving anticoagulant therapy o Creatinine ≤ 1.5 × ULN OR CL_{CR} ≥ 50 mL/min (as calculated by the Cockcroft-Gault formula); o serum phosphate ≤ ULN; o corrected serum calcium ≥ 1.75 mmol/L (≥ 7.0 mg/dL) AND ≤ 3.1 mmol/L (≤ 12.5 mg/dL); o serum sodium ≥ LLN. 10. Adequate hepatic function (with stenting for any obstruction, if required) including the following: o Total bilirubin ≤ 2 × ULN;

	o AST or ALT ≤ 3 × ULN (or ≤ 5 × ULN for subjects with liver metastases); o Prothrombin time ≥ 60%; o Albumin ≥ 2.8 g/dL. 11. For patients with active hepatitis B virus (HBV): • HBV DNA ≤ 500 IU/mL obtained within 28 days prior to initiation of study treatment, AND • Anti-HBV treatment (per local standard of care; e.g., entecavir) prior to study entry and willingness to continue treatment for the length of the study. 12. For patients with active hepatitis C virus (HCV): • Patients positive for hepatitis C virus (HCV) antibody are eligible, also if polymerase chain reaction testing is positive for HCV ribonucleic acid (RNA). • However, anti-viral therapy against HCV is only allowed prior to trial but not during the trial. 13. Negative HIV test. 14. Negative pregnancy test within 72 h prior to dosing. 15. 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 or for a period of at least 5 half-lives of the respective drug/IMP (whichever is longer) 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. 16. With female partners of childbearing potential, 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. 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 to avoid exposing the embryo. 17. 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. 18. Must have a life expectancy of at least 12 weeks. *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently.
OUTCOME(S)	**Primary efficacy endpoint:** Objective Response Rate (ORR [assessed every 8 weeks (±7days)]: Objective response rate (ORR) according to investigator-based RECIST 1.1 assessment, defined as the proportion of allocated subjects with best response of complete or partial response within 9 months after the date of first administration of study treatment. **Secondary efficacy endpoints:** • ORR@EOT:

	Objective response rate (ORR) according to investigator-based RECIST 1.1 assessment, defined as the proportion of allocated subjects with best response of complete or partial response within study treatment. • PFSR@6, 8 and 10 months: The proportion of patients known to be alive and without confirmed objective disease progression at 6, 8 and 10 months after first administration of study treatment, respectively. • PFS: Time from first administration of study treatmentuntil the date of first objective disease progression or death. Subjects who did not progress or die will be censored at the last evaluable tumor assessment date prior to subsequent anti-cancer therapy. • OS: Time from first administration of study treatment until death of a patient due to any cause. A subject who has not died will be censored at last known date alive. **Safety endpoints:** o Incidence of adverse events, serious adverse events and adverse events of special interest; o Severity of adverse events by CTCAE v5.0 grade; o Relationship of adverse events to atezolizumab and/ or derazantinib; o Frequency of clinically significant abnormal laboratory parameters.
STATISTICAL ANALYSIS	Prior to final analysis data verification with respect to completeness and plausibility (data cleaning) will be performed. Inconsistencies and mistakes will be clarified with the study centers and will be removed. The data cleaning process starts soon after first patients are enrolled and monitored. Major protocol violations and special cases will be listed. The statistical analysis plan (SAP) and the handling of special cases and major violations will be defined and completed prior to database lock and prior to any conduct of analyses. Study analysis populations such as ITT or PP populations will be defined once more in the SAP. Primary objective is to assess the efficacy of atezolizumab in combination with derazantinib by ORR after 9 months of study treatment according to RECIST 1.1 criteria. The primary efficacy analysis will include all allocated patients (ITT population). In addition, several pre-specified sensitivity analyses will be performed: (i) the ORR analysis will be repeated in the Per Protocol (PP) population; (ii) a different definition for ORR will be used (ORR@EOT) and analyzed in the ITT population and (iii) in the PP population.
SAMPLE SIZE	A total of 37 patients are planned to be enrolled taking into account, among others, an exact single-stage phase II design by A'Hern (A'Hern, 2001)
TRIAL DURATION	The estimated study duration at the trial sites is 48 months (24 months recruitment, 24 months follow-up after last patient in).
PARTICIPATING CENTERS	Up to 20 sites in Germany
FURTHER CENTERS DESIRED?	Yes (Participating centers will be recruited from the national HCC trials group of the AIO.)
NUMBER of PATIENTS	N=37
CURRENT NUMBER of PATIENTS	Recruitment not yet started

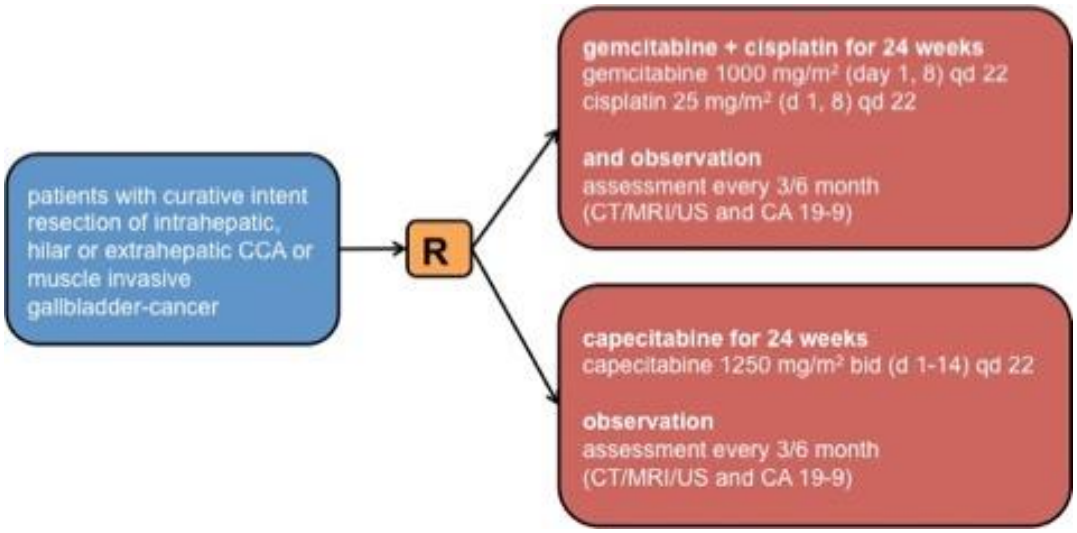
CCA, adjuvant

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

AIO-Studie

Studiennummer:	AIO-HEP-0112 - ACTICCA-1
Status:	in Rekrutierung
Rekrutierungszeitraum:	ab 2014
Zentren:	50 sites in Austria/Denmark/Germany/Italy/UK
Patienten:	716 pts included/666 pts randomized
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	10.10.2021

Indication	Patients after curative intent resection of cholangiocarcinoma (intrahepatic, hilar or distal cholangiocarcinoma) or muscle invasive gallbladder cancer without evidence of metastatic disease.
Condition	Adjuvant treatment for cholangiocarcinoma (CCA) and muscle invasive gallbladder cancer
Study design	Randomized, controlled, two stage, multicenter, open labelled phase III trial
Principle Investigator	Henning Wege, Hamburg
Sponsor	Universitätsklinikum Hamburg-Eppendorf Funded by Deutsche Krebshilfe and medac GmbH (Germany) International funding by Cancer Research UK, KWF Kanker Bestrijding The Netherlands, AGITG Australia
Contact	Studienkoordination: PD Dr. Alexander Stein, Universitäres Cancer Center Hamburg E-Mail: a.stein@uke.de E-Mail: acticca@uke.de
Endpoints	Primary endpoints: • Disease free survival (DFS) Secondary endpoints: • Disease free survival rate at 24 months (DFSR@24) • Recurrence free survival • Overall survival (OS) • Safety and tolerability of adjuvant chemotherapy • Quality of life (QoL) • Function of biliodigestive anastomosis (in terms of surgical revision, requirement of PTCD) • Rate and severity of biliary tract infections • Patterns of disease recurrence • Locoregional control
Number of patients/sites	781 patients to be randomized, 187 I in stage 1 and 594 in stage 2. 55 sites in Australia/Austria/Denmark/Germany/The Netherlands/United Kingdom
Start of recruitment	QII 2014

Study duration	Duration of recruitment (stage 2): 48 months. Expected total duration: 72 plus further 36 months follow up for overall survival (maximum of 5 years per individual patient).
Main selection criteria for treatment phase	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 2. Macroscopically complete resection (R0/1) within 6(-16) weeks before start of chemotherapy 3. No prior chemotherapy for CCA 4. Written informed consent 5. ECOG 0-1 6. Age >18 years 7. Adequat haematologic function: ANC ≥1.5 x 10^9/L, platelets ≥100 x10^9/L, haemoglobin ≥9 g/dl or ≥5.59 mmol/L 8. Adequate liver function as measured by serum transaminases (AST and ALT) ≤5 x ULN and conjugated (direct) bilirubin ≤3 x ULN 9. Adequate renal function, i.e. serum creatinine ≤1.5 x ULN, glomerular filtration rate ≥50 mL/min
	
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. **Arm A: Gemcitabine/cisplatin and observation** 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). **Arm B: Capecitabine and observation** 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). **Observation** 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. **Duration of treatment**

	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.

CCA, neoadjuvant

AIO-HEP-0421/ass - A Phase II study of immunotherapy with durvalumab and tremelimumab in combination with capecitabine or without capecitabine in ADJUvant situation for BILiary tract cancer - ADJUBIL

AIO-assoziierte-Studie	
Studiennummer/-Code:	**AIO-HEP-0421/ass - ADJUBIL**
Status:	in Vorbereitung
Rekrutierungszeitraum:	Q1 2022 – Q2 2023
Anzahl Zentren:	
Weitere Zentren:	sind sehr erwünscht
Anzahl Patienten:	
Letzte Aktualisierung	01.10.2021

APPLICANT/ COORDINATING INVESTIGATOR	Priv. Doz. Dr. med. Thorsten O. Götze Institute of Clinical Cancer Research UCT - University Cancer Center Frankfurt Krankenhaus Nordwest Steinbacher Hohl 2-26, 60488 Frankfurt am Main Tel: +49 69 7601 4187, Email: goetze.thorsten@khnw.de
CONDITION	In patients with histologically proven and curatively resected biliary tract cancer (intrahepatic, hilar or distal CCA as well gallbladder carcinoma) without metastatic disease
OBJECTIVE(S)	Primary objective: To assess the anti-tumor activity of the combination of durvalumab and tremelimumab with or without capecitabine by the recurrence-free survival rate after 12 months (RFS@12). Secondary objectives: To assess the efficacy by recurrence-free survival (RFS) and overall survival (OS); to assess safety of the combination treatments (AEs, impact on liver function, use of subsequent therapies); to assess quality of life (QoL). Exploratory objective: To perform correlation analysis between selected molecular parameters and clinical data to identify molecular biomarkers predictive for RFS and OS.
INTERVENTION(S)	Treatment Arm A (Capecitabine + Durvalumab + Tremelimumab) Treatment Arm B (Durvalumab + Tremelimumab)
KEY EXCLUSION CRITERIA	1. Presence of tumors other than biliary tract cancer or a secondary tumor other than squamous or basal cell carcinomas of the skin or in situ carcinomas of the cervix which have been effectively treated. Patients who have received curative treatment for other tumors and have been disease-free for at least 5 years at the time of screening are eligible for enrollment. 2. Metastatic biliary tract cancer (intrahepatic, hilar or distal CCA as well gallbladder carcinoma) disease.

	3. Simultaneous, ongoing systemic immunotherapy, chemotherapy, or hormone therapy not described in the study protocol. 4. Simultaneous treatment with a different anti-cancer therapy other than that provided for in the study (excluding palliative radiotherapy only for symptom control) written informed consent. 5. Previous therapy with a PD-1, PD-L1 inhibitor (including durvalumab) or CTLA4 inhibitor (including tremelimumab) or classical chemotherapy agents like platinum, fluoropyrimidine or gemcitabine based regimens. 4. 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 • Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the LKP. • Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the LKP. 7. Stage B cirrhosis according to Child-Pugh criteria (or worse) or cirrhosis (of any grade) with a history of hepatic encephalopathy or clinically significant ascites resulting from cirrhosis. Clinically significant ascites is defined as ascites resulting from cirrhosis requiring diuretics or paracentesis. 8. Known allergic / hypersensitive reactions to at least one of the treatment components. 9. Known dihydropyrimidine dehydrogenase (DPD) deficiency. 10. 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 within the last 12 months prior to the start of the study. 11. Presence of an active, uncontrollable infection. 12. .Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], 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: • Patients with vitiligo or alopecia • Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement • Any chronic skin condition that does not require systemic therapy • Patients without active disease in the last 5 years may be included but only after consultation with the study physician • Patients with celiac disease controlled by diet alone 13. Active disseminated intravascular coagulation. 14. Any other serious concomitant or medical condition that, in the opinion of the investigator, presents a high risk of complications to the patient or reduces the likelihood of clinical effect. 15. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable. 16. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes

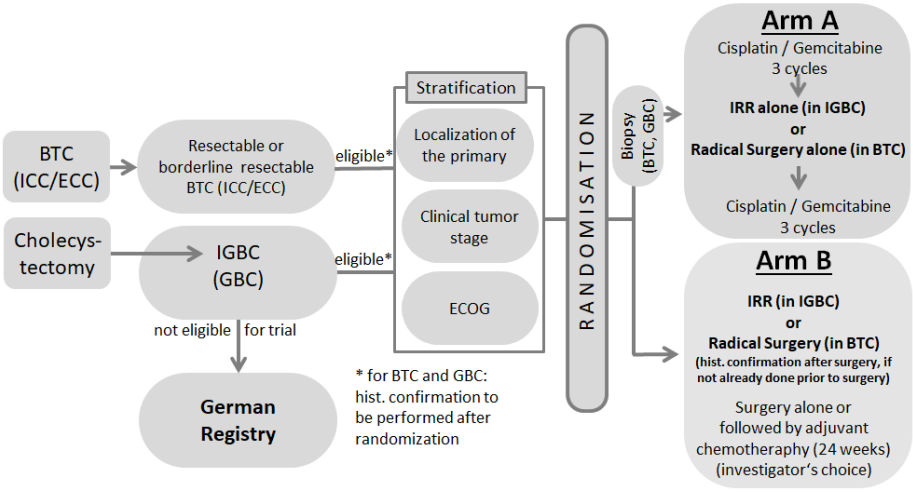
	apart) <<for durvalumab monotherapy and durvalumab + tremelimumab combination studies this criterion can be removed. For durvalumab ±tremelimumab in combination with an agent with pro-arrhythmic potential or where effect of the combination on QT is not known if this criterion should be retained. Patient safety and the cardiac SKG should be consulted as needed>>. Regardless of whether this criteria stays or not, all patients should have a baseline ECG 17. History of active primary immunodeficiency 18. 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, 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. 19. 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: • Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) • Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent • Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) 20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP. 21. 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 durvalumab monotherapy or180 days after the last dose of durvalumab + tremelimumab combination therapy
KEY INCLUSION CRITERIA	1. Capable of giving written informed consent, including participation in optional translational research if applicable, 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. 2. Histologically proven and curatively resected biliary tract cancer (intrahepatic, hilar or distal CCA as well gallbladder carcinoma) without metastatic disease, in the adjuvant situation (R0/R1) up to 12 weeks from surgery, with a maximum extension to 16 weeks from surgery. 3. Men or women* ≥ 18 years at time of study entry. *There is no data that indicates a specific gender distribution. Therefore, patients are included regardless of their gender. 4. Performance status (PS) ≤ 1 (ECOG scale),with no deterioration over the previous two weeks prior to baseline. 5. Must have a life expectancy of at least 12 weeks 6. Appropriate hematological, hepatic and renal function: • Absolute number of neutrophils (ANC) ≥ 1.5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Hemoglobin ≥ 9 g/dL (5.58 mmol/L) • Total bilirubin ≤ 1.5 times the upper limit of normal (UNL) or ≤3 x ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia)

	• AST (SGOT) and ALT (SGPT) ≤ 2.5 x UNL • Serum creatinine ≤ 1.5 x UNL or creatinine clearance (measured by 24h urine) ≥ 40 mL / min (i.e., if the serum creatinine level is > 1.5 x UNL, then a 24-h urine test must be performed to check the creatinine clearance to be determined). 7. Adequate coagulability, as determined by the International Normalized Ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) ≤ 5 seconds above the UNL (unless anti-coagulation therapy has been given). Patients receiving warfarin / phenoprocoumon must be switched to low molecular weight heparin and before starting study-specific procedures. 8. Patients of reproductive age must be prepared to use a suitable contraceptive method during the study and up to 3 months after the end of treatment. A suitable method of contraception is defined as surgical sterilization (e.g., bilateral fallopian tube ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double barrier methods (each two-fold combination of intrauterine pessary, condom for men, or women with spermicidal gel, Diaphragm, contraceptive sponge, cervical cap). Women of child-bearing potential must have a negative serum pregnancy test within the last 7 days prior to the start of study therapy. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving IMP 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 (durvalumab and tremelimumab). Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception). 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.
OUTCOME(S)	<u>Primary endpoint:</u> Recurrence free survival at 12 months (RFS@12) <u>Secondary endpoints:</u> • Recurrence free survival (RFS) • Overall survival (OS) • Safety (AEs, impact of liver function, use of subsequent therapies) • QoL <u>Exploratory endpoints:</u> Collection of tissue and blood samples for future evaluation of predictive biomarkers for RFS and OS.
STUDY TYPE	interventional, prospective multicenter, open-label, phase II study
STATISTICAL ANALYSIS	The trial design is based on the Simon, Wittes and Ellenberg's Pick-the-winner design [Simon et al., 1985]. The trial requires 18 patients per arm to detect a 14% difference in RFS@12 between arms with an 80% power, considering an RFS@12 of 56% for the combination of durvalumab and tremelimumab without capecitabine. If no difference in the recurrence-free survival rate is detected, the least toxic regimen will be selected. The dropout rate is set at 10%. Therefore, the total population is 40 patients (20 patients per arm). The primary endpoint can be analyzed as soon as events are available
SAMPLE SIZE	In the initial pilot trial phase, 40 patients will be enrolled in a 1:1 randomized design (i.e. 20 patients per Arm).
TRIAL DURATION	Considering an enrollment of 3-4 patients/month from 15 participating centers, a total of 12 months is estimated for enrollment. Last patient last visit is anticipated 12 months after the last patient enrolled.
PARTICIPATING CENTERS	15 sites planned

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		
Studiennummer/-Code:	AIO-HEP-0118/ass - GAIN/GEM/CIS	
Status:	Voten erhalten; Förderantrag der DFG ist genehmigt, über die Hälfte der Zentren ist initiiert, Rekrutierung ist angelaufen	
Rekrutierungszeitraum:	Q2/2019, 4 Jahre Rekrutierung	
Zentren:	geplant: 50	initiiert:33
Patienten:	geplant: 300	aktuell eingeschlossen: 24
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	30.09.2021	

STUDY TYPE	Multicenter, randomized, open label phase III study
PRINCIPAL INVESTIGATOR	Priv.Doz. Dr. med. Thorsten Oliver Götze Institute of Clinical Cancer Research (IKF) UCT- University Cancer Center Frankfurt, Krankenhaus Nordwest Steinbacher Hohl 2-26, 60488 Frankfurt am Main Tel.: +49 69 7601-4187; Fax -3655 Email: goetze.thorsten@khnw.de
TRIAL OFFICE / SPONSOR	Institute of Clinical Cancer Research (IKF) Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
Study Management	Ulli S. Bankstahl Dr. Claudia Pauligk Institute of Clinical Cancer Research (IKF) UCT- University Cancer Center Frankfurt, Krankenhaus Nordwest Steinbacher Hohl 2-26, 60488 Frankfurt am Main Tel.: +49 69 7601-4596, -3906; Fax -3655 Email: bankstahl.ulli@khnw.de; pauligk.claudia@khnw.de
CONDITION	Cholangiocarcinoma
DESIGN	This is a multicenter, randomized, controlled, open-label phase III study including patients with 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. 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), ECOG (0 and 1 vs. 2) and localization of the primary (ICC vs. ECC vs. IGBC(GBC)). 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 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. Arm A (gemcitabine plus cisplatin) 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. Arm B (standard postoperative management) 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. 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. 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.  Figure 1: Study Scheme. BTC (ICC/ ECC) = Biliary Tract cancer (Intrahepatic Cholangiocarcinoma/ Extrahepatic Cholangiocarcinoma); IGBC = Incidental Gallbladder Carcinoma; GBC = Gallbladder Carcinoma; IRR = Immediate Radical Re-resection
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. Safety Objectives • 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 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 • To evaluate the perioperative morbidity and mortality
INTERVENTION(S)	Arm A (gemcitabine plus cisplatin) 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. • Cisplatin (25 mg/m^2) 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. In case of reduced glomerular filtration rate the dose must be adjusted according to guideline or local standards. • Gemcitabine (1000 mg/m^2) in 250-500 ml 0.9% saline every three weeks on days 1 and 8 intravenously Arm B (standard postoperative management) 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). However, more than 50% of patients already exhibit unresectable disease at the time of diagnosis (Glimelius et al., 1996; Sharma et al., 2010). 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. 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 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. 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). 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. For improving disease control and cure rates in BTC (ICC/ ECC) and of IRR in 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. 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). 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 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. 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. 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 2. Other known contraindications to gemcitabine or cisplatin 3. Clinically significant valvular defect 4. Past or current history of other malignancies not curatively treated and without evidence of disease for more than two years, except for curatively treated basal cell carcinoma of the skin, in situ carcinoma of the cervix, and prostate cancer 5. Locally unresectable tumor or metastatic disease: - Radiological evidence suggesting inability to resect with curative intent whilst maintaining adequate vascular inflow and outflow, and sufficient future liver remnant - Radiological evidence of direct invasion into adjacent organs - Radiological evidence of extrahepatic metastatic disease 6. Other severe internal disease or acute infection 7. Chronic inflammatory bowel disease 8. 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. 9. 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. 10. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or ascites. 11. On-treatment participation in another clinical study 30 days or five half-lives (whichever is longer) prior to inclusion and during the study 12. Pregnant or breast feeding patient, or patient is planning to become pregnant within 7 months after the end of treatment. 13. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) 14. Any other concurrent antineoplastic treatment including irradiation

KEY INCLUSION CRITERIA	1. Incidental gallbladder carcinoma (IGBC), gallbladder carcinoma (GBC) or Biliary tract cancer (BTC) (intrahepatic, hilar or distal Cholangiocarcinoma (CCA)) scheduled for complete resection (mixed tumor entities with hepatocellular carcinoma are excluded). 2. No prior partial or complete tumor resection for BTC (intrahepatic, hilar or distal CCA), for IGBC/GBC prior Cholecystectomy is allowed. 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. 4. ECOG performance status of 0, 1, or 2. 5. Estimated life expectancy > 3 months. 6. Female and male patients ≥18 years. 7. Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures 8. No previous or preceding cytotoxic or targeted therapy for BTC or IGBC/GBC. 9. No previous malignancy within two years or concomitant malignancy, except for curatively treated basal cell carcinoma of the skin, in situ carcinoma of the cervix, and prostate cancer 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). 11. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent. 12. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to participate in the trial. 13. A) 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 7 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. B) Males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below: 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 6 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. 14. No pregnancy or lactation. 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 hemoglobin are allowed

	16. Adequate liver function as measured by serum transaminases (AST and ALT) ≤ 5 x ULN and bilirubin ≤ 3 x ULN. 17. Adequate renal function, i.e. serum creatinine ≤ 1.5 x institutional ULN, a calculated glomerular filtration rate ≥ 30 mL/min 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. 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). 20. No concurrent treatment with other experimental drugs or other anti-cancer therapy, treatment in a clinical trial within 30 days or five half-lives (whichever is longer) prior to randomization. 21. Negative serum pregnancy test within 7 days of starting study treatment in pre-menopausal women and women <1 year after the onset of menopause Please note that after randomization for patients in Arm A the histological confirmation of BTC or GBC must be performed before administering chemotherapy. For IGBC histological confirmation should already have been performed. For Arm B patients the histological confirmation can be performed after surgery with material from the surgery.
OUTCOME(S)	<u>Primary efficacy endpoint</u> • Primary efficacy endpoint is overall survival (OS) <u>Secondary efficacy endpoints</u> • Quality of life (EORTC QLQ- C30) • PFS rates at 3 and 5 years • OS rates at 3 and 5 years • progression free survival (PFS) • R0- resection rate • Toxicity, graded using CTC adverse events criteria version CTCAE V 5.0 • perioperative morbidity and mortality (30 days and 90 days mortality/morbidity)
SAMPLE SIZE	A total of n = 333 patients with IGBC/GBC or BTC(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) Duration of follow-up: overall 2 years (24 months), every 3 months 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=300

Biliäre Tumoren, 1st-line

AIO-HEP-0119/ass: A phase II study of immunotherapy with durvalumab (MEDI4736) or durvalumab and tremelimumab, both combined with Y-90 SIRT therapy in patients with advanced stage intrahepatic biliary tract cancer (BTC) scheduled to receive Y-90 SIRT therapy as standard of care (IMMUWHY)

AIO-assoziierte Studie		
Studiennummer/-Code:	AIO-HEP-0119/ass - IMMUWHY	
Status:	Rekrutiert	
Rekrutierungszeitraum:	Geplant FPI Q4/2020 – Q4/2022	
Weitere Zentren:	Sind absolut erwünscht	
Zentren:	geplant: 20	initiiert: 5
Patienten:	geplant: 50	aktuell eingeschlossen: 5
Letzte Aktualisierung	12 Oktober 2021	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover
CONDITION	Histologically documented diagnosis of locally-advanced **OR** limited metastatic intrahepatic BTC not amenable to curative treatment (tumor resection or ablation).
OBJECTIVE(S)	We hypothesize that the addition of durvalumab +/- tremelimumab to SIRT improves the objective response rate (ORR) in intrahepatic BTC compared to a historical control of SIRT alone.
INTERVENTION(S)	• standard of care SIRT + • (Arm A) Durvalumab i.v., fixed dose 1500 mg, q4w or • (Arm B) Durvalumab i.v., fixed dose 1500 mg, q4w + Tremelimumab i.v., fixed dose 300 mg, once
KEY EXCLUSION CRITERIA	➢ 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. ➢ Presence of peritoneal carcinomatosis or brain metastases. ➢ Prior radiotherapy treatment before the first dose of any study drug. ➢ History of allogenic organ transplantation.
KEY INCLUSION CRITERIA	➢ Histologically documented diagnosis of locally-advanced OR limited metasized intrahepatic, BTC not amenable to curative treatment (tumor resection or ablation), specified as ➢ Tumor being confined to the liver or ➢ In case of presence of extrahepatic lesions, metastasis must be stable AND of limited extent* AND patient must have a potential benefit from study participation in comparison to standard of care systemic therapy per local tumor board evaluation.

	*Limited extent is defined in this protocol as presence of ➢ EITHER ≤3 malignant extrahepatic lymph nodes (short axis diameter ≥3cm) ➢ OR metastatic lesions in one organ other than liver (if only single lesion is present diameter MUST be < 3cm; if up to 3 lesions in one organ each lesion MUST be ≤ 1cm). ➢ Presence of peritoneal or brain metastasis excludes patients from study participation (see exclusion criterion #4) ➢ Tumor tissue (block or at least 4 slides) is available for translational research. ➢ Patients with prior chemotherapy can be enrolled if ONE of the following criteria is met: ➢ Capecitabin or gemcitabine+cisplatin in the adjuvant setting ➢ Experienced progressive disease under gemcitabine+cisplatin therapy in the advanced setting ➢ Stable disease after 3 months of gemcitabine+cisplatin treatment ➢ Has been considered candidate for standard-of-care Y-90 SIRT therapy (Investigator decision) and does not display contraindications against SIRT. ➢ Performance status (PS) ≤ 1 (ECOG scale). ➢ At least one measurable site of disease as defined by RECIST 1.1 criteria. ➢ Must have a life expectancy of at least 12 weeks
OUTCOME(S)	Primary endpoint: Objective response rate (ORR) according to RECIST 1.1 Secondary endpoints: • Safety (rate of adverse events) • Duration of response (DoR) • Progression free survival (PFS) • Overall survival (OS) Exploratory: Predictive biomarkers for ORR, DoR, PFS, OS
STUDY TYPE	Randomized, open-label, two-arm, multicenter phase II trial
STATISTICAL ANALYSIS	This is a randomized phase II study incorporating two experimental treatment arms and aiming at the detection of a signal of improved efficacy compared to SIRT therapy only (based on assumptions from historical data). ORR analysed according to the ITT principle is the primary efficacy endpoint. The efficacy assumptions are derived from historical data. Descriptive analysis will be performed according to the study specific SAP.
SAMPLE SIZE	n=50
TRIAL DURATION	➢ Duration of recruitment: 24 months ➢ Maximum treatment duration will be 18 months ➢ The total followed up time required for the primary endpoint is 30 months from FPI.
PARTICIPATING CENTERS	Up to 20 sites planned

Biliäre Tumoren, 2nd-line

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: a randomized open-label phase 2 study (IRIBIL)

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)	
Studiennummer:	AIO-YMO/HEP-0316	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 – 2024	
Patienten	geplant: 23	aktuell eingeschlossen: 10
Zentren	geplant: 1	initiiert:1
Weitere Zentren:	sind leider nicht möglich!	
Letzte Aktualisierung	Okt. 2021	

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Oliver Waidmann
Die vollständige Synopse ist zu finden unter den Kurzprotokollen der Young Medical Oncologists.	

Register: Hepatozelluläres Karzinom / Gallengangskarzinom / Gallenblasenkarzinom / Pankreaskarzinom / Magen- und Speiseröhrenkarzinom – palliativ, first line

AIO-HEP/STO-0219/ass: PLATON Pilot-StudyPlatform for Analyzing Targetable Tumor Mutations – PLATON (Pilot-Study) and The PLATON Network (Main-Study)

AIO-assoziierte Studie	
Studiennummer/-Code:	AIO-HEP/STO-0219/ass// PLATON (pilot-study)
Status:	recruiting
Rekrutierungszeitraum:	FPI 25.11.2020 LPI planned Q1-2022 N=120 of 200 patients recruited
Zentren	40 sites actively recruiting
Weitere Zentren:	The PLATON network is open for study sites
Letzte Aktualisierung	18.10.2021

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str 1, 30625 Hannover and Prof. Dr. med. Salah-Eddin Al-Batran

	Krankenhaus Nordwest Institut für Klinisch-Onkologische Forschung UCT- University Cancer Center Frankfurt Steinbacher Hohl 2-26, 60488 Frankfurt/Main
CONDITION	Hepatocellular Cancer; Intra- and extrahepatic Cholangiocellular Carcinoma; Gallbladder Cancer; Pancreatic Cancer; Esophagogastic Cancer
OBJECTIVE(S)	The basic and first objective of the pilot study is to determine the local frequency of genetic alterations in hepatocellular cancer (HCC), intra- and extrahepatic cholangiocellular carcinoma (CCA), gallbladder carcinoma (GBCA), pancreatic cancer (PanCa) and esophagogastric cancer (EC/GC) in Germany and to correlate specific genetic alterations with tumour and patient characteristics. Additionally, we aim to profile paired primary/metastatic tumors and cfDNA from the patients to evaluate the heterogeneity of targetable alterations in primary/metastatic tissue and cfDNA. Moreover, one important objective of the trial is to inter-link participating physicians concerning key information on their clinical trials as well as clinical and molecular characteristics of their enrolled patients. This inter-linking would increase the probability of patients receiving treatments based on their molecular profile and/or enrolled in clinical trials of targeted therapy and would thus benefit patients and lead to a more efficient cancer therapy. In this pilot project, the feasibility of this approach is evaluated. The long-term vision is to enable cancer patients to receive the best available, scientifically founded, biomarker-based care, tailored to his or her individual needs.
INTERVENTION(S)	Biological specimens (Whole blood (2x10 ml EDTA) and Formalin Fixed and Paraffin Embedded Tumor Tissue (FFPE)) are used for Next generation sequencing (NGS) via FoundationOne Liquid and FoundationOne CDx (provided for study sites).
KEY EXCLUSION CRITERIA	• Not able to understand all implications of study participation • No written informed consent • age < 18 years
KEY INCLUSION CRITERIA	• Histologically confirmed diagnosis of hepatocellular carcinoma or intra-/extrahepatic cholangiocarcinoma or gallbladder carcinoma or pancreatic ductal adenocarcinoma or esophagogastric adenocarcinoma in the advanced setting (adjuvant or neoadjuvant therapy is allowed if completed 6 months prior to enrolment) and no local curative therapy available • Standard first line therapy is planned, or patient is currently receiving first line therapy (started within the last 2 months before enrolment) • ECOG 0-2 • Life expectancy ≥ 6 months
OUTCOME(S)	Primary: 1. Relative frequency of targetable* mutations (incl. TMB and MSI status) computed as the number of patients who harbors at least one mutation divided by the number of total patients in the pooled patient population. *defined as alterations with actionability (see figures above) excluding K-RAS as its frequency is well described in the literature and it is very frequent in some diseases like pancreatic cancer. Secondary: 1. Number of differences (heterogeneity) in targetable alterations in paraffin specimen vs. cfDNA 2. Relative frequency of targetable mutations (incl. TMB and MSI status) per disease group. 3. Number of patients receiving therapies in accordance to their genomic profiles An overall objective – although difficult to quantify – is to establish the network of investigators and assess the feasibility of the platform.

STUDY TYPE	PLATON is a prospective, multicentre, observational cohort study with biobanking. The study-type is interventional, non-AMG.
STATISTICAL ANALYSIS	This is an exploratory study, and the main goal is to generate hypotheses. It is not planned to test any statistical hypotheses in a confirmatory sense. All statistical analyses are exploratory even if confirmatory methods are used.
SAMPLE SIZE	n=200 (approx. 40 in every disease entity)
TRIAL DURATION	Duration of recruitment: 18 months Maximum duration of trial: 24 months
PARTICIPATING CENTERS	40-60 study sites are planned PLATON's pilot phase, thereof 40 study-sites are already actively recruiting

Interdisziplinäre Arbeitsgruppe Hodentumoren

AIO-GC-0121/ass: SAKK 01/18 - Reduced Intensity Radio-chemotherapy for Stage IIA/B Seminoma

AIO-assoziierte Studie	
Studiennummer/-Code:	**AIO-GC-0121/ass - SAKK 01/18**
Status:	offen
Rekrutierungszeitraum	Aktuell bis voraussichtlich 2026
Patienten:	geplant: 135 Pat. in der Schweiz und Deutschland aktuell eingeschlossen: 23 in D (54 insgesamt)
Zentren:	7 in der Schweiz, 9 Zentren in Deutschland
Weitere Zentren:	Nicht geplant
Erstellung	September 2021

Art der Studie	Phase II, international, multicentric, open-label, two-cohort study
Verantwortlicher Studienleiter nach AMG	Sponsor CH: SAKK, PI Dr. A. Papachristofilou, Basel Koordinator für Deutschland: LKP - Prof. Dr. med. Arndt Christian Müller, Ludwisgburg
Kontaktadresse/ Kontaktperson:	LKP für Deutschland: Prof. Dr. med. Arndt-Christian Müller Direktor der Klinik für Radioonkologie und Strahlentherapie arndt-christian.mueller@rkh-kliniken.de CRO für Deutschland: Dipl.-Biol. Martin Thoma CROLLL GmbH Wörnitzstr. 115a | 90449 Nürnberg Tel: 0049 911/25 26 88-29 Fax: 0049 911/25 26 88-40 martin.thoma@crolll.de
Studienziele/ Objectives	Primary end-point: • Progression-free sruvival at 3 years Secondary end-points: • Objektive Ansprechrate nach 3 Monaten & 3 Jahren • PFS • Time to progression (TTP) • OS • Seminoma-specific survival (CSS) • Time to distant metastasis • Time to next treatment • Localisation of progression
Zielparameter/ Objectives	See above
Patientenzahl Number of patients	Planned total: 135 patients
Rekrutierungzeitraum von/bis period of	Recruitment start CH: 07/2019 Recruitment start Germany: Q3 2020 Estimated completion recruitment: Q42026

Weitere teilnehmende Zentren erwünscht?	<u>The following German Centres have been initiated and are open for recruitment:</u> • Vivantes Klinikum am Urban • Helios Klinikum Berlin-Buch • Kliniken Essen Mitte • Uniklinik Hamburg-Eppendorf • Asklepios Klinik Hamburg-Altona • RKH Klinikum Ludwigsburg • Rotkreuz-Klinikum München • Uniklinik Tübingen • Uniklinikum Ulm. Activation of further trial sites in Germany is not planned at the moment.
Haupt-Einschlusskriterien / Key inclusion criteria	• Male gender • Age ≥ 18 years for Germany • WHO Performance Status 0 to 2 • GCT histology of pure seminoma CS IIA and IIB newly diagnosed or recurrent after primary active surveillance, adjuvant carboplatin or radiotherapy for stage I disease Unequivocal progression of measurable disease following one line of cisplatin-based chemotherapy • Completion of a full informed consent and baseline PRO questionnaires • Adequate bone marrow function: neutrophil count ≥ 1.0 x 109/L, platelet count ≥ 100x 109/L • Adequate renal function: creatinine clearance ≥ 60 ml/min calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula • Patient agrees to use highly effective contraception and not to donate sperm or to father a child during trial treatment and during 12 months thereafter. Patient has been proposed sperm conservation.
Therapieschema Scheme of therapy	CS IIA (primary stage IIA and recurrent stage IIA seminoma after active surveillance for stage): • One infusion of carboplatin AUC (Area under the curve) 7 at day 1 of trial treatment, followed 3 weeks later by 12 x 2 Gy involved-node radiation therapy (RT). CS IIB (primary stage IIB and recurrent stage IIB seminoma after active surveillance for stage I OR stage IIA/B seminoma after adjuvant carboplatin or radiotherapy for stage I): • One cycle of etoposide 100 mg/m2/d + cisplatin 20 mg/m2/d at days 1 to 5 of trial treatment, followed 3 weeks later by 15 x 2 Gy involved-node radiation therapy.
Tumorevaluierung Criteria for evaluation	• Physical examination (inspection, palpation, etc.) • Rising beta-hCG tumor marker • CT imaging • Ultrasound imaging • X-ray imaging • Other imaging (e. g. MRI, PET-CT)
Rationale	Therapy de-escalation in stage IIA/B seminoma represents an unmet need in clinical practice; efficacy of modern standard of care therapies for these patients is high and only a few patients show disease recurrence but short- and long-term toxicities are a major concern. The

	magnitude of long-term toxicities is often associated with the intensity of the prescribed treatment modality. A higher cumulative dose of chemotherapy agents and radiation dose has been linked to a sharp increase in long-term sequelae. Combining treatment modalities and diversifying toxicity may thus provide an opportunity to limit long-term treatment sequelae. In this trial carboplatin, cisplatin and etoposide are the Investigational Medicine Products (IMPs). They are all medications with a marketing authorization for several solid tumor types and are standard practice in the treatment of testicular cancer in Switzerland and in the European Union (EU). Radiotherapy is also a standard therapy in this indication. However, the trial investigates a stage-adapted (stage IIA or IIB) de-escalation of these standard treatments in the context of a multimodality treatment with chemo- and radiotherapy. The goal is to safely de-escalate treatment while maintaining/enhancing efficacy, which is not a standard practice yet. The SAKK 01/18 trial is designed with the aim to answer these three questions: • Can the dose of involved-node radiotherapy be safely reduced in the context of multimodality treatment with chemo- and radiotherapy? • Can a more potent chemotherapy in the form of cisplatin/etoposide reduce the rate of distant failure in comparison to carboplatin? • Can a combination of cisplatin/etoposide and involved-node radiotherapy pose a potent treatment regime for patients with recurrence after adjuvant carboplatin or radiotherapy for stage I seminoma? Furthermore, as active surveillance is becoming standard of care in stage I seminoma, it is projected that the amount of patients in need of treatment with stage IIA/B disease will rise, due to more patients developing disease progression during active surveillance. The German Testicular Cancer Study Group is one of the most active testicular cancer research groups worldwide. Based on the broad experience in clinical testicular cancer research and clinical trials, a substantial contribution to the recruitment and success of this sutdy is expected. Conduct of the study in Germany is granted in close collaboration with the Swiss Group for Clinical Cancer Research (SAKK) as trial sponsor and CROLLL GmbH, Nürnberg, as CRO for Germany.

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	
Studiennummer/-Code:	AIO-GC-0416/ass
Status:	offen
Rekrutierungszeitraum	Aktuell bis voraussichtlich Q2-3 2022
Patienten:	geplant: 70 – 75 Pat. in Deutschland (420 international) aktuell eingeschlossen: 59 in D (363/420 international)
Zentren:	11 Zentren in Deutschland
Weitere Zentren:	Nicht geplant
Letzte Aktualisierung	September 2021

Art der Studie	Phase-III; international, multizentrisch
Verantwortlicher Studienleiter nach AMG	Sponsor USA: Alliance; Darren Feldman; New York Sponsor Europa: EORTC; Thomas Powles MD; London Weiterer Sponsor: Movember Deutschland: gefördert durch die Deutsche Krebshilfe Koordinator für Deutschland: LKP - Prof. Dr. med. Marcus Hentrich CRO - KKS Marburg
Kontaktadresse/ Kontaktperson:	KKS Marburg Frau Harnisch/Frau Balthasar Karl-von-Frisch-Strasse 4 35043 Marburg Tel.: 06421 2866553 Fax: 06421 2866517 Susanne.harnisch@kks.uni-marburg.de Kerstin.balthasar@kks.uni-marburg.de Prof. Dr. med. Marcus Hentrich FA für Innere Medizin und Hämatologie und Onkologie Marcus.hentrich@swmbrk.de
Studienziele/ Objectives	Primäres Studienziel: Overall survival Sekundäres Studienziel: Progression-Free Survival (PFS) Favorable Response Rate (CR + PR-neg markers); Toxicity Prospective Evaluation of the IPFSG Prognostic Model
Zielparameter/ Objectives	OS, PFS, Favorable Response Rate (CR + PR-neg markers); Toxicity Prospective Evaluation of the IPFSG Prognostic Model Biologic correlates
Patientenzahl Number of patients	Geplant Gesamtstudie: 420 Patienten, pro Arm jeweils 210 Patienten Aus Deutschland: geplanter Einschluss von etwa 70-75 Patienten Studie in den USA in 08/16 gestartet, Studienstart in Europa im Sommer 2017 erfolgt. Start in Deutschland im Mai 2018 erfolgt (bislang insgesamt 59 Patienten in D eingeschlossen, Stand 09/2021)
Rekrutierungzeitraum von/bis period of	Initial geplant 08/16 – 08/20 für alle Zentren weltweit, jedoch Verlängerung bis ca. Mitte 2022 vorgesehen, auf Grund verspäteter Initiierungen an allen

	europäischen Zentren incl. Deutschland und zögerlicher Rekrutierung in den US-amerikanischen Zentren
Weitere teilnehmende Zentren erwünscht?	Folgende Zentren in Deutschland sind derzeit initiiert: Rot-Kreuz Klinikum München, UK Hamburg-Eppendorf, Berlin Charité, Berlin Vivantes Neukölln, UK Dresden, UK Essen, Städtisches Klinikum Koblenz, UK Marburg, UK Nürnberg, UK Ulm, NCT Heidelberg Weitere Zentren sind aktuell nicht vorgesehen.
Haupt-Einschlusskriterien / Key inclusion criteria	Male gender Age ≥ 18 years for Germany ECOG Performance Status 0 to 2 GCT histology (Seminoma and Nonseminoma) Unequivocal progression of measurable disease following one line of cisplatin-based chemotherapy Unequivocal progression of non-measurable disease with consecutive elevated markers following one line of cisplatin-based chemotherapy A minimum of three and maximum of six cisplatin-based treatment cycles No more than one prior line of chemotherapy for GCT Patients with late relapses who have unresectable disease Completion of a full informed consent
Therapieschema Scheme of therapy	4 Zyklen konventionelle Chemotherapie TIP **versus** 2 Zyklen TI gefolgt von 3 Zyklen CE- Hochdosischemotherapie
Tumorevaluierung 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). 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. 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. 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. 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. 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. Die Studie wird in internationaler Zusammenarbeit als „Intergroup Trial“ durchgeführt. 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 ein zentraler Beitrag bezüglich der Rekrutierung in dem Studienvorhaben erwartet. 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 wird das Studienvorhaben deutschlandweit nur an maximal zwölf Zentren durchgeführt werden, die geographisch möglichst über die verschiedenen Bundesländer verteilt sind. Die Studie ist durch die Deutsche Krebshilfe gefördert. Die Durchführung des Forschungsvorhabens in Deutschland erfolgt in Kooperation mit einem Koordinierungszentrum für Klinische Studien (KKS) am Uniklinikum Marburg als CRO.

Arbeitsgruppe Kolon-/Rektum-/ Dünndarmkarzinom

Metastasiertes kolorektales Karzinom

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

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0117	
Status:	Rekrutiert	
Rekrutierungszeitraum:	09/2018 – erweitert bis 09/2021 (geplant)	
Zentren:	geplant: 40	initiiert: 39
Patienten:	geplant: 124	bereits eingeschlossen: 90
Weitere Zentren:	Keine weiteren Zentren mehr gesucht	
Letzte Aktualisierung:	September 2021	

Phase	Randomized phase II
Coordinating Investigators	Prof. Dr. Ralf-Dieter Hofheinz Tagestherapiezentrum am ITM & III. Med. Klinik Universitätsmedizin Mannheim Theodor-Kutzer-Ufer 1-3 68167 Mannheim, Germany Phone: +49 - 621 – 3832855 Fax: +49 - 621 – 3832488
Study design	This is a controlled, open-label, randomized phase- II trial (1:1 randomization) investigating 5-FU + aflibercept and 5-FU + oxaliplatin in elderly and frail elderly patients with mCRC scheduled to receive first line treatment.
Duration of study	4,5 years
Indication	Metastatic colorectal cancer
Country Total number of sites	Germany 40 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: **Safety** - Dose intensities of study medication - Type, incidence and severity of AEs and SAEs - Laboratory parameters **Efficacy** - Response rate assessed by the local investigators - Overall and progression-free survival **Patient reported outcomes** - Quality of life - Geriatric assessment - 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** • Dose intensities of study medication • Type, incidence and severity of AEs, SAEs (CTCAE version 4.03) • Dose reduction or discontinuation of study drug due to adverse events • Rate of treatment discontination due to toxicity • Type, incidence and severity of laboratory abnormalities **Efficacy** • 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) • Overall and progression-free survival (OS) **Patient reported outcomes** • Quality of life using EQ5D • Geriatric assessment using G8, ADL and IADL • 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 were planned to be recruited. However, due to the slow recruitment process, sample size estimation was adjusted to 62 patients per treatment arm, and a total of 124 patients are 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 reason for entering the trial was advanced age alone or 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. Due to age or frailty, the patient might not be a candidate for standard full-dose combination therapy. 2. Patients have to have histologically confirmed mCRC with unidimensionally measurable inoperable metastatic disease 3. ECOG performance status of 2 or better. 4. Life expectancy of 3 months or longer at enrolment 5. Patients ≥70 years with no upper age limit 6. Previous adjuvant chemotherapy is allowed if completed more than 6 months before randomisation 7. Previous rectal (chemo)radiotherapy is allowed if completed more than 6 months before randomisation 8. Hematological status: • Neutrophils (ANC) ≥ 1.5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Hemoglobin ≥ 9 g/dL 9. Adequate renal function: • Serum creatinine level ≤ 1.5 x upper limit normal (ULN) 10. Adequate liver function: • Serum bilirubin ≤ 1.5 x upper limit normal (ULN) • Alkaline phosphatase < 5 x ULN • AST and ALT < 3 x ULN (unless liver metastases are present then < 5 x ULN in that case) 11. Proteinuria < 2+ (dipstick urinalysis) or ≤ 2 g/24hour 12. Signed and dated informed consent, and willing and able to comply with protocol requirements 13. Regular follow-up feasible

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

	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].
Treatment schedule after randomization	**Arm A (mFOLFOX7):** Patients in the 5-FU / oxaliplatin arm receive modified (m) FOLFOX 7: Folinic acid 350 mg/m² and oxaliplatin 68 mg/m² by concurrent 2-h intravenous infusion, 5-fluorouracil 1920 mg/m² 46-h intravenous infusion. This regimen represents the 80% dosage reduced mFOLFOX 7. The 80% dose reduction was shown to be a tolerable regimen in frail elderly patients in the FOCUS 2 study. **Arm B (Aflibercept + mLV5FU2):** Patients in the 5-FU / aflibercept arm receive aflibercept 4mg/kg as 1-h infusion followed by folinic acid 350 mg/m² by 2-h intravenous infusion, 5-fluorouracil 1920 mg/m² 46-h intravenous infusion (mLV5FU2). The decision to use reduced doses of 5-FU and folinic acid was made to have comparable doses to the reduced FOLFOX 7. Chemotherapy doses in both arms may be starting at 100% (beginning from C1D1), at the discretion of the investigator.
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. Provided the randomized phase-II study shows adequate efficacy of 5-FU / aflibercept and a tolerable safety profile, a subsequent phase-III trial may be planned. Description of the terms and conditions to expand the current trial are not part of this protocol.
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. Permuted block randomization will be applied. Stratification factors: G8 score ≤14 versus 15-17 & ECOG 0/1 versus 2

Statistical considerations and sample size calculation	**Sample Size Estimation:** The aim of the randomized phase-II trial is to gain a precise estimation of 6 months progression free-survival (PFS) rate of 5FU-Aflibercept for planning of a following phase III study in elderly and frail elderly patients with mCRC scheduled to receive first line treatment. Sample size calculation was done using R version 4.0.3 (R Core Team (2014). http://www.R-project.org/.).Assumptions: • Uniform recruitment of patients during randomized phase II-part • PFS exponential distribution PFS(t)=exp(rt) • Median $PFS_{5FU\text{-}Aflibercept}$=6 months equivalent to a mean $PFS_{5FU\text{-}Aflibercept}$=8.7 months With 88 evaluable patients in the 5-FU / aflibercept arm and an accrual of 24 months the lower limit of the 95% confidence limit for the 6 months PFS is 42.4%. Randomization of a total 176 patients will be stratified by G8 score and ECOG and will be performed on a 1:1-basis. Assuming a 10% drop out rate a total of 196 patients were planned to be recruited. However, due to the slow recruitment process, sample size estimation was adjusted to 62 patients per treatment arm In summary, with 62 evaluable patients in the 5-FU / aflibercept arm and an expected accrual duration of 39 months, the lower limit of the 95% confidence limit for the 6 months PFS is 41.3%. A total of 124 patients are recruited and randomized on a 1:1 basis. Stratification factors: G8 score ≤14 versus 15-17 & ECOG 0/1 versus 2
	Safety The dose intensities of study medication will be calculated over the whole study duration and will be summarized descriptively by summary statistics. AEs, will be summarized by presenting the number and percentages of patients having any AE and having an AE in each NCI-CTC category. Summaries will also be presented for AEs by severity and relationship to study medication. Tables will be broken down by study arm. All deaths and serious adverse events will be listed and briefly described. Laboratory evaluations will be analyzed by summary statistics per parameter, visit and treatment group. **Others** Vital signs will be analyzed using summary statistics broken down per treatment group and visit. Physical examination as well as ECOG will be analyzed by calculating frequencies and percentages broken down per treatment group and visit.
Number of patients, and location	Total number of patients: 124 Location of sites: Germany

AIO-KRK-0316/ass: Phase III study of Ramucirumab in combination with TAS102 vs. TAS102 monotherapy in chemotherapy refractory metastatic colorectal cancer patients [RAMTAS]

AIO-assoziierte Studie		
Studiennummer/-Code:	AIO-KRK-0316/ass - RAMTAS	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2018 - 2022	
Weitere Zentren:	sind leider nicht möglich	
Zentren:	geplant: 50	initiiert: 41
Patienten:	geplant: 426	aktuell eingeschlossen: 232
Letzte Aktualisierung	Oktober 2021	

Condition	metastatic colorectal cancer (mCRC)
Principal Investigator	Prof Dr. med. Stefan Kasper University Hospital Essen, West German Cancer Center Hufelandstr. 55, 45147 Essen, Germany Tel.: +49 201 723 3449 Fax.: +49 201 723 5549 Email: stefan.kasper@uk-essen.de
Study group	Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft e.V.
Sponsor Project Management Sponsor	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Sabine Junge Tel: +49 69 / 76 01-4186 Email: junge.sabine@ikf-khnw.de
Objectives	Primary objective: To determine the efficacy of Ramucirumab in combination with TAS102 vs. TAS102 monotherapy in patients with refractory mCRC. Primary endpoint will be overall survival (OS) according to Kaplan-Meier. Secondary objectives: Overall Response Rate (ORR) (complete remission and partial remission) Disease control rate (DCR) (complete remission, partial remission and stable disease) Progression Free Survival (PFS) OS rate at 6 and 12 months Efficacy (ORR, PFS, OS) in patients who develop neutropenia ≥ grade 2 (ANC≤1500/µl) in cycle 1 Toxicity/safety Quality of life (QoL) Tanslational research program
Study type	An interventional, prospective, randomized (1:1), controlled, open label, multicenter phase III study
Rationale	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.
Inclusion criteria	1. Metastatic and inoperable, colorectal cancer who has progressed on/after or did not tolerate, refuse or have contraindications to: - fluoropyrimidins, oxaliplatin, irinotecan, anti-angiogenic therapies (bevacizumab, aflibercept, regorafenib or ramucirumab) and if indicated anti-EGFR antibodies (cetuximab or panitumumab) Intolerance is defined as a permanent discontinuation of the respective treatment resulting from toxicity 2. Signed informed consent before start of specific protocol procedure 3. Histologically or cytologically documented diagnosis of adenocarcinoma of the colon or rectum 4. Presence of at least one measurable site of disease following RECIST 1.1 criteria 5. ECOG performance 0-1 6. Known RAS and BRAF V600E mutational status 7. Life expectancy of at least 3 months 8. Adequate hematological, hepatic and renal function parameters: a. Leukocytes ≥3000/mm³, platelets ≥100,000/mm³, neutrophil count (ANC) ≥1500/µL, hemoglobin ≥9 g/dL (5.58 mmol/L) 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 therapy). Patients receiving warfarin/ phenprocoumon must be switched to low molecular weight heparin and have achieved a stable coagulation profile prior to first dose of protocol therapy c. Serum creatinine ≤1.5 x upper limit of normal or clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed) 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) e. Bilirubin ≤1.5 x upper limit of normal, AST and ALT ≤3.0 x upper limit of normal, ≤5xULN if liver metastasis present, alkaline phosphatase ≤6 x upper limit of normal 9. Patient able and willing to provide written informed consent and to comply with the study protocol 10. Female and male patients ≥18. 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) or hormonal contraception (implantable, patch, oral). Women who use a hormonal contraception method should use an additional barrier method like 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.
Exclusion criteria	1. Known hypersensitivity against ramucirumab or TAS102 2. Other known contraindications against ramucirumab, TAS102, or other anti-angiogenic therapies 3. Prior therapy with TAS102 4. Drug-related severe adverse events upon pretreatment with anti-angiogenic drugs that would require permanent discontinuation and not allow re-challenge with the same class of drug (i.e. ramucirumab) such as noncontrollable severe hypertension or thromboembolic events (see Table 15 on p. 63 for additional examples)

	5. Any antineoplastic treatment including irradiation within 14 days (42 days for mitomycin c) prior to start of therapy. 6. Major surgery within 4 weeks of starting therapy within this study, 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 7. during the course of the clinical trial 8. Symptomatic brain metastasis 9. Clinically significant cardiovascular disease - NYHA>II°, myocardial infarction within 6 months prior study entry - Known clinically significant valvular defect - Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or >100 mmHg diastolic for >4 weeks) despite standard medical management - 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 - History of deep vein thrombosis (DVT), symptomatic 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 10. Active clinically serious infections (> grade 2 NCI-CTC version 4.0) 11. Chronic inflammatory bowel disease 12. History of uncontrolled HIV infection or chronic hepatitis B or C 13. Patients with evidence of bleeding diathesis 14. Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy 15. 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 16. History of gastrointestinal perforation or fistulae in past 6 months or risk factors for perforation 17. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy 18. 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 or bladder, or low/intermediate risk prostate cancer (Gleason score ≤7) with normal PSA levels 19. Any condition that could jeopardize the safety of the patient and their compliance of the study 20. Medical, psychological or social conditions that may interfere with the participation in the study 21. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or ascites. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis 22. On-treatment participation in another clinical study or received investigational drug therapy in the period 30 days prior to inclusion and during the study 23. Subject pregnant or breast feeding, or planning to become pregnant within 7 months after the end of treatment 24. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) 25. Any other concurrent antineoplastic treatment including irradiation

Sample Size	426 patients (randomization 1:1) Strata: previous anti-angiogenic therapies ≥ or <12 months in total; BRAF/RAS mutation status
Interventions	Arm A: ▪ Ramucirumab 8 mg/kg d1+15, q4w ▪ TAS102 35mg/m^2 BID d1-5, 8-12, q4w Arm B ▪ TAS102 35mg/m^2 BID d1-5, 8-12, q4w Safety analyses after 20 and 40 patients
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 0,025 with a logrank test (one-sided), if 213 patients per treatment group (426 in total) are included in the study. This calculation assumes an exponential shape of the survival curves, an accrual time of 36 months and a total observation time, i.e. maximum follow-up duration, of 48 months.
Time schedule	Start of trial/First patient in (FPI): QI/2019 Last patient in (LPI) QIII /2022 LPLV (last patient last visit) date QIII/2023 Recruitment period (months): 36 months Minimum follow-up-period: 12 months
Number of enrolled pts.	232
Participating centers	50 in total

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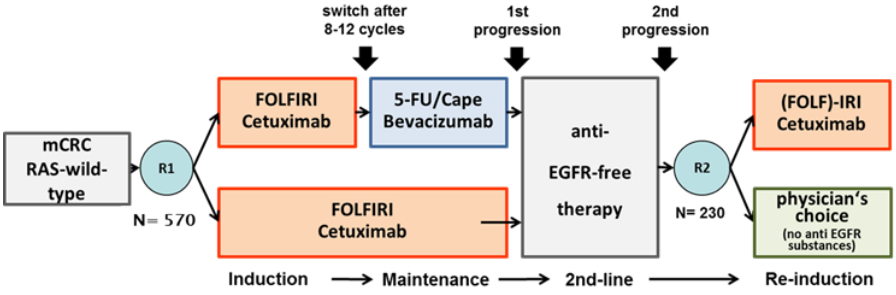
AIO-KRK-0114: Randomisierte Studie zur Wirksamkeit einer Cetuximab-Reexposition bei Patienten mit metastasiertem kolorektalem Karzinom (RAS Wildtyp) welche auf eine Erstlinien-Behandlung mit FOLFIRI plus Cetuximab ein Ansprechen zeigten (FIRE-4)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0114 - FIRE-4	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2015 - 2024	
Zentren:	geplant: 170 (in D und A)	initiiert: 140
Patienten:	geplant Erstlinie: 670 geplant Re-Challenge: 230	aktuell eingeschlossen: 673 aktuell eingeschlossen: 68
Weitere Zentren:	Aktuell keine neuen Zentren benötigt	
Letzte Aktualisierung	30.09.2021	

Art der Studie	Randomisierte, multizentrische Phase-III Studie
Verantwortlicher Studienleiter nach AMG	Klinikum der Universität München Marchioninistraße 15 81377 München Vertreten durch: Prof. Dr. med. Volker Heinemann
Kontaktadresse/ Kontaktperson:	Prof. Dr. V. Heinemann Medizinische Klinik III Sekr. Matthias Wolff Klinikum Großhadern LMU München Marchioninistr. 15 81377 München Tel: 089 4400 -72208 Fax: 089 4400 -75256 Dr. B. Deuß ClinAssess GmbH Abteilung Projektmanagement Birkenbergstr. 82 51379 Leverkusen Tel.: +49 (0) 2171 / 36 336 0 Fax: +49 (0) 2171 / 36 336 55
Studienziele	<u>Primäres Studienziel:</u> Prospektive Untersuchung des Gesamtüberlebens ab Beginn der Drittlinientherapie (OS3) unter einer Cetuximab-Reexposition gegenüber einer anti-EGFR freien Therapie bei Patienten, welche auf eine Erstlinientherapie mit Cetuximab oder Panitumumab und FOLFIRI oder FOLFOX oder FOLFOXIRI mit CR, PR oder SD >6 Monate angesprochen haben <u>Sekundäre Studienziele:</u> • Ansprechrate ORR • Progressions-freie Zeit PFS • Gesamtüberleben (OS1) ab Beginn der Erstlinientherapie • Early tumor shrinkage und der Remissionstiefe • Untersuchung von molekularen Biomarkern zur Prädiktion von Sensitivität und sekundärer Resistenz einer anti-EGFR Therapie mit Cetuximab • Prospektive Validierung eines Biomarker Scores • Prospektive Analyse des Tumormarkerverlaufs (CEA und CA 19-9) • Erfassung der Sicherheit und Verträglichkeit
Zielparameter	- Gesamtüberleben in der Drittlinientherapie (OS3) - Progressionsfreies Überleben im Rahmen der Erstlinientherapie (PFS1)
Patientenzahl	Geplant: 670 Patienten Bereits eingeschlossen:1st-line 673 Patienten 3rd-line 68 Patienten (Stand: Sep. 2021)

Haupt-Einschlusskriterien	Haupteinschlusskriterien: • Adenokarzinom des Kolons oder Rektums im UICC Stadium IV, primär nicht resektabel • RAS - Wildtyp-Status (KRAS und NRAS Exone 2-4) des Tumors (nachgewiesen in Primärtumor oder Metastase) • Alter ≥18 • ECOG 0-1 • Vorliegen mindestens einer messbaren Referenzläsion entsprechend der RECIST 1.1 –Kriterien (CT Thorax und Abdomen 4 Wochen oder weniger vor Randomisation) • Adäquate Knochenmarksfunktion: - Leukozyten ≥ 3,0 x 10^9/L mit Neutrophilen ≥ 1,5 x 10^9/L - Thrombozyten ≥ 100 x 10^9/L, - Hämoglobin ≥ 5,6 mmol/L (entspr. 9 g/dL) • Adäquate Leberfunktion: - Serumbilirubin ≤ 1,5 x obere Normwertgrenze, - ALAT und ASAT ≤ 2,5 x obere Normwertgrenze (bei Vorliegen von Lebermetastasen ALAT und ASAT ≤ 5 x obere Normwertgrenze) • INR < 1,5 und aPTT < 1,5 x obere Normwertgrenze (Patienten ohne Antikoagulation). • Adäquate Nierenfunktion: - Serumkreatinin ≤ 1,5 x obere Normwertgrenze oder Kreatinin Clearance (berechnet nach Cockroft und Gault) ≥ 50ml/min • adäquate Herzfunktion: EKG und Echokardiogram mit einer LVEF von ≥55% **Einschlusskriterium nur für Eingang 1:** • Zeit zur letzten Gabe einer vorangegangenen adjuvanten Chemotherapie >6 Monate **Zusätzliche Einschlusskriterien nur für Eingang 2:** • Stattgehabte Erstlinientherapie mit FOLFIRI und Cetxuximab; • Stattgehabte Zweitlinientherapie *ohne* FOLFIRI, Irinotecan oder eine gegen EGFR gerichtete Substanz • Letzte Gabe einer gegen den EGFR gerichteten Substanz ≥ 4 Monate vor Randomisation 2 • Nachweis eines RAS-Wildtyp Tumors innerhalb von 4 Wochen vor Randomisation • 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** • Nachweis einer RAS-Mutation oder fehlende Untersuchung auf RAS-Mutation • Primär resektable Metastasen und Patient wünscht Resektion • Herzinsuffizienz Grad III oder IV (NYHA-Klassifikation) • Myokardinfarkt, instabile Angina pectoris, Ballonangioplastie (PTCA) mit oder ohne Stenting innerhalb der letzten 6 Monate vor Studieneinschluss • Medizinische oder psychologische Beeinträchtigungen, die mit eingeschränkter Einwilligungsfähigkeit einhergehen oder die Durchführung der Studie nicht erlauben • 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) • Teilnahme an einer klinischen Studie oder experimentelle medikamentöse Behandlung innerhalb von 30 Tagen vor Aufnahme oder während der Studienteilnahme • Bekannte Hypersensitivität oder allergische Reaktion gegen eine der folgenden Substanzen: 5-Fluorouracil, Cetuximab, Oxaliplatin, Irinotecan, Bevacizumab und chemisch verwandte Substanzen • Bekannte oder klinisch vermutete Hirnmetastasen

	• Akuter oder subakuter Darmverschluss oder chronisch-entzündliche Darmerkrankung in der Anamnese oder chronische Diarrhoe • Arterielle Thromboembolien oder schwere Blutungen innerhalb von 6 Monaten vor Aufnahme in die Studie (Ausnahme Tumorblutung vor der Tumorresektionsoperation) • Bekannter DPD-Mangel (spezielles Screening nicht erforderlich) • Bekannter Glukuronidierungsdefekt (Gilbert-Meulengracht-Syndrom) (spezielles Screening nicht erforderlich) • 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. • Fehlende oder eingeschränkte juristische Geschäftsfähigkeit
Therapieschema	**FOLFIRI plus Cetuximab** ein Zyklus (Zykluslänge 14 Tage) besteht aus: • Irinotecan 180 mg/m² iv, 30 - 90 min Tag 1 • Folinsäure (racemisch) 400 mg/m² iv, 120 min Tag 1 • 5-FU 400 mg/m² Bolus Tag 1 • 5-FU 2400 mg/m² iv über 46 h Tag 1-2 • Cetuximab initial 400 mg/m² als 120 min Infusion, danach jeweils 250 mg/m² iv als 60 min Infusion Tag 1 + 8 **FUFA plus Bevacizumab** Ein Zyklus (Zykluslänge 21 Tage) besteht aus: • Folinsäure (racemisch) 400 mg/m² iv, 120 min Tag 1 • 5-FU 400 mg/m² Bolus Tag 1 • 5-FU 2400 mg/m² iv über 46 h Tag 1-2 • Bevacizumab 7,5 mg/kg KG iv **Capecitabine plus Bevacizumab** Ein Zyklus (Zykluslänge 21 Tage) besteht aus: • Capecitabin 1250 mg/m2 2 x tgl p.o. Tag 1-14 • Bevacizumab 7,5 mg/kg KG i.v **Irinotecan plus Cetuximab (2. Teil)** Ein Zyklus (Zykluslänge 42 Tage) besteht aus: • Irinotecan 125 mg/m² iv, 60 - 90 min wöchentlich (D1, D8, D15, D22) d.h. über 4 Wochen gefolgt von einer 14 tägigen Pause • 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) **Windowtherapie:** Nach Maßgabe des Prüfarztes z.B. XELOX/FOLFOX plus Bevacizumab, Capecitabin plus Bevacizumab **Studiendesign:** 
Tumorevaluierung	• Ansprechen nach RECIST 1.1 (nach 8, 16 und 24 Wochen, danach alle 12 Behandlungswochen) • Untersuchung des Primärtumors (erweiterte Mutations- und Expressionsanalysen)

	• Liquid Biopsies (Baseline und zum jeweiligen Progress) • 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 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: Um mit einer HR von 0,67 einen Unterschied bzgl. OS3 mit einer Power von 80% und einem einseitigen alpha von 2,5% nachzuweisen werden 196 Ereignisse benötigt. Bei 196 benötigten Ereignissen und einer angenommenen Dropout-Rate von 15% sind damit 230 Patienten (115 Patienten pro Therapiearm) erforderlich.

AIO-KRK/YMO-0519: Prospective, randomized, open, multicenter Phase II trial to investigate the efficacy of trifluridine/tipiracil plus panitumumab versus trifluridine/tipiracil plus bevacizumab as first-line treatment of metastatic colorectal cancer (FIRE-8)

AIO-Studie

Studiennummer/-Code:	AIO-KRK/YMO-0519 – FIRE-8	
Status:	aktiv	
Rekrutierungzeit:		
Anzahl Patienten:	geplant: 153	aktuell eingeschlossen: 0
Anzahl Zentren:	geplant: 40	initiiert: 1
Weitere Zentren:	Derzeit keine weiteren Zentren	
Letzte Aktualisierung	Okt. 2021	

Sponsor	Charité, Universitätsmedizin Berlin Charitéplatz1, 10117 Berlin
Coordinating investigator	Prof. Dr. med. Dominik Modest Charité -Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie am Campus Virchow Klinikum (CVK) Augustenburger Platz 1, 13353 Berlin
Investigational medicinal product(s)	Trifluridine/tipiracil, panitumumab, bevacizumab
Clinical trial phase	Phase II
Indication studied	First-line treatment of RAS wild-type metastatic colorectal cancer (mCRC)
Background and rationale	**Combination of bevacizumab and fluoropyrimidines or bevacizumab and trifluridine/tipiracil** The combination of a fluoropyrimidine (FP) with bevacizumab has been evaluated in several randomized studies [1-4] in metastatic colorectal cancer (mCRC). Consistently, these studies report response rates in the range of 19-38%, median progression-free survival (PFS) of 8-9 months, and median overall survival (OS) times of 21-22 months. The present evidence supports the contention that first-line treatment with FP plus bevacizumab is a valuable treatment option particularly in patients with disseminated metastases and without the need to achieve rapid tumor reduction as well as in patients ineligible for combination-chemotherapy. The TASCO study [5] compared capecitabine plus bevacizumab to trifluridine/tipiracil plus bevacizumab in untreated mCRC patients. The combination trifluridine/tipiracil with bevacizumab was similarly active compared to the combination capecitabine plus bevacizumab with a trend for the trifluridine/tipiracil based-therapy being associated with more favourable outcome. Therefore, it might be concluded that trifluridine/tipiracil is also a valuable partner for bevacizumab in untreated mCRC.

	Combination of panitumumab and trifluridine/tipiracil While the combination of bevacizumab plus mono-chemotherapy appears established in first-line therapy, this is less clear for EGFR-targeted agents in combination with fluoropyrimidines and derivates. In fact, the absence of such protocols prohibits patients that are unfit for the use of combination chemotherapy to benefit from EGFR-antibodies, too. This is particularly unfortunate as selected subgroups (RAS wild-type) derive a benefit in response rate of ~25% and a survival benefit of 6-8 months [6-8]. It might be concluded that development of a mono-chemotherapy plus EGFR antibody will address a clinical need and add to the available treatment option. The development on a phase II level can be justified based on the Apollon-study [9] that evaluated trifluridine/tipiracil plus panitumumab in refractory mCRC with no dose limiting toxicity using the standard doses of both trifluridine/tipiracil and panitumumab and promising activity in pre-treated patients. The following considerations support the use of trifluridine/tipiracil plus bevacizumab or alternatively trifluridine/tipiracil plus panitumumab as an initial treatment option: • Initial trifluridine/tipiracil plus bevacizumab is very well tolerated and may enable a good quality of life while patients receive treatment • Evidence from the TASCO study suggests that initial trifluridine/tipiracil plus bevacizumab leads to a median PFS in the range of 9 months. Median treatment duration is expected to be around 6 months. • Trifluridine/tipiracil in combination with panitumumab was found safe and active in pre-treated patients with mCRC. A favourable response rate of 37% has been demonstrated in a phase I/II study - even after failure of previous treatment.
Objectives	**Primary objective** ☐ To compare the efficacy of treatment with trifluridine/tipiracil plus panitumumab versus trifluridine/tipiracil plus bevacizumab **Secondary objectives** ☐ To compare efficacy, safety and patient reported quality of life (QoL) of treatment with trifluridine/tipiracil plus panitumumab versus trifluridine/tipiracil plus bevacizumab **Other exploratory objective** Further anti-tumor treatment after discontinuation of study treatment **Translational research objectives** Identification and characterization of patient subgroups with greatest or lowest benefit from respective treatment including efficacy and toxicity.
Endpoints	**Primary endpoint** • Objective response rate (ORR) according to RECIST 1.1 (assessment at the local trial center) **Secondary endpoints** **Efficacy** • Overall survival (OS) • Progression-free survival (PFS) • Objective response rate (ORR) according to RECIST 1.1 (assessment by central review) • Depth of response (DpR) (assessment by central review) • Early tumor shrinkage ([ETS]; assessment by central review) **Quality of life** • QoL as assessed with the QoL questionnaire EQ-5D-5L

	Safety • Type, incidence, severity, and causal relationship to IMPs of non-serious adverse events and serious adverse events (severity evaluated according to CTCAE version 5.0) **Other exploratory endpoints** • Subsequent anti-tumor treatment lines (monotherapy and combination therapy treatment lines including medicinal products [chemotherapeutics, antibodies and targeted therapy] and investigator reported efficacy of subsequent treatment lines
Trial design	This is an open-label, randomized, multicenter phase II study with two parallel arms. Patients suffering from RAS wild-type mCRC, who are not eligible to undergo combination chemotherapy according to investigator's assessment or unwilling to undergo such chemotherapy, are randomized in a 1:1 ratio to investigate the efficacy, patient reported quality of life and safety of trifluridine/tipiracil in combination with panitumumab (Arm A) versus trifluridine/tipiracil plus bevacizumab (Arm B) as first-line treatment of metastatic disease. During the randomisation process stratification will be performed according to the following parameters: ○ ECOG 0 vs. ECOG 1/ECOG 2 ○ Synchronous vs. metachronous disease (synchronous disease is defined as metastasis/metastases, detected at the time of initial diagnosis of the CRC or within 6 months after the initial diagnosis of the CRC whereas metachronous disease is defined as metastasis/metastases, first detected later than 6 months after the initial diagnosis of the CRC) Primary endpoint is ORR according to RECIST 1.1 (assessment at the local trial center). Treatment in both arms is continued until occurrence of progression according to RECIST 1.1 criteria as evaluated by the investigator or unacceptable toxicity. Patient are followed up with regard to survival and if applicable subsequent anti – cancer treatments until death or -after end of study treatment- for at least 5 years after randomisation, whichever date is earlier. **Abbreviations:** mCRC = metastatic colorectal cancer; R = randomisation; BSA = body surface area; BID = twice daily; BW = body weight

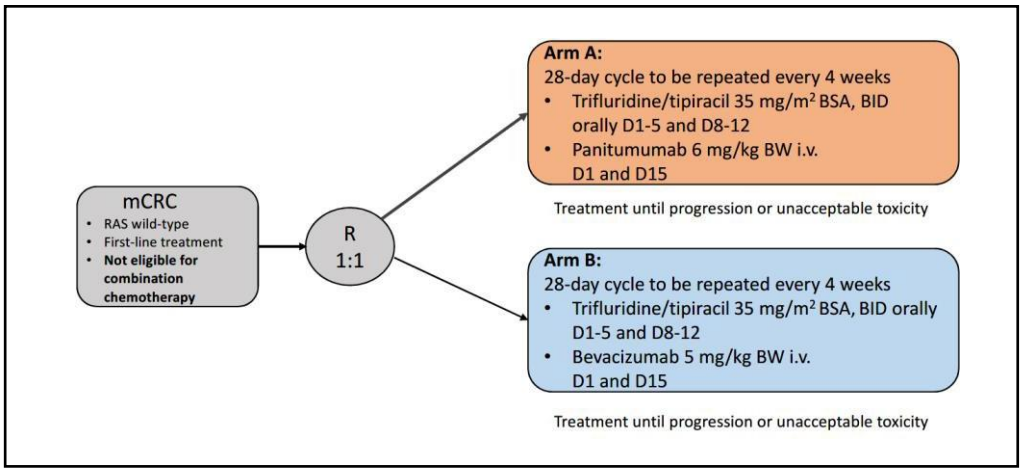
Inclusion criteria	1. Patient's signed informed consent 2. Patients ≥ 18 years at the time of signing the informed consent 3. Histologically confirmed adenocarcinoma of the colon or rectum 4. Metastatic colorectal cancer (mCRC) with at least one measurable lesion according to RECIST 1.1 in a computed tomography (CT) or magnetic resonance imaging (MRI) scan performed within 5 weeks prior to randomisation 5. Metastases are primarily unresectable or patient is unable/unwilling to undergo surgery 6. RAS wild-type (KRAS, exons 2, 3, 4 and NRAS, exons 2, 3, 4) mCRC, proven in the primary tumor or metastasis. The RAS mutational status must be determined by means of a validated test method. 7. Patient is not eligible to undergo combination chemotherapy according to investigator's assessment or unwilling to undergo combination chemotherapy. 8. ECOG performance status 0-2 9. Adequate bone marrow, hepatic and renal organ function, defined by the following laboratory test results: 9.1 Absolute neutrophil count ≥ 1.5 x 10^9/L (1500/µL) 9.2 Hemoglobin ≥ 80 g/L (8 g/dL) 9.3 Platelet count ≥ 75 x10^9/L (75,000/µL) without transfusion 9.4 Total serum bilirubin of ≤ 1.5 x upper limit of normal (ULN) 9.5 Aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) ≤ 2.5 × ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5 × ULN 9.6 Calculated glomerular filtration rate (GFR) according to Cockcroft –Gault formula or according to MDRD ≥ 30 mL/min or serum creatinine ≤ 1.5 x ULN 9.7 Urine dipstick for proteinuria < 2+ (within 14 days prior to randomisation), unless a subsequent 24-hour urine collection demonstrates < 1 g of protein in 24 hours. 10. Patients without anticoagulation need to present with an INR <1.5 x ULN and PTT <1.5 x ULN. Patients with anticoagulation may be enrolled if the patient receives the medication at a stable dose for at least 2 weeks before randomisation and provided that INR and PTT are < 1.5 xULN. 11. For females of childbearing potential (FCBP): negative pregnancy test within 14 days before randomisation and agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of study treatment. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 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 partner's sterilization, hormonal contraceptives that inhibit ovulation, hormone- releasing intrauterine devices, and copper 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. 12. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below: With female partners of childbearing potential, 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 6 months after the last dose of study treatment. Men must refrain from donating sperm during this same period. With pregnant female partners, men must remain abstinent or use a condom

	during the treatment period and for 6 months after the last dose of study medication to avoid exposing the embryo. 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.
Exclusion criteria	1. Prior systemic therapy of metastatic disease. **Note:** Prior adjuvant chemotherapy is permitted, if completed > 3 months prior to randomisation. Multimodal treatment of rectal cancer is not considered anti- metastatic therapy and does not preclude study participation 2. Known brain metastasis. In case of symptoms that are suggestive of brain metastasis, brain metastasis has to be ruled out by means of cranial CT/MRI. 3. Significant cardiovascular disease such as: New York Heart Association Class III or greater heart failure; myocardial infarction within 6 months prior to randomisation; balloon angioplasty (PTCA) with or without stenting within 6 months prior to randomisation; despite anti-arrhythmic therapy unstable cardiac arrhythmia > grade 2 NCI CTCAE; unstable angina pectoris 4. Transient ischaemic attack or cerebrovascular accident within 6 months prior to randomization, history of cerebral or aortic aneurysm or dissection 5. Medical history of deep vein thrombosis or pulmonary embolism within 6 months prior to randomisation or medical history of recurrent thromboembolic events (> 1 episode of deep vein thrombosis, pulmonary embolism, peripheral embolism) within the last 2 years. 6. Severe bleeding event within the last 6 months before randomisation (except tumor bleeding surgically treated by tumor resection) 7. Evidence of bleeding diathesis or significant coagulopathy 8. Uncontrolled hypertension defined as systolic blood pressure ≥160 mm Hg and/or diastolic ≥ 100 mm Hg under antihypertensive medication 9. Severe chronic non-healing wounds, ulcerous lesions or untreated bone fracture. 10. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation, or intra-abdominal abscess -unrelated to surgery- within 6 months prior to randomisation. 11. Acute or subacute bowel obstruction, active chronic inflammatory bowel disease or chronic diarrhea 12. History of keratitis, ulcerative keratitis or severe dry eye. 13. Hypersensitivity to trifluridine/tipiracil or panitumumab or bevacizumab or any of the excipients, known hypersensitivity to Chinese hamster ovary cell products, known hypersensitivity to human or humanized antibodies 14. Current or recent (within 10 days of randomisation) use of or anticipated need for continuous treatment during study treatment with acetylsalicylic acid > 325 mg/day or treatment with dipyramidole, ticlopidine > 2 x 250 mg/day, clopidogrel > 75 mg/day, and cilostazol. Combination of these drugs are not allowed. 15. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomisation, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 28 days prior to randomisation or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure 16. Core biopsy or other minor surgical procedure, excluding placement of a vascular access devices, within 3 days prior to the first dose of bevacizumab 17. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis/interstitial pneumonia, or idiopathic

	pneumonitis/interstitial pneumonia, or evidence of active pneumonitis or pulmonary fibrosis on screening chest imaging 18. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications. 19. Medical history of other malignant disease than mCRC with the following exceptions: - patients who have been disease-free for at least three years before randomisation - patients with adequately treated and completely resected basal cell or squamous cell skin cancer, in situ cervical, breast or prostate cancer, stage I uterine cancer – patients with any treated or untreated malignant disease that is associated with a 5 year survival prognosis of ≥90% and does not require active therapy 20. Known alcohol or drug abuse 21. Pregnant or breastfeeding females 22. Participation in a clinical trial or experimental drug treatment within 28 days prior to inclusion in the clinical trial or within a period of 5 half-lives of the substances administered in a clinical trial or during an experimental drug treatment prior to inclusion in the clinical trial, depending on which period is longest, or simultaneous participation in another clinical trial while taking part in this clinical trial. 23. Patient committed to an institution by virtue of an order issued either by the judicial or the administrative authorities 24. Patient possibly dependent from the investigator including the spouse, children and close relatives of any investigator 25. Limited legal capacity
Treatment, dosage and administration	**Arm A:** **28-day cycle to be repeated every four weeks** Trifluridine/tipiracil, 35 mg/m² BSA, BID, orally on Days 1–5 and 8–12 Panitumumab at 6 mg/kg BW, intravenous infusion* on Days 1 and 15 *First administration over about 60 min. If the first administration is tolerated without an infusion-related reaction, the subsequent infusions may be administered over about 30-60 min. **Arm B:** **28-day cycle to be repeated every four weeks** Trifluridine/tipiracil, 35 mg/m² BSA, BID, orally on Days 1–5 and 8–12 Bevacizumab at 5 mg/kg BW, intravenous infusion* on Days 1 and 15 *First administration over 90 ± 15 min. If the first administration is tolerated without an infusion-related reaction: the second administration may be infused over about 60 ± 15 min.; if the first and second administration are tolerated without an infusion-related reaction: subsequent infusions may be administered over about 30 min. The treatment is continued in Arm A and Arm B until progression according to RECIST 1.1 criteria or unacceptable toxicity.
Translational research	The translational research aims to identify and characterize patient subgroups with greatest or lowest benefit from the respective treatment. Among others, correlations of any patient subgroups with response according to radiological imaging criteria and survival as well as changes in circulating tumor DNA (ctDNA) or inflammation will be investigated. The translational research will focus on the following analyses: • BRAF and other mutations, gene expression subgroups and CMS subtypes will be analyzed in residual archival FFPE tumor tissue samples (primary tumor or metastasis permitted). These analyses might include analysis of germline mutations if these are of interest.

	• Tumor evolution (by means of ctDNA), inflammation- and immunomarkers are analyzed in blood. 20 mL blood in Streck – cell-free DNA blood collection tubes, 10 mL EDTA blood and 10 mL serum blood will be collected at each of the followed time points: ○ during screening within 21 days before randomisation, ○ at the first restaging, ○ upon progression on study treatment or at the EoT visit (**only** if study treatment was discontinued permanently without occurrence of progression, e.g. due to unacceptable toxicity). • Copies of CT- and /or MRI images sent for prespecified central review will be also used to analyze exploratorily possible correlation of radiological measurable criteria with tumor response, course of the tumor disease (e.g. overall survival and progression-free survival), type of tumor disease, interaction of patient/tumor characteristics and in further exploratory manners (i.e. RADIOMICS). This research might also analyze possible impact in subgroups. All the translational research subprojects are analyzed exclusively exploratively.
Statistical considerations	The primary endpoint ORR will be tested to demonstrate superiority induced by initial treatment with trifluridine/tipiracil plus panitumumab (Arm A) versus initial trifluridine/tipiracil plus bevacizumab (Arm B). Patients are randomized in a ratio 1:1 in Arm A and Arm B (see trial design). For Arm B, an objective response rate of 30% will be assumed, based on previous studies [1, 3, 4]. For Arm A, we hypothesize an improvement of 25 percentage points of the objective response rate, leading to an estimated response rate of 55% based on the result of the PANDA trial [10]. This difference corresponds to an odds ratio of 2.85. A Fischer r's exact test with a two-sided nominal significance level 0.05 will have at least 80% power to detect a significant difference when the sample size amounts to 138 patients. Given an estimated drop-out rate of 10% (i.e. patients who received no treatment within the study), 153 patients need to be enrolled. Secondary and exploratory endpoints will be analyzed in descriptive manner. All additional p- values will be estimated exploratorily without adjustment of the level of significance, using two- sided test procedures. Demographic and prognostic baseline measures will be analyzed for heterogeneity between the two treatment arms. The main population for analysis of the primary endpoint is the Full analysis set (FAS).
Duration and end of trial	Estimated duration of the clinical trial: 8 years Planned first patient first visit: QIII 2021 Planned recruitment period: 36 months Individual treatment duration: About 6 months Individual follow-up duration: After treatment end until death or for at least five years after randomisation, whichever date is earlier End of trial: Last Follow up visit of the last patient (LPLV); planned QIII 2029
GCP statement	The clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable regulatory requirements.

The study is displayed in the following figure:



References

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AIO-KRK-0120: Impact of a centralized tumour board on secondary intervention rate in patients with RAS mutant metastatic colorectal cancer after first-line treatment with FOLFOXIRI plus bevacizumab (FIRE-7)

AIO-Studie

Studiennummer/-Code:	**AIO-KRK-0120_FIRE-7**
Status:	rekrutierend
Rekrutierungszeit:	von: Q1/2021 bis: Q1/2023
Anzahl Zentren:	geplant: 40 aktuell initiiert: 1 aktiv rekrutierend: 1
Weitere Zentren:	sind sehr erwünscht
Anzahl Patienten:	geplant: 130 aktuell eingeschlossen: 1
Letzte Aktualisierung	06.10.2021

STUDY TYPE	Randomized, open-label, clinical trial
PRINCIPAL INVESTIGATOR	Prof. Dr. med. Volker Heinemann Medizinische Klinik und Poliklinik III Klinikum der Universität München – LMU München Marchioninistr. 15 81377 München Germany
TRIAL OFFICE	Matthias Wolff Medizinische Klinik und Poliklinik III Klinikum der Universität München – LMU München Marchioninistr. 15 81377 München Germany Tel.: +49 (0)89 4400 72208 Fax: +49 (0)89 4400 75256 Email: Matthias.Wolff@med.uni-muenchen.de
SPONSOR	Klinikum der Universität München – LMU München Marchioninistr. 15 81377 München Germany
CONDITION	Colorectal cancer
DESIGN	This is a randomised, multicentre observational study in patients suffering from RAS mutant mCRC with primarily unresectable metastases, who are planned to be treated with FOLFOXIRI and bevacizumab or who have already received ≤ four cycles FOLFOXIRI and bevacizumab as first-line treatment of metastatic disease. The patients are randomised in a 1:1 ratio to compare the rate of patients in whom secondary interventions (e.g. resection, ablation) are performed in curative intent when secondary intervention options are assessed by a multidisciplinary centralized tumour board (Arm A) versus when secondary intervention options are not assessed by a multidisciplinary centralized tumour board (Arm B). All patients evaluated in the study will receive chemotherapy with FOLFOXIRI plus bevacizumab. After this induction/conversion therapy, imaging (CT or MRI) will be performed to evaluate resectability. In Arm A, a multidisciplinary, centralized tumour board will assess options of secondary intervention to be performed in the context of a generally curative treatment approach. If there are secondary intervention options according to the judgement of the centralized tumour board, they will be listed in their respective sequence and the assessment will be communicated to the participating physician or his/her

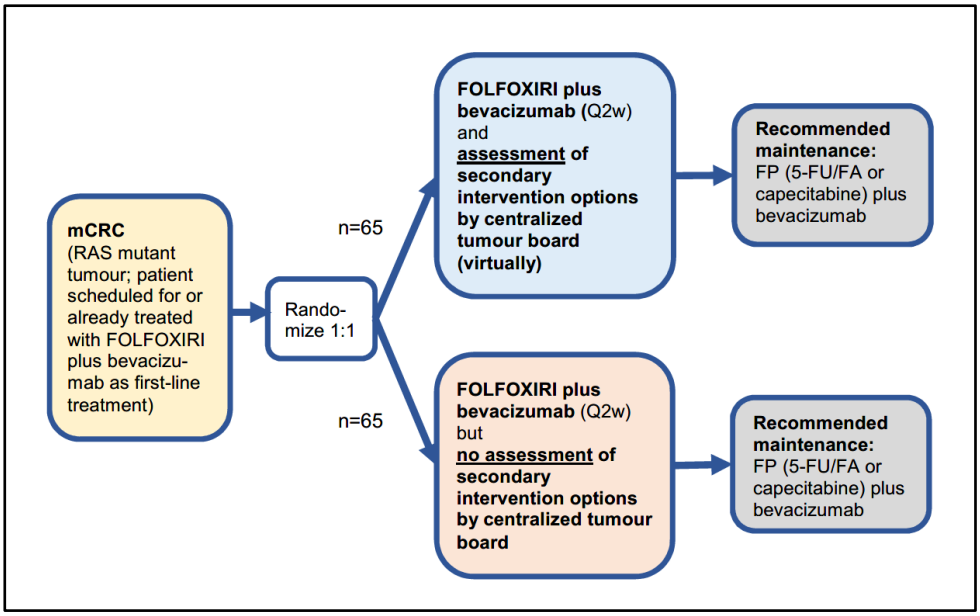
	deputy at the study center. The decision, whether or not any secondary intervention is performed as recommended by the centralized tumour board as well as the kind of interventional procedures is up to the discretion of the treating physicians and surgeons of each patient. Any secondary intervention is recorded. Evaluating the primary endpoint, the first interventions performed in one organ (e.g. liver) are rated when performed in a generally curative context (e.g. even in the presence of lung metastases that need to be approached in a further intervention). In Arm B, no centralized tumour board will be integrated in to clinical decision making and patients will be treated according to institutional guidelines. The number of treatment cycles with FOLFOXIRI and bevacizumab will be according to local clinical routine and medical guidelines, recommended are 8 to 12 cycles FOLFOXIRI in combination with bevacizumab, followed by a maintenance therapy with fluoropyrimidine (FP) plus bevacizumab until progression. The study design is displayed in the following figure: **Note:** Inclusion of patients already treated with FOLFOXIRI and bevacizumab is permitted if ≤ 4 cycles FOLFOXIRI plus bevacizumab have been administered, treatment is ongoing and the first restaging has not been conducted prior to inclusion. **Abbreviations:** mCRC = metastatic colorectal carcinoma; FOLFOXIRI = 5-fluorouracil, folinic acid, oxaliplatin, irinotecan; FP = fluoropyrimidine; 5-FU = 5-fluorouracil; FA = folinic acid
INDICATION	Treatment-naïve RAS mutant metastatic colorectal cancer
OBJECTIVE(S)	**Primary objective** • To compare the rate of secondary interventions performed in a generally curative context in patients with RAS mutant mCRC treated with FOLFOXIRI and bevacizumab when options for secondary interventions are either assessed by a centralized tumour board **versus** no centralized tumour board. **Secondary objectives** • to evaluate treatment efficacy in both study arms to evaluate safety of treatment with FOLFOXIRI and bevacizumab (including maintenance treatment with fluoropyrimidine (FP) plus bevacizumab)
INTERVENTION(S)	Additional centralized tumour board versus no centralized tumour board
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Not defined yet
BACKROUND/RATIONALE	The combination of a FOLFOXIRI and bevacizumab has been developed in phase 3 trials and is a valid treatment option - especially in patients with RAS mutant metastatic colorectal cancer (mCRC), who do not have the option to receive anti-EGFR therapy ((1), (2)). In particular, patients that might become candidates for secondary resection or ablation of metastases may benefit from FOLFOXIRI plus anti-VEGF therapy ((1), (2), (3)). Integration of surgery and ablative techniques into the treatment algorithm is associated with dramatically improved survival of patients with mCRC ((4), (5)). Central assessments for secondary resectability in mCRC suggest that more patients could undergo secondary interventions than actually is reported ((5), (6)). Central monitoring for interventional treatment options may help to improve the rate of patients with secondary operation and/or ablation.

	Thus, the study investigates in a randomized fashion whether the rate of patients in whom secondary interventions are performed in generally curative intent is improved when secondary intervention options are assessed virtually by a centralized tumour board. Only patients, who are planned to be treated with FOLFOXIRI plus bevacizumab or who have already received treatment with FOLFOXIRI plus bevacizumab are to be included to avoid bias as result of different treatment regimens. The number of treatment cycles with FOLFOXIRI plus bevacizumab will be according to local clinical routine and medical guidelines, recommended are 8 to 12 cycles FOLFOXIRI in combination with bevacizumab, followed by a maintenance therapy with a fluoropyrimidine (5-fluorouracil/folinic acid [5-FU/FA] or capecitabine) plus bevacizumab until progression.
KEY EXCLUSION CRITERIA	1. Pregnant or breast-feeding women. Females of childbearing potential (FCBPs) who do not practice adequate contraceptive measures as required according to SmPCs of the administered medicinal products. 2. Contraindication to intensive chemotherapy with FOLFOXIRI plus bevacizumab 3. Contraindications to treatment with 5-FU, oxaliplatin, folinic acid, irinotecan (FOLFOXIRI) and/or bevacizumab according to SmPCs of the administered medicinal products. 4. Patients with confirmed cerebral metastasis. In case of clinical suspicion of brain metastasis, a cranial CT or MRI must be performed to rule out brain metastasis before study inclusion. 5. Documentation of > 5 lung metastases (however, no limitation for the number of metastases in the liver) 6. Isolated distant nodal metastasis, isolated peritoneal metastasis or isolated bone metastasis 7. Limited legal capacity
KEY INCLUSION CRITERIA	8. Written informed consent to participate in the study 9. Patients ≥ 18 years at the time of signing the informed consent 10. Histologically confirmed (in primary tumour or metastasis) UICC stage IV metastatic adenocarcinoma of the colon or rectum (mCRC) with primarily unresectable metastases 11. RAS mutant CRC (as determined by local pathology in tissue of primary tumour or metastasis) 12. At least one measurable lesion according to RECIST version 1.1 in a CT/MRI scan performed within 4 weeks prior to randomisation 13. ECOG performance status 0-1 14. Patients planned to receive chemotherapy with FOLFOXIRI plus bevacizumab as first-line treatment of metastatic disease. In these patients de-escalation of FOLFOXIRI to FOLFIRI or FOLFOX is allowed in case of toxicity. Patients can also be included if they had already received ≤ 4 cycles of induction/conversion therapy with FOLFOXIRI plus bevacizumab and the first restaging has not been conducted prior to randomization. 15. Completion of adjuvant therapy for colorectal cancer > 3 months prior to study entry. 16. Patient's ability for treatment with FOLFOXIRI and bevacizumab according to participating physician's judgement.
OUTCOME(S)	**<u>Primary endpoint</u>** • Rate of patients in whom secondary interventions (e.g. resection, ablation treatment or combination of both) are performed in curative intent **<u>Secondary endpoints</u>** **Efficacy** • Objective response rate (ORR) according to RECIST 1.1

	• Progression-free survival (PFS) rate at 6, 12 and 24 months • Overall survival (OS) rate at 6, 12 and 24 months **Safety** Type, incidence, relatedness, and severity of adverse events with severity ≥ Grad 3 (severity according to NCI CTCAE version 5.0)
STATISTICAL ANALYSIS	Primary objective of the study is to compare the rate of secondary interventions performed in a generally curative context in patients with RAS mutant mCRC treated with FOLFOXIRI and bevacizumab when secondary intervention options are assessed by a centralized tumour board **versus** no centralized tumour board. Primary endpoint is the rate of patients in whom secondary interventions (e.g. resection, ablation treatment or combination of both) are performed in curative intent. Evaluating the primary endpoint, the first interventions performed in one organ (e.g. liver) are rated when performed in a generally curative context with the objective to achieve a no-evidence-of-disease situation in the respective organ (e.g. even in the presence of lung metastases that need to be approached in a further intervention). Secondary intervention with objective to achieve a no-evidence-of-disease situation in the respective organ is defined as any (combination of) procedure/procedures that eliminates/eliminate all tumour lesions in the respective organ with radiologically documented success about 8-12 weeks (time interval of radiological restaging according to local routine) after the intervention. In addition, patients who underwent resection must have a R0/R1 resection for a no-evidence-of-disease status. A secondary intervention rate of about 15% is expected in study Arm B without assessment of secondary intervention options based on the resection rate of metastases in molecularly unselected patients of the FIRE-3 study (5) by a multidisciplinary centralized tumour board, whereas a secondary intervention rate of ≥ 35% would be considered as successful (7) in the study Arm A with assessment of secondary intervention options by a centralized tumour board. Hence the hypotheses to be tested are: H_0: Intervention rate (with assessment by a centralized tumour board) ≤ Intervention rate (without assessment by a centralized tumour board) H_1: Intervention rate (with assessment by a centralized tumour board) > Intervention rate (without assessment by a centralized tumour board) The primary endpoint will be evaluated by a one-sided Chi-square test. In order to reject the null hypothesis at a one-sided significance level of 5% with a power of at least 80% in total 114 patients are required, 57 patients per arm. The primary analysis of the secondary intervention rate will be performed in the following population: - Randomized patient in whom the planned treatment with FOLFOXIRI and bevacizumab has been initiated and who have received at least four cycles FOLFOXIRI and bevacizumab. - CT- and/or MRI images from baseline before the effective start of treatment with FOLFOXIRI plus bevacizumab) and at least one restaging examination after baseline (during treatment phase or during follow up) are available

	It is expected that 15% of the randomized patients will not be evaluable for the primary analysis. Hence, 130 patients (65 patients per arm) have to be randomized.
SAMPLE SIZE	130 patients planned (65 per arm)
TRIAL DURATION	Estimated duration of the study: 4 years, estimated Q1 2021 to Q1 2025 Planned first patient first visit: Q1 2021 Planned recruitment period: 24 months; estimated Q1 2021 to Q1 2023 Individual treatment duration: Estimated treatment duration with FOLFOXIRI and bevacizumab and subsequent maintenance therapy will be 6-8 months. Individual documentation duration: Documentation until death or the end of the study (but for at least 2 years after first administration of FOLFOXIRI in combination with bevacizumab in the latter case), whichever is earlier Planned end of the study: Q1 2025
PARTICIPATING CENTERS	40 active centers planned

FIRE-7



AIO-KRK-0320/ass: A phase 1/2 multiple-indication biomarker, safety, and efficacy study in advanced or metastatic Gastrointestinal cancers explOring treatment comBinations with peLarEorep and aTezolizumab (GOBLET Study)

AIO-Studie

Studiennummer/-Code:	**AIO-KRK-0320/ass - GOBLET**		
Status:	In Rekrutierung		
Rekrutierungszeit:	von: 2021	bis: 2023	
Anzahl Zentren:	geplant: 25	aktuell initiiert: 3	aktiv rekrutierend: 3
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant: 55	aktuell eingeschlossen: 1	
Letzte Aktualisierung	15.10.2021		

STUDY TYPE	Phase 1/2
PRINCIPAL INVESTIGATOR	Prof. Dr. med. Dirk Arnold
TRIAL OFFICE	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, Fax +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
SPONSOR	Oncolytics Biotech, Inc. Suite 804, 322 11th Avenue SW Calgary Alberta T2R 0C5
CONDITION	• Cohort 1 : First-line locally advanced/metastatic unresectable pancreatic ductal adenocarcinoma (PDAC) • Cohort 2 : First-line mCRC, MSI-H or dMMR • Cohort 3 : Third-line mCRC, independent of MSI/dMMR status • Cohort 4 : Second-line (or higher) locally advanced/metastatic unresectable squamous cell carcinoma of the anal canal (SCCA) after prior systemic chemotherapy
DESIGN	multiple-indication, open label, non-randomized
OBJECTIVE(S)	Primary objective To evaluate the response to treatment measured by ORR at week 16 in patients treated with the combination of pelareorep plus atezolizumab as stand-alone therapy (Cohorts 2, 4) or in combination with SOC chemotherapy (Cohorts 1, 3) Secondary objectives To assess the anti-tumor activity of the treatment combinations based on Progression-free survival (PFS) and Overall survival (OS) To evaluate the tolerability of the combination of pelareorep plus atezolizumab as stand-alone therapy (Cohorts 2, 4) or in combination with SOC chemotherapy (Cohorts 1, 3)
INTERVENTION(S)	Cohort 1: pelareorep and atezolizumab added to SOC gemcitabine and nab paclitaxel Cohort 2: pelareorep and atezolizumab Cohort 3: pelareorep and atezolizumab added to SOC trifluridine/tipiracil Cohort 4: pelareorep and atezolizumab
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	To evaluate the immunological changes within tumor tissue and peripheral blood and to examine potential biomarkers of response to treatment in each cohort

BACKROUND/RATIONALE	Within the last 10 years, our understanding of the relationship between the immune system and cancer has led to profound advancements in oncology. Immunotherapy with monoclonal antibodies directed against programmed cell-death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) has changed the treatment paradigm for many cancers. Despite advances in immunotherapy, this therapeutic approach for GI cancers has demonstrated limited efficacy. The checkpoint blockade inhibitors, nivolumab and pembrolizumab, are used for the treatment of only a small subset of pretreated patients with tumors characterized as having a high predisposition for genetic mutations, known as MSI. MSI-H tumors are also immunologically 'hot' and poised to respond to checkpoint blockade therapy through their high number of tumor-infiltrating lymphocytes (TILs), specifically CD8+ T cells, and high levels of PD-L1 expression. Within CRC, MSI makes up approximately 15% of all CRCs and its prevalence is stage-dependent, with ~15% of stage II-III disease and only 4–5% for mCRC (Kalyan et al., 2018). Across all cancers, MSI is present in 3.8% (Bonneville et al., 2017). In contrast, checkpoint blockade has shown little efficacy in tumors with a low number of genetic mutations, known as microsatellite stable (MSS) tumors. These MSS tumors are considered 'cold' tumors, having low levels of immune cell infiltration and PD-L1 expression, and comprise most GI cancers. Use of oncolytic virus to sensitize GI tumors to checkpoint blockade. To overcome resistance to immunotherapy within GI cancer, one promising strategy is to increase the number of cytotoxic immune cells within the TME via the use of an oncolytic virus. Oncolytic viruses have shown notable activity in several cancer types and activate both innate and adaptive anti-viral immunological responses that in turn coax anti-tumor immunity (Gujar et al., 2018). In this study, we will explore if the oncolytic virus, pelareorep, can turn 'cold' tumors 'hot' and sensitize GI tumors to checkpoint blockade, thereby improving responses and broadening the number of patients that can be treated. Several existing oncolytic viruses require tumor site injection. This is perceived as a barrier to treatment due to difficulties with accessing these tumors. The oncolytic virus pelareorep is administered intravenously (IV) and is not associated with human disease (Sabin, 1959). Pelareorep is a propriety formulation of a naturally occurring, non-genetically modified, non-enveloped human reovirus serotype 3-Dearing strain, which contains a live, replication-competent virus. Pelareorep selectively kills tumor cells and promotes tumor-directed innate and adaptive immune responses, resulting in the priming of the TME for checkpoint blockade, allowing for treatment with anti-PD-L1 or anti-PD-1 therapies (Samson et al., 2018). Pelareorep has demonstrated in vitro and in vivo activity in many cancers, including CRC and pancreatic cancer, and has been delivered intratumorally (ITu) and IV in clinical studies. Pelareorep's anti-tumor activity is based on a complementary, dual mechanism of action: 1. Direct oncolytic activity in tumor cells permissive to viral replication (Strong et al., 1998; Norman et al., 2002; Kim et al., 2010; Carew et al., 2013). 2. Induction of anti-tumor immunity through: • Innate immunity against virally infected tumor cells and upregulation of inflammatory cytokines (Errington et al., 2008; Prestwich et al., 2009; Steele et al., 2011; Adair et al., 2013; El-Sherbiny et al., 2015). • Adaptive immunity through the increased presentation of tumor- and virus-associated epitopes by tumor cells or antigen-presenting cells, allowing for the generation of an adaptive anti-tumor immune response (White et al., 2008; Prestwich et al., 2009; Gujar et al., 2010; Kim et al., 2015; Rajani et al., 2016). Thus, in addition to functioning as an oncolytic agent, pelareorep overrides the absence of anti-tumor immunity present in cancer patients, activating innate and adaptive anti-tumor immune responses.

KEY EXCLUSION CRITERIA	1. Undergone systemic chemotherapy, radiotherapy, or surgery, <4 weeks before study treatment. 2. Received previous treatment with immune checkpoint inhibitors. 3. Uncontrolled hypertension (systolic blood pressure ≥150 mmHg and diastolic blood pressure ≥90 mmHg) despite treatment with hypotensive agents. 4. Acute coronary syndrome (including myocardial infarction and unstable angina) and/or a history of coronary angioplasty or stent placement performed within 6 months of enrollment. 5. A large amount of pleural effusion or ascites requiring more than weekly drainage. 6. A history of (non-infectious) pneumonitis that required steroids or currently active pneumonitis. 7. A ≥grade 3 active infection according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. 8. Symptomatic brain metastasis. (Patients with asymptomatic and stable brain metastasis are eligible for study enrollment). 9. Interstitial lung disease with symptoms or signs of activity. 10. In C1, C2, and C3 only: Positive test results for either anti human immunodeficiency virus (HIV)-1 antibodies, anti-HIV-2 antibodies, anti-human T cell leukemia virus type 1 (HTLV-1) antibodies, hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV) antibodies.* Testing is not required unless deemed necessary by the investigator. *Patients who test positive for anti-HBc antibodies or have detectable HBV-DNA will also be excluded. In C4 only: Positive test results for either anti HIV-1 or HIV-2 antibodies if the CD4+ T cell is <300 cells/µl.* Testing for HIV status is required. * To be eligible, HIV+ patients must have an undetectable viral load and be receiving highly active antiretroviral therapy (HAART). Patients must be on established HAART therapy for at least 4 weeks prior to study entry. 11. Autoimmune disease that has required systemic treatment in the past 2 years with disease modifying agents, corticosteroids, or immunosuppressive drugs. [Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment]. 12. A history or findings of ≥grade 3 congestive heart failure according to the New York Heart Association functional classification. 13. A seizure disorder that requires pharmacotherapy. 14. Proteinuria ≥grade 3 (using spot testing; if grade 3, repeat with mid-stream urine; if still grade 3, then urine collection for 24 hours to confirm grade) as per NCI CTCAE. 15. A medical contraindication to undergoing biopsies 16. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation. 17. A non-healing wound, non-healing ulcer, or non-healing bone fracture within 4 weeks prior to the start of study drug. 18. Women who are pregnant or breastfeeding. 19. A diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing >10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study drug. 20. Any vaccine during screening and the first cycle of treatment. 21. Legal incapacity or limited legal capacity to consent.
KEY INCLUSION CRITERIA	C1: Locally Advanced/Metastatic Unresectable Pancreatic Ductal Adenocarcinoma 1L • Patients with histologically or cytologically confirmed, locally advanced/metastatic unresectable PDAC who are eligible for 1L SOC chemotherapy with gemcitabine plus nab-paclitaxel C2: Metastatic Colorectal Cancer 1L (MSI-H/dMMR)

	• Patients with histologically or cytologically confirmed mCRC with MSI-H/dMMR tumors and no prior systemic treatment for metastatic disease C3: Metastatic Colorectal Cancer 3L • Patients with histologically or cytologically confirmed mCRC, independent of MSI/dMMR status, who failed (and/or did not tolerate) 2 prior lines of treatment, including oxaliplatin, irinotecan, 5-FU, ± targeted agents such as bevacizumab and/or an anti-epidermal growth factor receptor (EGFR) antibody who are eligible for 3L SOC chemotherapy with trifluridine/tipiracil C4: Locally Advanced/Metastatic Unresectable Anal Cancer ≥2L • Patients with histologically or cytologically confirmed locally advanced/metastatic unresectable SCCA of viral (HPV) or non-viral origin who failed (and/or did not tolerate) prior systemic chemotherapy All Cohorts: Patients must: 1. Provide written informed consent prior to study participation. 2. Be at least 18 years of age on the day of providing consent. 3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days of start of treatment. 4. Have evaluable or measurable lesions per RECIST v1.1. 5. Have adequate organ function at the time of enrollment as defined by: • Absolute neutrophil count ≥1200/mm3 • Platelet count ≥7.5 × 104/mm3 • Hemoglobin >8 g/dL (blood transfusion >2 weeks before testing is permitted) • Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤2.5 x the upper limit of normal (ULN; ≤5 x ULN in patients with liver metastasis) • Total bilirubin ≤1.5 x ULN • Creatinine ≤1.5 x ULN • Lipase ≤1.5 x ULN • International normalized ratio (INR) ≤1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤1.5 x ULN unless receiving treatment with therapeutic anticoagulation. Patients being treated with anticoagulant, e.g. heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring per local SOC will be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local SOC. 6. Have recovered to ≤grade 1 or baseline for all adverse events (AEs) due to previous therapies or surgeries. 7. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly-effective form(s) of contraception (i.e., one that results in a low failure rate [<1% per year] when used consistently and correctly) and to continue its use for 6 months after the last dose of study drug.
STATISTICAL ANALYSIS	All the methods described below will be performed separately in each of the 4 study cohorts. The primary endpoint is calculated by dividing the number of patients achieving CR or PR as best response at week 16 according to RECIST v1.1 by the total number of patients in the ITT population. Exact 90% and 95% confidence intervals will be provided for this proportion. As a sensitivity analysis, a similar calculation will be performed in the per-protocol population. All other efficacy and toxicity parameters will be evaluated in an explorative or descriptive manner, providing proportions, means, medians, ranges, standard deviations and/or confidence intervals, or Kaplan-Meier estimates, as appropriate.

SAMPLE SIZE	A total of 55 patients in all 4 cohorts for the primary endpoint ORR (C1=12; C2=19; C3=14; C4=10), with the option for extension if the predefined clinical efficacy criteria are met
TRIAL DURATION	Total trial duration is expected to be 43 to 50 months. This reflects the expected enrollment period (7 to 14 months) plus the per patient follow-up period (36 months). If any of the 4 cohorts meets the criteria for expansion, the duration of the study will increase accordingly.
PARTICIPATING CENTERS	25 sites planned
FURTHER CENTERS DESIRED?	Yes, site selection is pending

Kolorektales Karzinom, last-line/4th-line

AIO-KRK-0119: A phase I/II trial of D,L-methadone and mFOLFOX6 in the treatment of advanced colorectal cancer (MEFOX)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0119	
Status:	in Vorbereitung, Protokoll final	
Rekrutierungszeitraum:	FPI Q4/2021 geplant	
Zentren:	geplant: Phase I 3 / Phase II 10	initiiert: 2
Patienten:	geplant: Phase I 18 / Phase II 66	aktuell eingeschlossen:
Weitere Zentren:	sind erwünscht, Abfrage über AIO-Verteiler folgt in Kürze	
Letzte Aktualisierung	Oktober 2021	

Principal investigator	Prof. Dr. med. Thomas Seufferlein Dept. of Internal Medicine I, University of Ulm Albert-Einstein-Allee 23, 89081 Ulm, Germany Phone: +49 731 50044501 E-mail: thomas.seufferlein@uniklinik-ulm.de
Sponsor:	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany Tel: +49 30-8145 344 32, Fax: +49 30-3229329-26 E-Mail: info@aio-studien-ggmbh.de
Condition	Chemorefractory colorectal cancer
Primary aim of the study	Evaluation of patient related benefit of D-/L-methadone plus mFOLFOX6 compared to mFOLFOX6 alone in the treatment of patients with advanced colorectal cancer
Secondary aims of the study	• DCR 12 weeks after randomization (per protocol analysis) • Effect on tumor response according to RECIST 1.1 • Effect on progression free survival (PFS) • Effect on overall survival (OS) • Health related quality of life (EORTC QLQ-C30) • Patient-reported outcomes

	• Correlation of DCR, PFS, OS and tumor regression with pharmacogenomic markers, tumor biomarkers and molecular analyses (µ opioid receptor expression on tumor cells, ctDNA, transcriptome, miRNA-arrays) • Evaluation of the safety and tolerability profile. • Evaluation of the methadone levels under treatment • Correlation of µ opioid receptor expression in tumor tissue and efficacy
Study design	Phase I: 3+3 dose escalation study Phase II: Open-label, 2:1 randomized, controlled trial Patients in the mFOLFOX6 alone arm are allowed to cross over and receive methadone hydrochloride in combination with mFOLFOX6 upon disease progress
Study population	Patients with histologically confirmed, chemorefractory colorectal carcinoma
Sample Size	Phase I: At maximum 18 patients Phase II: 66 patients (44 / 22 patients as 2:1 randomized)
Therapy	Phase I: Step up with dose escalation of D,L-methadone hydrochloride in 3 cohorts (15 – 17,5 – 20 mg/bid orally) combined with mFOLFOX6 (day 1-3: Oxaliplatin 85mg/m² IV infusion, given as a 120 minutes IV infusion in 500 mL D5W, concurrent with leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²) IV infusion, followed by 46-hour 5-FU infusion (2400 mg/m²) Phase II: Continuous intake of pre-defined (phase I) D,L-methadone hydrochloride dose orally combined with mFOLFOX6 (day 1-3: Oxaliplatin 85mg/m² IV infusion, given as a 120 minutes IV infusion in 500 mL D5W, concurrent with leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²) IV infusion, followed by 46-hour 5-FU infusion (2400 mg/m²) compared to mFOLFOX6 alone
Primary endpoint	Disease control rate at week 12 after randomization
Secondary endpoints	Disease control rate 12 weeks after randomization (per-protocol-population), overall response rate according to RECIST 1.1, patient-reported outcomes, PFS, overall survival, quality of life, safety, correlation of µ opioid receptor expression in tumor tissue and efficacy.
Biometrics	The main outcome as the disease control rate at week 12 will be compared in a confirmatory fashion by a two-sided chi-square test at a significance level of 5%.
Time schedule	**Phase I:** First patient in to last patient out (months): at minimum 11 (3 cohorts), at maximum 22 (6 cohorts) Duration of the entire trial (months): at minimum 11 (3 cohorts), at maximum 22 (6 cohorts) Recruitment period (months): 9 Data evaluation and determination of recommended dose for phase II (months): 1 **Phase II:** First patient in to last patient out (months): 36 Duration of the entire trial (months): 36 Recruitment period (months): 24 Data evaluation and coverage (months): 12
Centers	Phase I: 3 national sites Phase II: 10 national sites
Main selection criteria	Inclusion criteria: • Advanced, histologically confirmed, metastatic colorectal carcinoma not suitable for resection and chemorefractory~~—or~~. Previously employed

	chemotherapy regimens and agents should comprise the following: Fluoropyrimidines, oxaliplatin, irinotecan, antiangiogenic agents (bevacizumab, aflibercept or ramucirumab), anti-EFGR-mAbs (in case of all-Ras-wildtype and left-sided primary tumor) and Trifluridin/Tipiracil (TAS102) • Microsatellite stable subset (MSS) of colorectal cancer • Prior antineoplastic therapy or radiochemotherapy is allowed up to two weeks prior to start of the study medication. However, for the phase II part of the trial, failure of this strategy must be confirmed. In case of prior radiotherapy/radiochemotherapy the target lesion used for tumor evaluation must not be in the radiation field. • There must be an oxaliplatin free period of at least 6 months prior to start of the study medication. • No polyneuropathy of > grade 1 • Tumor-related ECOG performance status 0-2 • Anticipated life expectancy ≥ 12 weeks • Creatinine clearance ≥ 30 ml/min • Serum total bilirubin level ≤ 3 x ULN. • ALT and AST ≤ 2.5 x ULN or ≤ 5.0 x ULN in the presence of liver metastasis (established after adequate biliary drainage) • White blood cell count ≥ 3.5 x 106/ml, neutrophil granulocytes count ≥ 1,5 x 106/ml, platelet count ≥ 100 x 106/ml • Pain must be controllable without the need of concomitant use of opioids including methadone • Signed informed consent according to ICH/GCP and national/local regulations (participation in translational research is obligate) • None of the following concomitant medications: MAO-B-Inhibitors, strong inductors or inhibitors of CYP3A4, antiarrhythmic drugs of class I and III or other drugs that have potential for QT-prolongation • Age ≥ 18 years • At least one measurable target lesion according to RECIST 1.1, Pre-irradiated or locally treated lesions must not be used as target lesions. Exclusion criteria: • Microsatellite unstable CRC (MSIhigh) • Chronic infectious diseases, immune deficiency syndromes • Polyneuropathy ≥ grade II according to CTCAE • Premalignant hematologic disorders, e.g. myelodysplastic syndrome • Disability to understand and sign written informed consent documents • Past or current history of malignancies except for the indication under this study and curatively treated: ▪ Basal and squamous cell carcinoma of the skin ▪ In-situ carcinoma of the cervix ▪ Other malignant disease without recurrence after at least 3 years of follow-up • Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment • History of or evidence upon physical examination of CNS disease unless adequately treated (e.g. primary brain tumor, seizure not controlled with standard medical therapy or history of stroke). • Pre-existing neuropathy > grade I (NCI CTCAE) • Severe non-healing wounds, ulcers or bone fractions • Evidence of bleeding diathesis or coagulopathy • Patients not receiving therapeutic anticoagulation must have an INR ≤ 1.4 and PTT ≤ 40 sec 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 of the institution) • Major surgical procedures or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgical procedure during the course of the study. • Pregnancy or breastfeeding women.

	• Use of cannabinoids because of possible overlap and /or potentiation of side effects • Concomitant daily use of opioids in the last 3 months including methadone prior start of study medication • Subjects with known allergies to the study drugs or to any of its excipients. • Treatment with another investigational drug or participation in another interventional trial (within the 14 days prior randomization or 5 plasma half-lifes of the used investigational drug, whatever is longer) • 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

Kolonkarzinom, frühe Stadien

AIO-KRK-0220 - Perioperative/Adjuvant atezolizumab with or without the immunomodulatory IMM-101 in patients with MSI-high or MMR-deficient stage III colorectal cancer ineligible for oxaliplatin-based chemotherapy– a randomized Phase II study (ANTONIO)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0220 - ANTONIO
Status:	in Vorbereitung, geplanter Start Q4/2021
Rekrutierungszeit:	von: Q4/2021 bis: Q1/2023
Anzahl Zentren:	geplant: 40 aktuell initiiert: 2 aktiv rekrutierend: 0
Weitere Zentren:	ja
Anzahl Patienten:	geplant: 120 aktuell eingeschlossen: 0
Letzte Aktualisierung	Oktober 2021

STUDY TYPE	Phase-II, open-label, prospective, randomized, multicenter study
PRINCIPAL INVESTIGATOR	Prof. Dr. Stefan Kasper Department of Medical Oncology West German Cancer Center, University Hospital Essen Hufelandstr. 55 45147 Essen Tel: +49 201 723 3449, FAX: +49 201 723 5549 E-Mail: stefan.kasper@uk-essen.de
SPONSOR	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin Phone: +49 30 814 534 431, Fax: +49 30 322 932 926 E-Mail: info@aio-studien-ggmbh.de
CONDITION	colorectal cancer
DESIGN	Main study: 2-arm, open label, randomized phase II study Sub-study: Single-arm, open label, exploratory phase II study
INDICATION	Patients with MSI-high or MMR-deficient stage III colorectal cancer who are ineligible for oxaliplatin-based adjuvant chemotherapy or who refuse to receive an oxaliplatin-based adjuvant chemotherapy.

	For the main study, patients must have undergone R0 tumor resection. For the sub-study, R0 tumor resection must be planned.
STUDY OBJECTIVES	Primary objective: In the Main study, the primary objectives are: • To determine whether atezolizumab alone or atezolizumab combined with IMM-101 can significantly improve disease-free survival rate at 3 years compared to historical control when used as adjuvant treatment in patients with MSI-H/dMMR stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option. Secondary objectives, main study: • To determine whether atezolizumab monotherapy or atezolizumab combined with IMM 101 show promising efficacy (DFS and OS) compared to historical control when used as adjuvant treatment in patients with MSI-H/dMMR stage III colon or rectal cancer for whom oxaliplatin regimens are not a viable treatment option. • To assess the safety and tolerability profile of atezolizumab with or without IMM 101 in patients with MSI-high stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option. • To determine the impact of atezolizumab with or without IMM 101 on patient-reported outcomes and health-related QoL, and functional domains of health-related QoL. Explorative objectives, main study: • To estimate the ctDNA-free rate defined as the proportion of patients without detectable ctDNA after 12 months of adjuvant treatment. • To explore the biologic activity of study treatment in terms of biomarkers in liquid biopsies, immune-related biomarkers and gene expression in peripheral blood mononuclear cells, the role of the gut microbiome in immunotherapy, as well as the predictive value of tumor mutational burden for response to immunotherapy. Primary objective, sub-stuy: • To assess the efficacy of perioperative atezolizumab with IMM 101 in patients with MSI-high clinical stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option in terms of pathological complete (pCR) or subtotal (<10% vital tumor cells) regression after 5 weeks of neoadjuvant treatment. Secondary objectives, sub-study: • To asses efficacy in terms of disease-free survival and overall survival. • To assess safety, tolerability, and QoL of perioperative atezolizumab with IMM 101 in patients with MSI-high clinical stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option. Exploratory objectives, sub-study: • To estimate the ctDNA-free rate defined as the proportion of patients without detectable ctDNA after 12 months of adjuvant treatment. • To explore the biologic activity of study treatment in terms of biomarkers in liquid biopsies, immune-related biomarkers and gene expression in peripheral blood mononuclear cells, the role of the gut microbiome in immunotherapy, as well as the predictive value of tumor mutational burden for response to immunotherapy.

SCHEME OF THERAPY	Main study: **Arm A** ▪ Atezolizumab 840mg i.v., on Day 1 and Day 15 (q2w) of every 28-day treatment cycle for a total of 12 cycles (24 doses) **Arm B** ▪ One initial dose of IMM-101 intradermally at 1.0 mg 14 ±2 days before start of atezolizumab treatment Followed by 12 treatment cycles Q4W: ▪ On C1D1 and C1D15: IMM-101 intradermally at a dose of 0.5 mg, ▪ On Day 1 of every 28-day treatment cycle (q4w) 0.5 mg intradermally ▪ Atezolizumab 840mg i.v., on Day 1 and Day 15 of every 28-day treatment cycle for a total of 12 cycles (24 doses) Sub-study: **Neoadjuvant treatment**: ▪ IMM-101 at 1.0 mg intradermally on Day 35 before surgery ▪ Atezolizumab at 1200 mg i.v. on Day 28 before surgery ▪ IMM 101 at 0.5 mg intradermally on Day 21 before surgery ▪ Atezolizumab at 1200 mg i.v. on Day 7 before surgery ▪ IMM 101 at 0.5 mg intradermally on Day 5 before surgery **Adjuvant treatment:** is identical to Arm B of the main study; to begin within 70 days after surgery and after adequate recovery of the patient.
STUDY RATIONALE	The current standard of care for adjuvant treatment of oxaliplatin-ineligible patients with stage III dMMR/MSI-H colon cancer is fluoropyrimidine monotherapy. In the COLOPREDICT registry, the 3 years DFS rate for such patients >70 years of age is 63% (95%CI: 53-75%) (Reinacher-Schick, *unpublished data*). In contrast to patients with mismatch repair proficient (pMMR) colon cancer, however, it is not established whether patients with stage III dMMR/MSI-H colon cancer benefit from adjuvant fluoropyrimidine monotherapy at all. For patients with stage II colon cancer in an otherwise identical setting, there is no indication for adjuvant treatment due to a lack of clinical benefit compared to surgery alone. Clinical results suggests a similar situation for stage III malignancy. Similar to other checkpoint inhibitors (CPI), the PD-L1 antibody atezolizumab demonstrated impressive activity and good tolerability in patients with metastatic MSI-H CRC. Recently, the randomized phase III Keynote-177 trial was presented. In Keynote-177, patients with dMMR metastatic CRC were randomized to the PD-1 antibody pembrolizumab or to chemotherapy (mFOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab as per Investigator`s choice). Pembrolizumab treatment resulted in a statistically significant prolongation of Progression-free survival (16.5 mo [95%CI 5.4-32.4 mo] vs. 8.2 mo [95%CI 6.1-10.2 mo]; HR=0.60 [95%CI 0.45-0.80]; p=0.0002) and higher objective response rate (43.8% [95%CI 35.8-52.0%] vs. 33.1% [95%CI 25.8-41.1%] along with a markedly longer duration of response (duration of ≥ 24 mo in 82.6% vs. 35.3%). In addition, side effects were lower with pembrolizumab and quality of life was improved compared to conventional chemotherapy. Thus, pembrolizumab will become the new standard of care in patients with dMMR metastatic CRC in first-line therapy. Perioperative chemotherapy is the standard of care in advanced gastric and esophageal cancer. In both diseases, the implementation of neoadjuvant therapy has improved the outcome dramatically. In locally advanced colon cancer, perioperative chemotherapy was compared to conventional adjuvant chemotherapy in the FOXTROT trial. 1052 patients were randomized 2:1 between experimental and conventional treatment. Neoadjuvant chemotherapy was well tolerated and safe, with no increase in perioperative morbidity and a trend toward fewer serious postoperative

	complications. The rate of R0 resection was even higher in patients receiving neoadjuvant chemotherapy (95% vs. 90%, p=0.001). However, patients with dMMR or MSI high tumors had no benefit from neoadjuvant chemotherapy with no improvement in disease free survival and significantly reduced pathological remission compared to patients with pMMR tumors. Thus, neoadjuvant chemotherapy will become the standard of care in patients with locally advanced pMMR colon cancer, but leaving patients with dMMR colon cancer without treatment improvements. However, in the recently published explorative NICHE trial in 20 patients with locally advanced dMMR tumors, a 6-week neoadjuvant immunotherapy with two cycles nivolumab with or without ipilimumab induced dramatical pathological remission rates with 12 pathological complete responses and 19 major pathological responses (≤10% residual viable tumor). The neoadjuvant therapy was well tolerated, and all patients underwent radical resections without delays. Based on these results, neoadjuvant immunotherapy represents a promising treatment option for dMMR colon cancer patients and should be evaluated further. Previous clinical experience demonstrated the safety of IMM-101 as monotherapy and in combination with chemotherapy or CPIs. Therefore, the combination of atezolizumab and IMM-101 could be a promising strategy especially in MSI-H CRC patients who are not candidates for extensive surgery.
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 2. Male or female ≥ 18 years of age 3. Histologically confirmed adenocarcinoma of the colon or rectum 4. For the main study: Pathological Stage III disease For the perioperative sub-study: Clinical stage III disease 5. <u>For the main study</u>: R0-resected primary tumor <u>For the perioperative sub-study</u>: Resectable primary tumor; R0 resection anticipated (R1-resected patients can remain on study.) 6. Tumor is MSI-high (MSI-H) or MMR-deficient (dMMR) <u>For the main study:</u> assessed from biopsy or from resected tumor tissue <u>For the perioperative sub-study:</u> assessed from biopsy 7. ECOG status 0 – 2 8. Ineligible for oxaliplatin-based adjuvant chemotherapy or patient's refusal of oxaliplatin-based adjuvant chemotherapy. Oxaliplatin ineligibility criteria are: - Age ≥70 - Peripheral sensory neuropathy > grade 1 - QT interval prolongation or co-medication with drugs known to prolong the QT interval - Renal impairment (glomerular filtration rate <60ml per min) - Suboptimal controlled diabetes mellitus (HbA1C>6,5%) with the risk of aggravation upon corticoid premedication for oxaliplatin based chemotherapy 9. Adequate blood count, liver enzymes, and renal function – re-testing can be undergone once in case of initial results near cutoff ▪ White blood cell count ≥ 3.5 x 10^6/mL ▪ Platelet count ≥ 100 x 10^9/L (>100,000 per mm^3) ▪ Hemoglobin ≥ 9 g/dL (blood transfusion > 2 weeks before testing is permitted) ▪ AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal ▪ Serum Creatinine ≤ 1.5 x institutional ULN and a calculated glomerular filtration rate ≥ 30 mL per minute

	10. 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 11. 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. 12. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly-effective contraception (i.e., one that results in a low failure rate [<1% per year] when used consistently and correctly) and to continue its use for 6 months after the last dose of study drug.
EXCLUSION CRITERIA	1. Severe infection within 4 weeks prior to randomization, including, but not limited to, hospitalization for complications of infection, bacteremia, known active pulmonary disease with hypoxia, or severe pneumonia or any active infection (bacterial, viral or fungal) requiring systemic therapy within 4 weeks prior to randomization. Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study. Patients with positive test result for SARS-CoV2 should be managed as per local institutional guidelines. 2. <u>For the main study</u>: Distant metastases or residual disease <u>For the perioperative sub-study</u>: Distant metastases or macroscopic residual disease (R2 resection status) 3. Neoadjuvant radiotherapy or radio-chemotherapy (enrollment of rectal cancer patients without prior radio- or radio-chemotherapy is allowed); prior neoadjuvant radio-chemotherapy (RCT) or radiotherapy (RT) for rectal cancer is allowed if >5 years and secondary colorectal cancer 4. Prior adjuvant chemotherapy for colorectal cancer; allowed if >5 years and secondary colorectal cancer 5. Prior treatment with atezolizumab or any other checkpoint inhibitor (anti-PD-1, anti-PD-L1, anti CTLA-4) 6. Prior exposure to IMM-101. 7. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to treatment start, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions: Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible. Inhaled corticosteroids for chronic obstructive pulmonary disease or bronchial asthma, supplemental mineralo-corticosteroids or low-dose corticosteroids for adrenal-cortical insufficiency are allowed 8. Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment. 9. History of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins. 10. Known hypersensitivity to CHO cell products or any component of the atezolizumab formulation. 11. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. If any of these lung diseases is suspected based on the patient's history or the integrated

	evaluation of clinical and radiological records, an additional spirometry should be conducted. 12. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening. Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening followed by a negative HBV DNA test, are eligible for the study. The HBV DNA test will be performed only for patients who have a positive total HBcAb test. Patients are also eligible if HBV DNA < 500 IU/mL obtained within 28 days prior to initiation of study treatment, AND anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study. 13. Anti-viral therapy against HCV during the trial (but allowed prior to trial) 14. Positive human immunodeficiency virus (HIV) test. As an exception, known HIV+ patients may be included if they have: ▪ A stable regimen of highly active anti-retroviral therapy (HAART) ▪ No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections ▪ A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests 15. a) Treatment with a live, attenuated vaccine within 4 weeks prior to first dose of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the last dose of study treatment. b) Treatment with any vaccine during screening and the first cycle of treatment. 16. Active tuberculosis (as ruled out by clinical evaluation including medical history, physical examination, radiographic findings on baseline CT/ MRI of chest/abdomen/pelvis; if active tuberculosis is suspected, tuberculosis testing should be performed as per local standard of care). 17. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis. The following exceptions apply: ▪ Patients with a history of autoimmune-mediated hypothyroidism who are on thyroid replacement hormone are eligible for the study. ▪ Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study. ▪ Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (i.e., patients with psoriatic arthritis are ▪ excluded) are eligible for the study provided all of following conditions are met: ▪ Rash must cover < 10% of body surface area ▪ Disease is well controlled at baseline and requires only low-potency topical corticosteroids ▪ 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 18. Prior (<3 years) or concurrent malignancy that 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] 19. History of hypersensitivity to any of the study drugs or any excipient IMM-101 20. History of allergic reaction to any mycobacterial product 21. Prior allogeneic stem cell or solid organ transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy

	22. Severe non-healing wounds, ulcers or bone fractions 23. Evidence of bleeding diathesis or coagulopathy 24. Major gastrointestinal bleeding within 4 weeks prior to treatment start, unless cause of bleeding was the resected tumor. 25. Major surgical procedures other than primary tumor resection, 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. 26. Medication that is known to interfere with any of the agents applied in the trial. 27. Female subjects who are pregnant or breast-feeding; male or female patients of reproductive potential who are not employing an effective method of birth control as listed in the protocol) (failure rate of less than 1% per year, see protocol section **Fehler! Verweisquelle konnte nicht gefunden werden.**). Women of childbearing potential must have a negative pregnancy test. 28. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or affect patient safety or study results 29. Participation in another clinical study with an investigational drug within 28 days prior to treatment start or 7 half-lives of previously used trial medication, whichever is longer 30. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities (AMG § 40, Abs. 1 No. 4) 31. Affected persons who might be dependent on the sponsor or the investigator
STATISTICAL ANALYSIS	We hypothesize that atezolizumab with or without IMM-101 will improve the prognosis of patients with stage III dMMR CRC ineligible for or refusing oxaliplatin-based adjuvant chemotherapy compared to SOC and that these could therefore be promising therapeutic options. The current standard of care for adjuvant treatment of oxaliplatin-ineligible patients with stage III dMMR colon cancer is fluoropyrimidine monotherapy. In the COLOPREDICT registry, the 3 years DFS rate for such patients >70 years of age is 63% (95%CI: 53-75%) (Reinacher-Schick, *unpublished data*). In contrast to patients with mismatch repair proficient (pMMR) colon cancer, however, it is not established whether patients with stage III dMMR colon cancer benefit from adjuvant fluoropyrimidine monotherapy at all. For patients with stage II colon cancer in an otherwise identical setting, there is no indication for adjuvant treatment due to a lack of clinical benefit compared to surgery alone. Clinical results suggests a similar situation for stage III malignancy. Similar to other checkpoint inhibitors (CPI), the PD-L1 antibody atezolizumab demonstrated impressive activity and good tolerability in patients with metastatic dMMR CRC. Recently, the randomized phase III Keynote-177 trial was presented. In Keynote-177, patients with dMMR metastatic CRC were randomized to the PD-1 antibody pembrolizumab or to chemotherapy (mFOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab as per Investigator`s choice). Pembrolizumab treatment resulted in a statistically significant prolongation of Progression-free survival (16.5 mo [95%CI 5.4-32.4 mo] vs. 8.2 mo [95%CI 6.1-10.2 mo]; HR=0.60 [95%CI 0.45-0.80]; p=0.0002) and higher objective response rate (43.8% [95%CI 35.8-52.0%] vs. 33.1% [95%CI 25.8-41.1%] along with a markedly longer duration of response (duration of ≥ 24 mo in 82.6% vs. 35.3%). In addition, side effects were lower with pembrolizumab and quality of life was improved compared to conventional chemotherapy. Thus, pembrolizumab will become the new standard of care in patients with dMMR metastatic CRC in first-line therapy. Preoperative short-term administration of a combination of CPIs in MSI-high colorectal cancers has induced high rates of pathological regression in a recently presented small explorative phase II study. Six weeks of preoperative administration of the CTLA-4 antibody ipilimumab and the PD-1 antibody nivolumab

	resulted in a 100% complete or subtotal pathological remission in 7 patients with early-stage (I to III) mismatch repair deficient colon cancer. Therefore, the combination of atezolizumab and IMM-101 could be a promising strategy especially in MSI-high CRC patients who are not candidates for extensive surgery. In order to avoid treating an unacceptably high number of patients with an experimental regimen, a standard single stage design according to Fleming is applied in each randomized arm separately. The hypothesis test is conducted against historical control. In the COLOPREDICT registry, the 3-year DFS rate for patients >70 years with stage III dMMR tumors treated with adjuvant fluoropyrimidine therapy is 63% (95%CI: 53-75%) (Reinacher-Schick, unpublished data). The observed DFS rate of the COLOPREDICT registry will serve as historical control for a formal hypothesis test. Assuming a true DFS rate of 80% at 3 years, the study requires 46 subjects (in each arm) to decide whether the proportion surviving without disease relapse is less than or equal to 63% or greater than or equal to 80% with a one-sided significance level of 0.05 and power of 80%. If the number of responses is 35 or more, the hypothesis that H0 ≤ 0.63 is rejected with a target error rate of alpha=0.05. If the number of responses is 34 or less, the hypothesis that H0 ≤ 0.63 cannot be rejected. To facilitate a Per-Protocol analysis, the formal sample size is inflated by 8% to yield 50 patients per treatment arm as the accrual goal for the main study. The sample size for the exploratory sub-study was chosen on grounds of feasibility. The treatment is more experimental than the main study, therefore a smaller sample size is warranted. The pathological complete or subtotal regression in the sub-study will be evaluated exploratively. A complete or subtotal (<10% vital tumor cells) regression rate >30% will be considered as clinically meaningful to provide a rationale for further investigation of this strategy. With a sample size of n=20 patients it is possible to test a rate of complete or subtotal regression of 30% ± 13.5% with a 1-sided type I error of 10%. The final decision if the strategy will be regarded as successful will be made after calculating the respective confidence interval.
TRIAL DURATION	Q4/2021-Q1/2023; 1.5 years enrollment, 1 year treatment LPI Q1/2023 LPLV Q1/2026
NUMBER OF PATIENTS	Randomized phase II study. Both arms will be independently compared to patients with MSI high CRC in the COLOPREDICT registry (both historic control and updated real-world data available at the time of primary analysis), which are only treated with a fluroropyrimidine or which received no adjuvant therapy. In addition 20 patients will be enrolled into a perioperative, explorative sub-study in 5 selected study centers. Patients with clinical stage III tumors assessed by CT or MRI in these selected centers will be asked to be enrolled into the perioperative sub-study. A total of 120 patients will be enrolled (50 in arm A, 50 in arm B and 20 patients in an explorative perioperative sub-study). Stratification T stage: T3N1 vs. T4 and/or N2; Left-sided vs. right-sided In the explorative sub-study 20 patients with clinical stage III disease based on a preoperative CT or MRI scans will receive neo-adjuvant atezolizumab and IMM-101 for 6 weeks. After resection these patients will receive the adjuvant therapy with atezolizumab and IMM-101 for additional 12 months.

AIO-KRK-0420 - Neoadjuvant encorafenib, binimetinib and cetuximab for patients with BRAFV600E mutated/pMMR localized colorectal cancer (NEOBRAF)

AIO-Studie		
Studiennummer/-Code:	AIO-KRK-0420 - NEOBRAF	
Status:	In Vorbereitung	
Rekrutierungszeitraum:	24 Monate (geplant)	
Zentren:	geplant: 20	initiiert: n/a
Patienten:	geplant: 48	aktuell eingeschlossen: n/a
Weitere Zentren:	Auf Anfrage	
Letzte Aktualisierung	Oktober 2021	

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Study design	Single-arm, open label, multicentre, phase II trial
Duration of study	Duration of recruitment: 24 months at a rate of 2 patients/month (counted from first patient in). Treatment for 8 weeks neoadjuvant and additional 16 weeks postoperatively in patients with tumor regression grade of 2-4. Follow-up for survival until trial termination 2 years after last patient in. Expected total trial duration 4.5 years.
Indication	Patients with unresected BRAF mutated/pMMR localized colorectal cancer (CRC)
Target population	Radiologically (CT) staged disease as: T3-4 and/or nodal positive (N+), M0. BRAF V600E mutation and pMMR or MSS (determined by either IHC or PCR) ECOG Performance status ≤ 1 Life expectancy > 3 months
Total number of sites	16 sites in Germany and 4 sites in Austria planned
Number of patients	48 patients planned
Primary objective	The targeted triplet combination of encorafenib, binimetinib and cetuximab should improve clinically relevant tumor regression (TRG2-4) compared to the rate achieved with neoadjuvant fluoropyrimidines and oxaliplatin in the FOxTROT trial.
Secondary objective	The triplet combination of encorafenib, binimetinib and cetuximab should be feasible in the neoadjuvant treatment of localized CRC and should have a positive impact on DFS compared to previous data on neoadjuvant chemotherapy with fluoropyrimidines and oxaliplatin. Translational data will inform about molecular mechanisms of response/resistance to triplet combination and the potential utility of liquid biopsy monitoring during treatment.
Primary endpoint	• Tumor regression grade (TRG)

Secondary endpoints	• Safety and tolerability (according to NCI CTC AE v5) incl. vital signs, clinical parameters and overall feasibility of the regimen • Perioperative morbidity and mortality • R0-resection rate • Overall response rate (according to RECIST v1.1) • Disease free survival (according to RECIST v1.1) • Overall survival • Correlation of quantitative BRAF V600E levels (measured by ddPCR) with TRG • Evaluation of mechanism of relative resistance in patients with less response (evaluated by tumor and liquid biopsy NGS profiling at baseline and after treatment) • Comparison of ctDNA clearance and TRG with a BRAF mutant/pMMR cohort from the planned neoadjuvant PROTECTOR study receiving neoadjuvant chemotherapy
Translational Research	The following translational research is currently planned, but may be adapted taking into account new research data. • the role of monitoring BRAF V600E in the blood during treatment by ddPCR, • the correlation between BRAF levels in the blood and tumor regression grade • the possibility to evaluate mechanisms of resistance in patients with poor/less tumor regression grade
Inclusion criteria	19. Biopsy-confirmed adenocarcinoma of the colon or upper rectum if too high for radiotherapy. 20. Radiologically (CT) staged disease as: T3-4 and/or nodal positive (N+), M0. 21. BRAF V600E mutation and pMMR or MSS (determined by either IHC or PCR). 22. ECOG Performance status ≤ 1. 23. Life expectancy > 3 months. 24. Age ≥ 18 years. 25. Haematologic function as follows: ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x10^9/L. 26. Adequate liver function as measured by serum transaminases (AST & ALT) ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN. Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled. 27. Adequate renal function: serum creatinine ≤ 1.5 x ULN. 28. Negative serum pregnancy test at screening for women of childbearing potential. 29. Highly effective contraception for both male and female subjects if the risk of conception exists. (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required at least 21 days prior, throughout and for at least 30 days after study treatment and 6 months after standard chemotherapy. 30. Signed and dated written informed consent. 31. Ability to take oral medication. 32. Ability to comply with the protocol for the duration of the study, including hospital/office visits for treatment and scheduled follow-up visits and examinations.
Exclusion criteria	1. Any prior systemic therapy, surgery or radiotherapy of the colorectal cancer disease.

	2. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes). 3. 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, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent). 4. Known severe hypersensitivity reactions to monoclonal antibodies or BRAF-/MEK-inhibitors (grade ≥ 3 NCI-CTCAE v 5), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma). 5. Pregnancy or lactation. 6. Known alcohol or drug abuse. 7. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (≤ 6 months prior to enrolment); myocardial infarction (≤ 6 months prior to enrolment), acute coronary syndromes [including unstable angina, coronary artery bypass graft (CABG), coronary angioplasty or stenting) ≤ 6 months prior to enrolment]; congestive heart failure (≥ New York Heart Association Classification Class II); or history or current evidence of clinically significant arrhythmia and/or conduction abnormality (≤ 6 months prior to enrolment), except rate controlled atrial fibrillation and paroxysmal supraventricular tachycardia. 8. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy. 9. Impaired GI function or disease that may significantly alter the absorption of encorafenib or binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption). 10. History of thromboembolic or cerebrovascular events ≤ 6 months prior to enrolment, including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli. 11. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy). 12. Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. 13. All other significant diseases, which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment. 14. Any psychiatric condition that would prohibit the understanding or rendering of informed consent. 15. Any approved anticancer therapy, including chemotherapy, hormonal therapy or radiotherapy, within 5 half-lives or 4 weeks (the longer period applies) prior to initiation of study treatment. 16. Current treatment with a non-topical medication or current intake of herbal preparations / supplements / foods known to be a strong inhibitor of CYP3A4. However, patients who either discontinue such treatment/intake or switch to another medication at least 7 days prior to starting study treatment are eligible. 17. Concomitant use of St. John's Wort (hypericum perforatum).
Scheme of therapy	All eligible patients will receive encorafenib, binimetinib and cetuximab at the following dosage. **Encorafenib** tablets, dose of 300 mg qd **Binimetinib** tablets, dose of 45 mg bid **Cetuximab** infusion, weekly dose of 250 mg/m^2 (1st dose 400mg/m^2) Duration of treatment: Treatment will be administered for 8 weeks preoperatively and 16 weeks postoperatively in responding patients (TRG 2-4). In non-responding patients

	(TRG 0-1) standard chemotherapy with fluoropyrimidines and oxaliplatin (e.g. CAPOX) may be applied postoperatively outside the trial at Investigators discretion.
Rationale / Hypothesis	BRAF mutations confers a dismal prognosis in colorectal cancer (CRC) patients, in localized and particular metastatic disease. In localized CRC (stage II and III) the overlap with dMMR/MSI-H tumors (about 30%) results in a similar disease-free survival (DFS), but a worse survival after recurrence, compared to BRAF wildtype. Notably, the BRAF mutant and pMMR/MSS cohort (about 65%) is the subgroup with the worst DFS, even if treated with intensive adjuvant treatment like FOLFOX with or without cetuximab (Sinicrope, Shi et al. 2015, Taieb, Zaanan et al. 2016). In second and third line metastatic CRC (mCRC) as investigated in the BEACON phase III study, the triplet combination of encorafenib, binimetinib and cetuximab demonstrated superior efficacy in terms of response and survival compared to irinotecan-based chemotherapy and cetuximab (confirmed ORR 26% vs. 2%, p<0.001; OS median 9.0 vs. 5.4 months, HR 0.52, p<0.001) and a trend towards higher efficacy compared to the doublet combination (ORR 26% vs. 20%; OS median 9.0 vs. 8.4 months, HR 0.79, 95% CI 0.59-1.06); however, the study was not powered to compare triplet vs. doublet (Kopetz, Grothey et al. 2019). Despite the similar OS, based on the numerically better ORR of 26% with the triplet (27% updated) vs. 20% with the doublet, the triplet should be evaluated in this curative setting requiring maximum response (Tabernero, Grothey et al. 2021). Furthermore, in the curative and particular neoadjuvant setting response may have a closer correlation to survival compared to the metastatic setting. In a single arm study with 93 evaluable patients in the first line setting (ANCHOR trial) an confirmed ORR of 48% with 88% of patients showing some tumor regression or stability was noted with the triplet regimen (Van Cutsem, Taieb et al. 2021). These data clearly show the high efficacy of the triplet regimen with increasing response induction in earlier disease settings. In addition, the triplet showed a manageable safety profile with comparable incidence of higher grade (3/4) adverse events compared to control arm with chemotherapy (65.8 vs. 64.2) in the metastatic setting (Tabernero, Grothey et al. 2021). Discontinuation of all therapy primarily due to an adverse event was seen in 9% of patients in the triplet arm and 11% in the chemotherapy arm. Deaths resulting from AEs occurred in 5%, and 4% of patients treated with the triplet and control, respectively. Investigators deemed three of the deaths to be at least possibly related to treatment: one death was from colonic perforation (triplet), one was from anaphylaxis (control), and one was from respiratory failure (control). Based on these results in the metastatic setting, the safety profile of triplet combination of encorafenib, binimetinib and cetuximab is considered to be adequate, justifying its use in the early treatment setting. Thus, the evaluation of the treatment known to have the highest efficacy in terms of tumor response and a manageable safety profile as evaluated in the metastatic setting in this prognostically dismal patient subgroup of BRAF mutant (pMMR/MSS) patients is warranted. The duration of neoadjuvant treatment of 8 weeks was chosen to align with other ongoing neoadjuvant trials with 8-12 weeks of treatment (AIO Protector trial, AIO-KRK-0620) and to allow for the development of relevant response, which were noted in the metastatic trials only after at least 6 weeks of treatment (Pierre Fabre Pharma GmbH. 2020). Recently presented results of the FOxTROT trial paved the way for neoadjuvant treatment by showing a beneficial impact for 6 weeks of neoadjuvant (and adjuvant) chemotherapy with 5FU and oxaliplatin compared to adjuvant chemotherapy alone in terms of recurrence rate at 2 years (HR 0.75, p=0.08) (Seymour et al ASCO 2019). In the FOxTROT trial, patient with neoadjuvant

	showed significantly improved tumor regression grade (TRG). Notably, TRG was clearly associated with cumulative recurrence rate. Based, on the above mentioned very poor prognosis, the efficacy of the triplet combination in mCRC and the positive trend for neoadjuvant start of chemotherapy in stage III, the evaluation of the triplet as neoadjuvant treatment in BRAF mutant and pMMR/MSS patients is proposed, aiming to further improve tumor regression with a targeted and chemo-free treatment compared to chemotherapy. The clinical data for BRAF mutant/pMMR stage III patients obtained from the FOxTROT trial, the AIO Colopredict registry and a parallel BRAFmutant/pMMR cohort within the planned neoadjuvant AIO FOxTROT trial receiving neoadjuvant chemotherapy and liquid biopsy monitoring and central pathological evaluation will inform about the comparative efficacy of this approach. After surgery tumor regression grade will inform about further treatment, in case of TRG2-4 (indicating response to neoadjuvant treatment, referring to figure 1) the triplet will be continued postoperatively for further 16 weeks for overall 24 weeks/6 months of molecular targeted treatment. In case of insufficient response to neoadjuvant triplet (TRG0-1) chemotherapy with oxaliplatin should be applied, in general 3 (6) months CAPOX (duration: investigator decision). Based on the above-mentioned background, neoadjuvant treatment with the triplet combination of encorafenib, binimetinib and cetuximab is aimed at improving clinically relevant tumor regression (TRG 2-4) compared to the rate achieved with neoadjuvant fluoropyrimidines and oxaliplatin in the FOxTROT trial. Rational: The triplet combination has a more than 10 times higher efficacy in terms of RECIST response in the metastatic setting and at least in the metastatic setting response to standard chemotherapy in BRAF mutants is very limited. TRG has demonstrated a close correlation to relapse rate in the FOxTROT trial (figure 3) and thus serves as a validated and early assessable endpoint. The choice of dosing of encorafenib, binimetinib and cetuximab is based on the above-mentioned phase III BEACON trial with a change to the cetuximab schedule (Kopetz, Grothey et al. 2019). In the pivotal licensing trials cetuximab was applied in a weekly schedule with 250mg/m^2 after an initial loading dose of 400mg/m^2. Based on the relative impractical close meshed schedule, later pharmacokinetic and -dynamic trials evaluated a biweekly schedule with 500mg/m^2 to improve feasibility of the regimen and limit outpatient visits, which is of particular value taking into account public emergencies as pandemics (Tabernero, Cervantes et al. 2010, Tabernero, Ciardiello et al. 2010). The biweekly schedule of cetuximab is a widely adopted standard of care. Thus, for NeoBRAF a biweekly cetuximab schedule in combination with the established encorafenib (1x300mg) and binimetinb (2x45mg) dose was chosen.
Sample size estimation and statistical analysis considerations	With neoadjuvant chemotherapy a tumor regression grade (TRG) of at least 2 (moderate regression or more) was achieved in 20% of pMMR/MSS patients treated with chemotherapy (Seymour and Morton 2019). The triplet combination of encorafenib, binimetinib and cetuximab should achieve a TRG of at least 2 in 35% of patients. Thus, by applying a phase II single stage design according to A'Hern with a one-sided test, an alpha of 0.1 and a beta of 0.2 (power 80%) 44 evaluable patients need to be included, with a 10% drop out rate 48 patients should be included (Stat. Med. 2001, 20:859-866).

AIO-KRK-0620xx: Pre-Operative Treatment in rEseCTable cOlon cancer (PROTECTOR)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0620xx - PROTECTOR
Status:	in Vorbereitung
Rekrutierungszeit:	von: bis:
Anzahl Zentren:	geplant: 80 aktuell initiiert: aktiv rekrutierend:
Weitere Zentren:	sind sehr erwünscht
Anzahl Patienten:	geplant: 525 aktuell eingeschlossen:
Letzte Aktualisierung	09.12.2020

STUDY TYPE	Intervention
PRINCIPAL INVESTIGATOR	**Medical Oncology:** Prof. Dr. med. Dominik Paul Modest, Med. Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin **Pathology:** Prof. Dr.med. Andrea Tannapfel, Institut für Pathology, Ruhr-Universität Bochum
TRIAL OFFICE	Prof. Dr. med. Dominik Paul Modest, Med. Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin
SPONSOR	Charité Universitätsmedizin Berlin
CONDITION	Colon cancer staged T3-4 and/or nodal positive without distant metastases.
DESIGN	Randomized, open-lable, Phase 3
INDICATION	Colon cancer
OBJECTIVE(S)	Preoperative therapy improves the outcome of patients with resectable colon cancer vs direct surgery followed by adjuvant therapy
INTERVENTION(S)	**Experimental intervention:** 12 weeks of neoadjuvant chemotherapy prior to surgery for colorectal cancer, followed by surgery **Control intervention:** direct surgery followed by standard of care adjuvant therapy
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	- ctDNA as a predictor for treatment response (or ctDNA level as predictors for response and survival) - QCL-IR-Imaging and artificial intelligence derived tissue based multivariate classifier for treatment response using neural networks - Influence of molecular subgroups on efficacy (consensus molecular subgroups, MAP-kinase alterations) - Immunprofiling and its influence on outcome parameters - Tumor regression according to Becker
BACKROUND/RATIONALE	The concept of perioperative therapy in advanced gastrointestinal cancers has raised momentum in various entities and represents standard of care in gastric/gastroesophageal junction cancers. The level of evidence in colorectal cancer is clearly driven by the management of rectal cancers with the development of total-neoadjuvant-therapy and also by the first colon cancer studies promoting pre-operative chemotherapy. Therefore, it can be concluded that the principle of neoadjuvant therapy in resectable abdominal cancers is established. Data from rectal cancer trials and also colon cancer suggest that the algorithm to establish early systemic therapy is safe and also likely associated with improved long-term outcome. We hypothesize that given the demonstrated effect size in FOXTROT with the adjustment of few design aspects (duration of therapy and exclusion of dMMR/MSI tumors as well as evaluation of accuracy of CT-based study entry), the

	strategy of neoadjuvant therapy in advanced colon cancer will improve disease-free survival.
KEY EXCLUSION CRITERIA	1. Not medically fit for surgery or chemotherapy 2. Acute bowel obstruction without intervention prior to study participation 3. Evidence of distant metastatic disease (indeterminate lung nodules with low clinical suspicion of metastases permitted)
KEY INCLUSION CRITERIA	1. Biopsy-confirmed adenocarcinoma of the colon 2. Proficient mismatch-repair system (pMMR) tested by immunohistochemistry or PCR 3. Radiologically (CT) staged disease as: T3-4 (as invasion of surrounding tissue structures or organs) **and/or** nodal positive (N+ defined as regional lymph node(s) without fat hilus and short axis diameter of ≥1cm), M0. 4. Intent for curative resection 5. Patients with bowel obstruction are only eligible if first stented or defunctioned 6. Tissue is available for pMMR/dMMR testing (centrally and/or locally) 7. Informed consent 8. Adequate bone marrow, liver, kidney, organ and metabolic function, 9. ECOG performance status 0 – 2 10. Age ≥ 18 at the time of registration
OUTCOME(S)	**Primary endpoint:** disease-free survival (DFS) **Secondary endpoint(s):** tumor regression score (TRS) by central review according to Dworak's score, overall survival (OS), safety of surgery, safety of chemotherapy, quality of life, treatments (including efficacy), outcome in molecular subgroups **Assessment of safety:** **For surgery:** length of hospitalisation, frequency of complication (anastomotic insufficiency, infections, redo surgery), 30/60 day morbidity and mortality **For chemotherapy:** NCI CTC AE assessment of toxicity,
STATISTICAL ANALYSIS	**Primary analysis:** The null hypothesis to be tested in confirmatory analysis states that the hazard ratio for DFS comparing intervention versus control equals 1. This hypothesis will be tested by means of Cox-regression adjusting for the above mentioned strata for randomization. The two-sided significance level is set to 0.05. The Cox-regression adjusted for additional factors provides a power advantage compared to the logrank test used for sample size calculation and this procedure thus provides a conservative approach. The primary analysis will be conducted based on the full analysis set which is defined as the intention to treat population. In a survival analysis setting, missing values are treated as non-informative censoring values so there is no need for imputation.
SAMPLE SIZE	Based on the best available evidence described above 2-year DFS is 70.0% in the straight to surgery group and we hypothesise that DFS will be 78% in the neo-adjuvant treatment followed by surgery group. To demonstrate an increase of 8 percentage points in 2-year DFS (hazard ratio = 0.696) requires observing 270 DFS events, with the recruitment of 525 (350:175 per arm) patients with an allocation ratio of 2:1 (experimental vs. standard). These calculations assume DFS follows an exponential distribution, a 2-sided 5% level of significance, 80% power, and allow for 2% dropout prior to meeting the DFS endpoint, with 5-year recruitment and 3-year follow-up periods. The event rate in the straight to surgery group will be monitored annually by the independent data monitoring and ethics committee to ensure these assumptions are appropriate.
TRIAL DURATION	102 Monate
PARTICIPATING CENTERS	Up to 80
FURTHER CENTERS DESIRED?	yes
NUMBER of PATIENTS	1000 screened, 525 recruited
CURRENT NUMBER of PATIENTS	0

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

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0317 (ATOMIC)	
Status:	in Vorbereitung, geplanter Studienstart (FPI) Q4/2021	
Rekrutierungszeitraum:	geplant 2021 – 2022	
Zentren:	geplant: 16	initiiert:
Patienten:	geplant: 700 in total /200 in D/AT	aktuell eingeschlossen in D: 0
Weitere Zentren:	nicht geplant	
Letzte Aktualisierung	Oktober 2021	

STUDY TYPE	Open label, multicenter phase III trial
PRINCIPAL INVESTIGATOR (International)	MD Frank Sinicrope, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Tel: +1 - 507-266-5365, sinicrope.frank@mayo.edu
PRINCIPAL INVESTIGATOR (Germany)	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, Tel: +49 – 234 509-3591, onkologie@klinikum-bochum.de
SPONSOR	National Cancer Institute (Cancer Therapy Evaluation Program, CTEP)
LEGAL REPRESENTATIVE OF THE SPONSOR (EU)	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin. Phone: +49 30 814534431 Fax +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
CONDITION	colon carcinoma
DESIGN	Open label, multicenter phase III trial
INDICATION	colon adenocarcinoma stage III
OBJECTIVE(S)	**Primary objective**: Aim of the study is to determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve DFS compared to FOLFOX alone in patients with stage III colon cancers and dMMR. **Secondary objectives:** to determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve overall survival compared to FOLFOX alone in patients with stage III colon cancers and dMMR. To assess the adverse events (AE) profile and safety of each treatment arm, using the CTCAE and PRO-CTCAE. The quality of life objective will be to determine the impact of the addition of atezolizumab to FOLFOX on patient-reported neuropathy, health-related QoL, and functional domains of health-related QoL. The quality of life analysis will also access the efficacy of atezolizumab adjusting for baseline QOL and fatigue measurements. Testing of banked specimens will not occur until an amendment to the recent treatment protocol (or separate correlative science protocol) is reviewed and approved.
INTERVENTION(S)	This is a Phase III, randomized, comparative, multicenter, open-label, two-arm study designed to evaluate the efficacy and safety of atezolizumab combined with FOLFOX and its continuation as monotherapy compared to FOLFOX alone. This study will enroll approximately 200 patients in Germany and Austria (and with USA 700 in total) randomized in a 1:1 ratio to one of two treatment arms:

	Arm 1: mFOLFOX6 for 12 cycles total with atezolizumab starting at Cycle 1 or Cycle 2 of mFOLFOX6 with continuation of atezolizumab for a total of 12 months (6 months of atezolizumab monotherapy). Arm 2: mFOLFOX6 for 12 cycles, which is a total of 6 months. One cycle will be defined as 14 days of treatment. Both arms: Cycle 1 of mFOLFOX6 must be started within 10 weeks of surgical resection of the primary cancer. Please note that best practice is 3 to 6 weeks between surgery and Cycle 1 of chemotherapy. Cycle 1 of mFOLFOX6 may be given prior to registration. Randomization will be stratified according to the following stratification factors: 4. Number of Positive Lymph Nodes: N1 (1-3 positive nodes)/N1C vs. N2 (> 4 positive nodes) (per AJCC 7) 5. T Stage: Tx/T1-T3 vs. T4 6. Primary Tumor Location: proximal (cecum, ascending colon, hepatic flexure, and transverse colon) vs. distal (splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction) <u>Treatment discontinuation</u> Patients who continue to be in remission will continue on therapy for a total of 12 cycles mFOLFOX6 + atezolizumab followed by 6 months of atezolizumab alone if assigned to Arm 1 or 12 cycles mFOLFOX6 in total if assigned to Arm 2. After treatment is completed, patients will be followed per the Study Calendar. Remove from protocol therapy any patient with disease recurrence.
BACKGROUND/RATIONALE	The ability of immunotherapy to unleash a patient's own T cells to kill MSI-H tumor cells is expected to occur in the adjuvant setting, as demonstrated in metastatic disease [1], and may result in reduced recurrence and improved patient survival. The rationale for combination of FOLFOX and atezolizumab is based upon the fact that FOLFOX is standard of care as adjuvant therapy for stage III colon cancer and promising data for combining chemotherapy with atezolizumab, including suggestion of immune priming. Since FOLFOX is standard adjuvant chemotherapy for stage III disease [2], it serves as the control arm for studies aiming to further improve patient outcomes. Atezolizumab will be continued as monotherapy for an additional 6 months following completion of FOLFOX for 6 months (12 cycles). The rationale for this approach is late and sustained responders with the use of pembrolizumab in metastatic MSI-H CRC, the importance of a definitive study, and alignment with ongoing/planned adjuvant studies using atezolizumab in other malignancies. Furthermore, sustained stimulation of the immune system may be key for long-term benefit with immunotherapy. There is a precedent with the anti-CTLA-4 antibody ipilimumab that is approved for the adjuvant therapy of melanoma with treatment duration up to 3 years. It is intended for the study outlined in the protocol to be definitive, and regard this study to have the potential to be practice-changing.
KEY INCLUSION CRITERIA	(1) Histologically proven stage III colon adenocarcinoma (any T [Tx, T1, T2, T3, or T4], N1-2M0; includes N1C). Tumors must be deemed to originate in the colon including tumors that extend into/involve the small bowel (e.g. those at the ileocecal valve) (2) Presence of deficient (d) DNA mismatch repair (dMMR). MMR status must be assessed by immunohistochemistry (IHC) for MMR protein expression (MLH1, MSH2, MSH6, PMS2) where loss of one or more proteins indicates dMMR. Note: loss of MLH1 and PMS2 commonly occur together. Patients who are known to have Lynch syndrome and have been found to carry a specific germline mutation in an MMR gene (MLH1, MSH2, MSH6, PMS2) are eligible to participate without dMMR screening by IHC. Note that patients who did not show dMMR (loss of MMR protein) are not eligible to participate. Patients whose tumors show MSI-H by polymerase chain reaction (PCR)-based assay are not eligible to participate unless they also have MMR testing

	by IHC and are found to have dMMR (i.e. loss of one or more MMR proteins). (3) Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue for subsequent retrospective central confirmation of dMMR status. (4) Tumors completely resected. In patients with tumor adherent to adjacent structures, en bloc R0 resection must be documented in the operative report or otherwise confirmed by the surgeon; near or positive radial margins are acceptable so long as en bloc resection was performed; proximal or distal margin positivity is not permitted (5) Entire tumor in the colon (rectal involvement is an exclusion).[Note: Surgeon confirmation that entire tumor was located in the colon is required only in cases where it is important to establish if the tumor is a colon versus (vs.) rectal primary.] (6) Age ≥ 18 years (7) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (8) Not pregnant and not nursing. For women of childbearing potential (WOCBP) only, a negative pregnancy test done ≤ 7 days prior to registration is required. A WOCBP is a sexually mature female who: 1) is not naturally postmenopausal (defined as at least 12 consecutive months with no menses without an alternative medical cause); OR 2) has not had a hysterectomy and/or bilateral oophorectomy (Note: Women with tubal ligation are still considered of child-bearing potential according to CTFG Guidance). (9) Absolute neutrophil count (ANC) ≥ 1500/mm³ (10) Platelet count ≥ 100,000/mm3; platelets ≥ 75,000/mm³ required for patients who received cycle 1 of mFOLFOX6 prior to registration (11) Creatinine ≤ 1.5 x upper limit of normal (ULN) or Calculated creatinine clearance ≥ 45 mL/min by Cockcroft-Gault equation (12) Total bilirubin ≤ 1.5 x upper limit of normal (ULN), except in the case of Gilbert disease (13) Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) (14) Thyroid-stimulating hormone (TSH) within normal limits (WNL). Supplementation is acceptable to achieve a TSH WNL. In patients with abnormal TSH, if free T4 is normal and patient is clinically euthyroid, patient is eligible
KEY EXCLUSION CRITERIA	(1) Evidence of residual involved lymph node disease or metastatic disease at the time of registration based on clinician assessment of imaging. The treating physician will determine if incidental lesions on imaging require workup to exclude metastatic disease. If based on review of images, the treating physician determines the patient to be stage III, then the patient is eligible. (2) Prior medical therapy (chemotherapy, immunotherapy, biologic or targeted therapy) or radiation therapy for the current colon cancer, except for one cycle of mFOLFOX6. Cycle 1 of mFOLFOX6 must have been administered per main protocol. (3) Active known autoimmune disease, including colitis, inflammatory bowel disease (i.e. ulcerative colitis or Crohn's disease), rheumatoid arthritis, panhypopituitarism, adrenal insufficiency (4) Known active hepatitis B or C • Active hepatitis B can be defined as:

	▪ Hepatitis B virus surface antigen (HBsAg) detectable for > 6 months; ▪ Serum hepatitis B virus (HBV) DNA 20,000 IU/mL(10^5 copies/mL); lower values 2,000-20,000 IU/mL(10^4-10^5 copies/mL) are often seen in hepatitis B virus e antigen (HBeAg)-negative chronic hepatitis B ▪ Persistent or intermittent elevation in ALT/AST levels ▪ Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation • Active hepatitis C can be defined as: ▪ Hepatitis C antibody (AB) positive AND ▪ Presence of hepatitis C virus (HCV) RNA (5) Known active pulmonary disease with hypoxia defined as: • Oxygen saturation < 85% on room air, or • Oxygen saturation < 88% despite supplemental oxygen (6) Grade ≥ 2 peripheral motor or sensory neuropathy (7) Patient HIV-positive, unless they meet all of the following: • A stable regimen of highly active anti-retroviral therapy (HAART) • No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections • A CD4 count above 250 cells/μL, and an undetectable HIV viral load on standard PCR-based tests (8) Other planned concurrent investigational agents or other tumor directed therapy (chemotherapy, radiation) while on study (9) Systemic daily treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days of registration (10) Known history of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins (11) Known hypersensitivity to Chinese hamster ovary (CHO) cell products or any component of the atezolizumab formulation (12) Known allergy to 5-fluorouracil, oxaliplatin or folinic acid
STATISTICAL ANALYSIS	**Primary Endpoint** The primary endpoint of this study is the disease-free survival (DFS), defined as the time from randomization to first documentation of disease recurrent or death. Patients who do not have a DFS event will be censored for DFS at their last disease assessment date. Confirmed second primary colon cancer and second primaries of other types will not be included as an event for the DFS endpoint. **Secondary Endpoints** *Overall Survival (OS)* The secondary endpoint of this study is the overall survival, defined as the time from randomization to death, from any cause. Patients who do not have an OS event will be censored for OS at the date they were last known to be alive. *Adverse Events (AEs)* CTCAE AEs and the maximum grade for each type of AE will be recorded for each patient separately for the first 12 cycles (mFOLFOX6 +/- atezolizumab) and the 6 months of continuation of atezolizumab. Similarly, scores (0-4) and maximum score for each PRO-CTCAE item will be recorded for each patient separately for these two periods. **Sample Size and Accrual** It is anticipated randomizing a maximum of 700 patients (350 per arm) per statistical design (200 of them in Germany and Austria).
SAMPLE SIZE	N_{total} = 700 patients randomized into 2 arms, each of 350 patients $N_{GER/AT}$=200 patients randomized into 2 arms, each of 100 patients

TRIAL DURATION AND TIMELINE	Enrollment (GER/AT): 18 Months, Maximal duration: 9,5 years (114 months) including follow-up
COUNTRY	USA, GERMANY, AUSTRIA

REFERENCES
[1] Le, D.T., et al., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med, 2015. 372(26): p. 2509-20.
[2] André , T., et al., Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. New England Journal of Medicine, 2004. 350(23): p. 2343-2351.

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

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0217 - CIRCULATE	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	36 Monate	
Patienten:	geplant: 231 rand.	aktuell eingeschlossen: 153
Zentren:	geplant: 150	initiiert: 107
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	Oktober 2021	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Gunnar Folprecht University Hospital Carl Gustav Carus University Cancer Center / Medical Department I Fetscherstr. 74, 01307 Dresden, Germany
CONDITION	Colon cancer UICC stage II without microsatellite instability
OBJECTIVE(S)	The study evaluates the value of postoperative circulating tumor DNA (ctDNA) as selection criterion in patients with colon cancer UICC stage II. Primary: - 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 Secondary: - 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 - 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. Experimental intervention: Chemotherapy (oxaliplatin / fluoropyrimidine, in pts who are positive for postoperative ctDNA; elderly pts: fluoropyrimidine) Control intervention: Follow up (no chemotherapy) Duration of intervention per patient: 6 months (chemotherapy cohort)

	Follow-up per patient: 5 years
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: - Histologically proven colon cancer stage II, microsatellite stable - Resection of the primary 3 – 8 (max.12) weeks before randomization - Age > 18 years Key exclusion criteria: - Clinical high risk situation, if it is regarded as certain indication for adjuvant therapy by the treating physician and the patient - Contraindication to chemotherapy (inadaequate bone marrow, hepatic, renal function) - Comorbidity influencing the prognosis of the patients (i.e. secondary cancer) - Participation at another interventional study for postoperative therapy
OUTCOME(S)	Primary efficacy endpoint: - DFS of patients with positive postoperative ctDNA at study enrolment by treatment arm Key secondary endpoint(s): - OS of pts with positive postoperative ctDNA by treatment arm - DFS and OS of untreated pts by postoperative ctDNA Assessment of safety: - Toxicity
STUDY TYPE	Investigator intiated, prospective, controlled, randomized, confirmatory study
STATISTICAL ANALYSIS	Efficacy: - DFS in pts positive for postoperative ctDNA by treatment arm Description of the primary efficacy analysis and population: - Stratified log rank test for DFS in all randomized pts positive for postoperative ctDNA treated with or without chemotherapy Safety: 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 Secondary endpoint(s): - Overall survival by treatment arm - 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) To be allocated to trial: n = 231 (randomized pts) To be analysed: n = 231
TRIAL DURATION	Time for preparation of the trial (months): 9 Recruitment period (months): 36 First patient in to last patient out (months): 60 Time for data clearance and analysis (months): 8 (primary analysis) Duration of the entire trial (months): 77 (including preparation); plus 3 years long term follow-up for overall survival

Lebermetastasen

AIO-KRK-0115xx: Comparative Evaluation of the quality of LIfe adjusted survival between surgical and non-surgical treatment of Metastatic colorectal cancer patients (CELIM3)

AIO-Studie		
Studiennummer/-Code:	AIO-KRK-0115/xx - CELIM-3	
Status:	Das Studienkonzept wurde weiterentwickelt Ein erneuter Förderantrag wurde gestellt	
Studiendauer:	Rekrutierung für Beobachtungsteil: 3 Jahre (2020 – 2023) Rekrutierung für randomisierten Teil: 2 Jahre (2023 – 2025)	
Zentren:	geplant:	initiiert:
Patienten:	geplant:	eingeschlossen:
Weitere Zentren:	sind sehr erwünscht, Interessenten wenden sich direkt an Prof. Folprecht	
Letzte Aktualisierung	April 2020	

Studientyp	Two stage observational / randomised trial
Sponsor	Technische Universität Dresden, 01062 Dresden
Studienkomitee	Prof. Dr. med. Gunnar Folprecht (Studienleiter) Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus, Dresden; Gunnar.Folprecht@uniklinikum-dresden.de Tel.: +49 351 458 4794 / Fax: +49 351 458-88 4794 Prof. Dr. med. Jürgen Weitz (Studienleiter Chirurgie) Klinik für Gefäß-, Thorax- und Viszeralchirurgie, Universitätsklinikum Carl Gustav Carus, Dresden Prof. Dr. rer. pol. Wolfgang Greiner (Studienleiter Lebensqualität) Lehrstuhls für Gesundheitsökonomie und Gesundheitsmanagement, Universität Bielefeld Prof. Dr. Dr. h.c. Pompilio Piso, Klinikum der Barmherzigen Brüder Regensburg, Repräsentant der Assoziation Chirurgische Onkologie (ACO) Prof. Dr. med. Ralf Hofheinz, Universitätsklinikum Mannheim, Repräsentant der AIO und verantwortlich für die unabhängige Stelle für die Lebensqualität
Ziele	Primäres Ziel des Beobachtungsteils: - Entwicklung eines Modells, das die qualitätsadjustierte Lebenszeit für die chirurgische oder konservative Therapiestrategie in Abhängigkeit von den Faktoren für das krankheitsfreie Überleben und von der Intensität der Eingriffe beschreibt Primäres Ziel des Randomisierten Teils: - Validierung des o.g. Modells Sekundäre Ziele: - Gesamtüberleben - Krankheitsfreies Überleben nach Resektion der Metastasen - Therapiefreie Zeit in Abhängigkeit von Therapiestrategie - Lebensqualität in Abhängigkeit von Therapiestrategie - Lebensqualität in Abhängigkeit von Intensität des Eingriffs - Prognostisches Modell für krankheitsfreies Überleben mit klinischen Risikofaktoren - Resektabilität anhand des chirurgischen Reviews

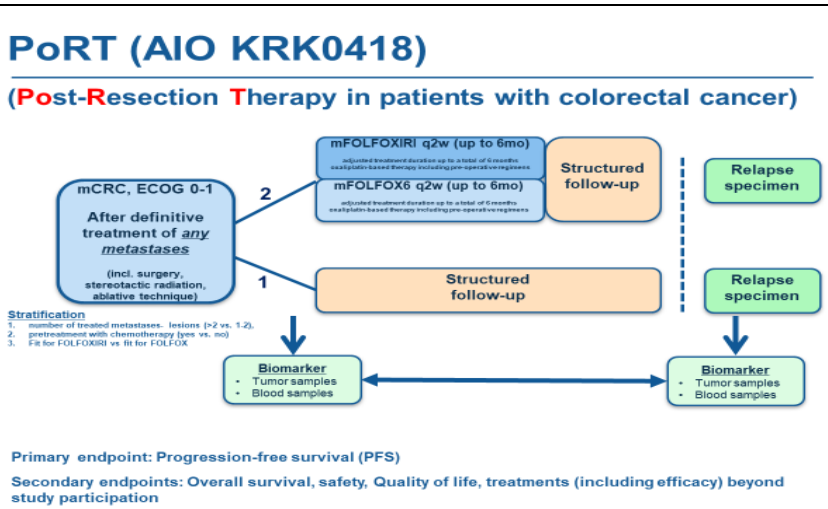
	- Entwicklung eines Value Sets für die Berechnung des qualitätsadjustierten Überlebens (parallele Kohorte)
Interventionen (Beoachtungsteil)	Die Behandlung erfolgt wie vom Prüfzentrum / dem Tumorboard besprochen. Der Behandlungsplan der Patienten wird erfasst, ferner die Daten der weiteren Therapie (Operation [einschl. Ablation] bzw. konservative Therapie [Chemotherapie bzw. Behandlungspause]). Die Patienten werden von einer unabhängigen Stelle regelmäßig angerufen und die Lebensqualität mit dem EQ5D erfasst. Die Telefonate erfolgen im ersten Jahr 1 x / 2 Wochen, im zweiten Jahr 1 x / Monat, im 3. – 5. Jahr 1 x / Quartal. Zum Studieneinschluss wird optional das archivierte Tumormaterial und eine Plasmaprobe (ctDNA) eingesandt. Nachverfolgung pro Patient: 5 Jahre Zusätzlich wird in der Zeit der Beobachtungsstudie das Value Set für die Lebensqualität an Patienten mit einem kolorektalen Karzinom validiert. Dieses Value Set wird an einer Gruppe von Patienten validiert, die nicht mit der Studienpopulation übereinstimmen muss.
Interventionen (randomisierter Teil)	Nach der Überprüfung der Ein- und Ausschlusskriterien erfolgt eine Randomisation in die Gruppen Operation oder konservative Therapie. In der Gruppe Operation werden alle Metastasen reseziert (Ablation, mehrzeitige Eingriffe und zusätzliche Chemotherapie erlaubt). In der Gruppe konservative Therapie erfolgt eine Therapie mit Chemotherapie oder Behandlungspause nach Wahl des Prüfarztes. Eine Operation oder Ablation ist nur erlaubt, wenn sich die medizinischen Verhältnisse geändert haben. Der Behandlungsplan der Patienten wird erfasst, ferner die Daten der weiteren Therapie (Operation bzw. medikamentöse Therapie). Die Patienten werden von einer unabhängigen Stelle regelmäßig angerufen und die Lebensqualität mit dem EQ5D erfasst. Die Telefonate erfolgen im ersten Jahr 1 x / 2 Wochen, im zweiten Jahr 1 x / Monat, im 3. – 5. Jahr 1 x / Quartal. Zum Studieneinschluss wird optional das archivierte Tumormaterial und eine Plasmaprobe (ctDNA) eingesandt. Nachverfolgung pro Patient: 5 Jahre
Einschlusskriterien für den Beobachtungsteil	1) Metastasiertes kolorektales Karzinom 2) Vorstellung im Tumorboard unter der Frage Resektion / Ablation 3) Vortherapie mit ≥ 3 Monaten Chemotherapie 4) Keine Hirn- oder Knochenmetastasen 5) Schriftliche Einwilligung für die Studie einschl. der Beobachtung der Lebensqualität 6) Alter ≥ 18 Jahre
Einschlusskriterien für den randomisierten Teil	1) Metastasiertes kolorektales Karzinom 2) Vorstellung im Tumorboard unter der Frage Resektion / Ablation 3) Kein klarer Vorteil für Chirurgie oder konservatives Vorgehen nach prognostischem Modell 4) Keine Hirn- oder Knochenmetastasen 5) Vortherapie mit ≥ 3 Monaten Chemotherapie 6) Schriftliche Einwilligung für die Studie einschl. der Beobachtung der Lebensqualität 7) Alter ≥ 18 Jahre.
Endpunkte	Primärer Endpunkt: - Qualitätsadjustiertes Überleben Sekundäre Endpunkte: - Gesamtüberleben - Krankheitsfreies Überleben nach Resektion der Metastasen - Lebensqualität nach EQ-5D

	- Therapiefreie Zeiten - Rate der vollendeten Behandlungspläne - Resektabilität nach chirurgischem Review
Statistische Analyse	Für den Beobachtungsteil wird für jeden die qualitätsadjustierte Lebenszeit mittels des EQ5D und des zu etablierenden Value Set berechnet. Anhand der prognostischen Faktoren wird erfolgt die Entwicklung eines Risikoscores für das krankheitsfreie Überleben, anhand der Zahl und der Art der Interventionen eine Kalkulation des Aufwandes für den Patienten. Mit diesen Parametern wird mittels eines Support Vector Machine Ansatzes die Entwicklung eines Modells, das die Gruppen mit einem Nutzen für die konservative Therapie, einem Nutzen für die chirurgische Therapie und eine indifferente Gruppe beschreibt. Im randomisierten Teil werden nur Patienten, die zu der indifferenten Gruppe gehören, randomisiert. In dieser Gruppe wird eine Abweichung vom Modell untersucht.
Patientenzahl	Beobachtungsteil: 500 Patienten Randomisierter Teil: 244 Patienten

AIO-KRK-0418/xx: Post-resection/ablation chemotherapy in patients with metastatic colorectal cancer (FIRE9/PORT)

AIO-Studie	
Studiennummer/-Code:	**AIO-KRK-0418/xx – FIRE 9/PORT**
Status:	in Vorbereitung,
Rekrutierungszeitraum:	QVI-2021 - geplante Rekrutierungszeit: 48 Monate
Weitere Zentren:	Derzeit keine neuen Zentren
Letzte Aktualisierung	Oktober 2021

STUDY TYPE	**Interventional trial**: [X] **Key elements:** open label, randomised, controlled phase II trial
COORDINATING INVESTIGATOR	• Prof. Dr. med. Dominik Modest, Charité – Universitätsmedizin Berlin; Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie Tumorimmunologie am Campus Virchow Klinikum (C Augustenburger Platz, 13353 Berlin, Germany • 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 Prof. Modest, Berlin
CONDITION	After removal or ablation of metastases from colorectal cancer

DESIGN	
OBJECTIVE(S)	Primary objective • To compare the efficacy of active additive chemotherapy after definitive treatment of metastases to structured follow-up only Secondary objectives • To compare efficacy, safety and patient reported quality of life (QoL) of active treatment to structured follow-up only Further secondary objective Further anti-tumor treatment Exploratory objectives To identify and characterize molecularly-defined patient subgroups and correlate their genetic and molecular tumor characteristics with clinical efficacy and toxicity using tumor specimen and blood-based biomarker candidates.
INTERVENTION(S)	**Experimental procedure**: Additive therapy with up to 12 cycles Patients fit for triplett therapy: modified FOLFOXIRI, Patients fit for doublet therapy: modified FOLFOX6 Both regimnes adjusted individually for the total dose of oxaliplatin, i.e. a maximum o 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-agen fluoropyrimidine (depending on regimen and tolerability) to reach a total postoperative treatment duration of 6 months. **mFOLFOXIRI:** (d1: 2.4g 5-FU in 46 hours, 400mg/qm leucovorin, 85mg/qm oxaliplatin, 150mg/qm irinotecan) **mFOLFOX:** (d1: 2.4g 5-FU in 46 hours, 400mg/qm leucovorin, 85mg/qm oxaliplatin) **Control intervention:** structured oncological observation (no chemotherapy) **Follow-up per patient:** 36 months **Duration of intervention per patient:** up to 6 months
BACKROUND/RATIONALE	In Germany, colorectal cancer has a prevalence of 65-80/100.000, resulting in a total of ~60.000 new cases every year. Up to 50% of patients develop metastases during the course of their disease while 15-25% already present with synchronous metastases at first diagnosis [Howlader et al., 2011]. The current 5-year mortality of appr. 50% [Robert-Koch-Institut, 2019]. 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 [Soerjomataram et al., 2012]. Patients with metastates from colorectal cancer (appr. 40-50% of all patients develop metastases) can benefit from the resection or ablation of metastates, although relapse occurs in the majority (appr. 70-80%) of these patients [Folprecht et al., 2014; Kopetz et al., 2009; Nordlinger et al., 2008; Nordlinger et al., 2013; Van Cutsem et al., 2016]. Clearly, a further

	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. The present clinical trial aims to generate the missing evidence that additive therapy after resection or ablation of metastases may improve PFS and OS in patients with colorectal cancer. This is of specific importance since both improvements in localized, but also systemic therapies have resulted in increasing numbers of mCRC patients undergoing resection and/or ablation of metastases [Kopetz et al., 2019; Choti et al., 2016; Cremolini et al., 2015; Cremolini et al., 2017; Heinemann et al., 2014; Luo et al., 2014; Modest et al., 2018]. The translational research program consists of the following steps but might be modified or expanded taking latest scientific data into account: 1. Characterization of the initial resected/ablated tumor (primary and/or metastases) for DNA mutations and RNA expressions (for example panel NGS and mRNA expression analysis) 2. Longitudinal assessment of tumor markers and circulating tumor DNA (according to initial tumor characteristics), assessments should include the baseline, 3 months and 6 months timepoints (and further timepoints as long as no relapse occurred). 3. Characterisation of tumor specimen obtained after relapse of disease during or after study (if occurring and available) for DNA mutations and RNA expressions. 4. Correlation of 1) with 3) and eventually also correlation of relapse with acquired changes in samples of 2) 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).
KEY EXCLUSION CRITERIA	**Key exclusion criteria:** • Other previous malignancies within 3 years prior to study start, • History of severe cardiac disease, • Previous palliative chemotherapy with >6 cycles of FOLFOX or >4 cyles of CAPOX • Radiotherapy, major surgery or any investigational drug 21 days before randomization, Conditions prohibiting the use of study drugs
KEY INCLUSION CRITERIA	**Key inclusion criteria:** • Resected (R0 or R1) and/or effectively treated metastases (all techniques allowed) of colorectal cancer within 3-10 weeks before randomisation AND resected primary tumor (synchronous or metachronous) • No radiographic evidence of active metastatic disease at study entry according to RECIST 1.1 scan no older than 8 weeks). • Signed written informed consent, • Adequate bone marrow, liver, kidney, organ and metabolic function, • ECOG performance status 0 – 2.

OUTCOME(S)	Primary endpoint Progression-free survival (PFS) time at the 24 month follow-up defined as tin randomisation to death or evidence of disease (whatever ossurs first) Secondary endpoint: • PFS in patients with/without prior systemic therapy • PFS in patients with R1 vs R0 resected lesions as well as ablated vs. purely r lesions • Overall survival (OS) • Treatments (including efficacy) beyond study participation • Local control of lesions according to ablative technique (surgery vs. abla radiation) Safety • Type, incidence, severity, and causal relationship to active chemotherapy serious adverse events and serious adverse events (severity evaluated acc CTCAE version 5.0) Quality of life • Quality of life (QoL) as assessed with the QoL questionnaire EQ-5D-5L Exploratory endpoints Translational analyses including evaluation of tumor specimen of primary and/or m tissue as well as blood samples at different time points • PFS and OS according to circulating tumor DNA at baseline (ctDNA pos negative) • Outcome in molecular subgroups
STATISTICAL ANALYSIS	Prof. Dr. rer. Nat. Geraldine Rauch Institut für Biometrie und Klinische Epidemiologie (iBikE), Campus Charité Mitte Charitéplatz 1 10117 Berlin; Germany The primary endpoint will be PFS (progression-free survival, defined as progression/relapse or death from any cause) at 30 months after randomization. Our assumptions are based on the only available analysis of two pooled, earlystopped trials in the adjuvant/additive setting using fluoropyrimidine monotherapies18 that reported a hazard ratio for PFS in favor of active treatment of 0.76 (the originally reported hazard ratio was reported reversed as 1.32) that translated into a similar effect for the endpoint overall survival. This again support the validity of the primary endpoint PFS in this application. We hypothesize a slightly larger effect for PFS in favor of active therapy due to the 2-3 drug regimens resulting in an estimated hazard ration of 0.70. For the PORT trial18 for the control arm (surgery alone) with structured follow-up, a progression/relapse/death-free rate of 40% at time point 24 months was observed translating into a 60% progression/relapse/death-rate at this time (according to the reported control arm18). With a hazard ratio 0.70 (= I C C=0.0267/0.0382) favoring active treatment, the hypothesized relapse rate at 24 monthsin the intervention arm is assumed to be: 47%. With a power of 80%, a 2-sided alpha of 0,05, a total of 276 events are need to be observed in order to detect a difference in progression-free survival of a hazard ratio of 0.70- favoring active treatment vs. observation (Schoenfeld formula). Assuming an accrual time of 48 months and a follow-up time of 24 months, a drop-out/censoring rate of 40% after 24 months after randomization, a total of 480 patients (320/160 in the respective arms, rounded to receive integers and maintain the allocation ratio) is expected to yield the required number of events if the accrual rate is constant. The computation was done using the software R Version 3.5.1 and the package Rpact. We account for additional 5% of patients that directly leave the study after randomization and never received the study medication. Thus a total of 507 patients (480/507≈0,95) are planned to be recruited.
SAMPLE SIZE	To be assessed for eligibility: (n ~ 750) To be assigned to the trial: (n = 507) corresponding to 338/169 per arm

	To be analysed: (n = 507) 276 events needed
TRIAL DURATION	First patient in to last patient out (months): 48 Duration of the entire trial (months): 60 (or until 80% of DFS events will have taken place) Recruitment period (months): 48 It is intended to apply for a second funding period
PARTICIPATING CENTERS	No. of cities to be involved: 80 No. of centres to be involved: 80 Names of cities and centres: FIRE-Study Group (Germany)
NUMBER of PATIENTS	~ 550 CURRENT NUMBER of PATIENTS:

Rektumkarzinom

AIO-KRK-0419: Kurzzeit-Radiotherapie versus Radiochemotherapie, gefolgt von konsolidierender Chemotherapie und selektivem Organerhalt für Patienten mit MRT-definierten intermediären und Hoch-Risiko- Rektumkarzinom - Eine randomisierte Phase III-Studie der German Rectal Cancer Study Group (ACO/ARO/AIO-18.1)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0419 – ACO/ARO/AIO-18.1
Status:	in Rekrutierung
Rekrutierungsdauer	geplant von/ bis: Q3/2020 - Q3/2025
Anzahl Patienten:	geplant: 702 eingeschlossen: 10
Anzahl Zentren:	geplant: 80 initiiert: rekrutierend:
Weitere Zentren:	Interessierte Zentren wenden sich bitte an: ralf.hofheinz@umm.de
Letzte Aktualisierung	Dezember 2020

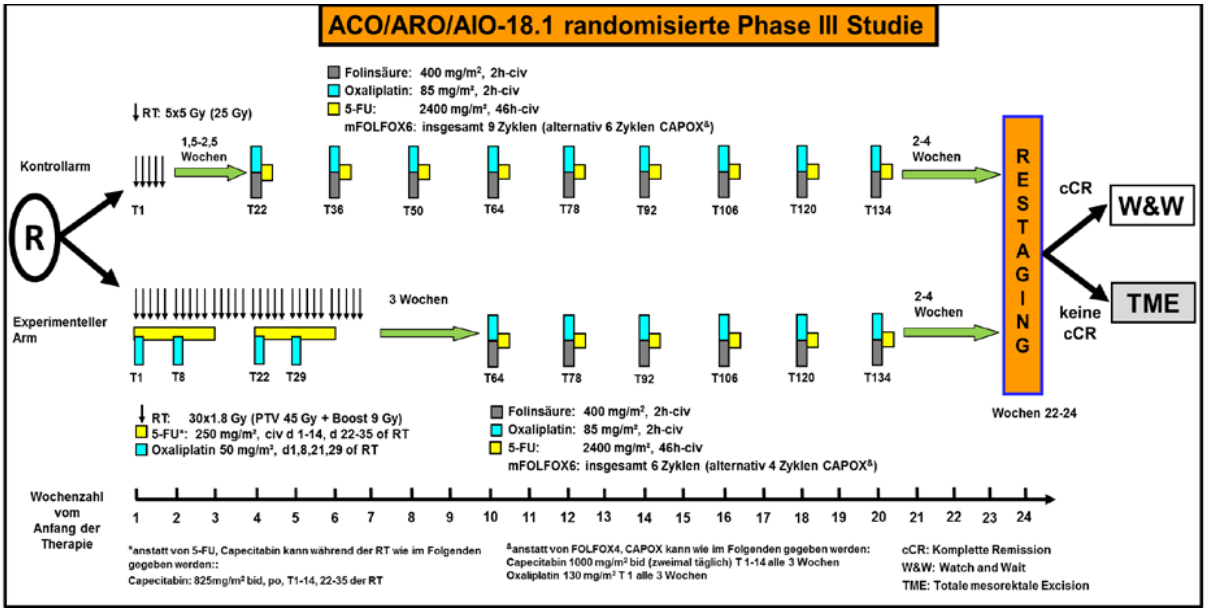
Sponsor der Studie	Dekan der Medizinischen Fakultät der Goethe-Universität Frankfurt
Koordininierende Gruppe	**German Rectal Cancer Study Group** in Kooperation mit ACO, ARO, AIO (**A**rbeitsgemeinschaft **C**hirurgische **O**nkologie, **A**rbeitsgemeinschaft **R**adio-**O**nkologie, **A**rbeitsgemeinschaft **I**nternistische **O**nkologie) der Deutschen Krebsgesellschaft
Leiter der klinischen Prüfung:	Prof. Dr. Claus Rödel, Frankfurt Klinik für Strahlentherapie und Onkologie Universitätsklinikum Frankfurt - Goethe-Universität Theodor-Stern-Kai 7 60590 Frankfurt am Main E-Mail: claus.roedel@kgu.de
Studienkoordinator:	Prof. Dr. Michael Ghadimi (ACO, Chirurgische Onkologie) Prof. Dr. Emmanouil Fokas (ARO, Radioonkologie) Prof. Dr. Ralf Hofheinz (AIO, Internistische Onkologie)
Protokollkomitee:	U. Attenberger, D. Arnold, T. Beissbarth, R. Fietkau, P. Wild, T. Friede, G. Folprecht, E. Fokas, C. Gani, M. Ghadimi, F. Greten, U. Graeven, R. Grützmann, A. Hartmann, R.-D. Hofheinz, P. Ströbel, C. Reißfelder, C. Rödel, J. Weitz, C. Wittekind, D. Zips

Monitoring:	Institut für Klinische Krebsforschung IKF GmbH
Biometrie:	Prof. Dr. Tim Friede, Institut für Medizinische Statistik Universitätsmedizin Göttingen
EudraCT No.:	2018-000876-14
Rationale	Nach neuesten Erkenntnissen der durchgeführten Phase III- Studien bei Patienten mit intermediären bzw. Hochrisiko- Rektumkarzinomen hat die totale neoadjuvante Therapie (TNT) mit entweder 5 × 5 Gy gefolgt von einer FOLFOX / CAPOX- Konsolidierungschemotherapie (RAPIDO-Studie) oder einer Induktionschemotherapie (mFOLFIRINOX) gefolgt von einer 5- FU-basierten Radiochemotherapie (5-FU-RCT) (PRODIGE- Studie) die pathologische komplette Remmission (pCR) und das krankheitsfreie Überleben (DFS) im Vergleich zur präoperativen 5-FU-RCT (+/- adjuvante Chemotherapie) deutlich verbessert. Darüber hinaus wurde in randomisierten Phase-2-Studien zur Optimierung der TNT-Sequenz (CAO / ARO / AIO-12, OPRA) eine RCT gefolgt von einer Konsolidierungschemotherapie anstelle einer Induktionschemotherapie gefolgt von einer RCT als bevorzugtes Regime für TNT basierend auf erhöhter pCR und Organerhaltungsraten bei gleichzeitig ausgezeichneter Compliance, Kontrolle von Fernmetastasen und DFS etabliert. Die hier vorgeschlagene randomisierte ACO / ARO / AIO-18.1- Studie zielt darauf ab, die neu etablierten TNT-Konzepte, die entweder eine Kurzzeit-RT gemäß RAPIDO oder eine RCT gemäß CAO / ARO / AIO-04 / -12 anwenden, direkt zu vergleichen, wobei beiden eine Konsolidierungschemotherapie und eine Operation oder eine Watch & Wait (W & W) -Option für Patienten mit klinisch kompletter Remission (cCR) folgen. Die ACO / ARO / AIO-18.1-Studie umfasst mehrere neuartige und innovative Aspekte zur weiteren Optimierung der multimodalen Behandlung von Rektumkarzinomen, die teilweise durch unsere randomisierten Vorläuferstudien CAO / ARO / AIO-04 und CAO / ARO / AIO-12 ermittelt wurden: (1) Die Patientenauswahl basiert auf strikten, qualitätskontrollierten MRT-Kriterien mit mittleren und hohen Risikomerkmalen (und ist somit eine Ergänzung zu unserer ACO / ARO / AIO-18.2-Studie bei Rektumkarzinomen mit niedrigen Risikomerkmalen). (2) Das RCT-Regime umfasst 5-FU / Oxaliplatin mit Dosierungen und Intensitäten, die sich als wirksam und gut verträglich erwiesen haben, ohne die Adhärenz der Behandlung in CAO / ARO / AIO-04 zu beeinträchtigen. (3) Die Sequenz von RCT, CT und Chirurgie bzw. W & W basiert auf dem durch unsere CAO / ARO/ AIO-Studie etablierten TNT- Ansatz. (4) und ermöglicht die chirurgische Stratifikation das W & W-Management für streng ausgewählte Patienten mit klinisch vollständigem Ansprechen (cCR). Wir nehmen an, dass die TNT mit einer 5-FU / Oxaliplatin-RCT gefolgt von einer Konsolidierungschemotherapie den Anteil der Patienten mit Organerhalt bei vergleichbarem DFS im Vergleich zu (Standard-) Kurzzeit-RT mit anschließender Konsolidierungschemotherapie erhöhen kann.
Studientyp und -design	Prüferinitiierte, multizentrische, offene, randomisierte Phase-III-Studie

Primares Ziel und Endpunkt	Der primäre Endpunkt dieser Studie, der Organerhalt, ist wie folgt definiert: Überleben mit intaktem Rektum, keine größere Operation, kein Stoma. Der primäre Endpunkt: der Organerhalt wird nicht erreicht, wenn eines der folgenden Ereignisse eintritt: Tod, eine größere Operation als die lokale Exzision (R0), die nach der Randomisierung, während der TNT oder bei der Restaging in der 22. bis 24. Woche nach Beginn der TNT durchgeführt wird, aufgrund der nicht kompletten Remmission oder einem lokoregionären Wachstums nach einer initialer, klinischer Komplettremission, die eine Salvage-TME erfordert, oder ein Stoma (nicht rekonvertiertes Schutzstoma oder Stoma, das für Toxizität oder schlechte Funktion erforderlich ist), je nachdem, was zuerst auftritt. Wir stellten die Hypothese auf, dass sich die 3-Jahres-Organerhaltungsrate von 30% im Kontrollarm auf 40% im experimentellen Arm verbessern wird (Hazard Ratio von 0,76). Bei einem Power von 90% und einem zweiseitigen Typ-I-Fehler von 5% beträgt die Stichprobengröße, die erforderlich ist, um einen statistisch signifikanten Unterschied zu erhalten, insgesamt 702 Patienten (564 Ereignisse).
Sekundäre Ziele und Endpunkte	• Krankheitsfreies Überleben • Rate an klinischen Komplettremissionen nach TNT • Rate der sofortigen TME nach TNT • Kumulative Inzidenz des lokoregionären nach cCR • Rate an Salvage Operationrationen (LE / TME mit oder ohne APR / Stoma) nach lokoregionärem Nachwachsen • Kumulative Inzidenz von Lokalrezidiven nach (Salvage) Operationen
	• Postoperative Komplikationen einer Salvage Operation • Rate der sphinkterschonenden (Salvage-) Operationen • Pathologische TNM-Staging • R0 Resektionsrate, negative circumferentiellen Resektionsrate • Tumor Regressions Grading gemäß Dworak • Neadjuvante rektale Score • Qualität von TME gemäß MERCURY • Bewertung der akuten und späten Toxizität gemäß NCI CTCAE V.5.0) • Lebensqualität und funktionelles Ergebnis basierend auf Behandlungsarm und chirurgischen Eingriffen / Organerhaltung • Kumulative Inzidenz von Fernmetastasen • Gesamtüberleben • Translational / Biomarkeruntersuchungen

Einschlusskriterien	• Männliche und weibliche Patienten mit histologisch gesicherter Diagnose eines rektalen Adenokarzinoms, lokalisiert 0 - 12 cm von der anokutanen Linie entfernt, gemessen durch starre Rektoskopie (d. H. Unteres und mittleres Drittel des Rektums) • Staging-Anforderungen: Die hochauflösende, Dünnschicht (d. H. 3 mm)-Magnetresonanztomographie (MRT) des Beckens ist das obligatorische lokale Staging- Verfahren. • MRT-definierte Einschlusskriterien: Vorhandensein mindestens einer der folgenden Hochrisikobedingungen: • - jedes cT3, wenn die distale Ausdehnung des Tumors <6 cm von der anokutanen Linie entfernt ist, oder • - cT3c / d im mittleren Drittel des Rektums (≥ 6-12 cm) mit MRT-Nachweis einer Ausbreitung des extramuralen Tumors in das mesorektale Fett von mehr als 5 mm (> cT3b), oder • - cT3 mit klarem cN + basierend auf strengen MRT-Kriterien (siehe Anhang) • cT4 Tumoren, oder • - jedes T mittleres / niedriges Drittel des Rektums mit klaren MRT-Kriterien für N + • - mrCRM+ (≤ 1mm), oder • - Extramural venöse Invasion (EMVI+) • Transrektaler endoskopischer Ultraschall (EUS) wird zusätzlich verwendet, wenn die MRT nicht endgültig ist, um eine frühe cT1 / T2-Erkrankung im unteren Drittel des Rektums oder frühe cT3a / b-Tumoren im mittleren Drittel des Rektums auszuschließen • Spiral-CT von Bauch und Brust, um Fernmetastasen auszuschließen. • Mindestens 18 Jahre alt. Keine Altersobergrenze. • WHO / ECOG-Lebenstatus ≤1 • Angemessene hämatologische, hepatische, renale und metabolische Funktionsparameter: - Leukozyten ≥ 3.000 / mm ^ 3, ANC ≥ 1.500 / mm ^ 3, Blutplättchen ≥ 100.000 / mm ^ 3, Hb> 9 g / dl - Serumkreatinin ≤ 1,5 x Obergrenze des Normalwerts - Bilirubin ≤ 2,0 mg / dl, SGOT-SGPT und AP ≤ 3 x Obergrenze des Normalwerts • Einverständniserklärung des Patienten

Ausschlusskriterien	• Der untere Rand des Tumors befindet sich mehr als 12 cm von der anokutanen Linie entfernt, gemessen durch starre Rektoskopie • Fernmetastasen (auszuschließen durch CT-Scan von Thorax und Bauch) • Vorherige antineoplastische Therapie bei Rektumkrebs • Vorherige Strahlentherapie der Beckenregion • Größere Operation innerhalb der letzten 4 Wochen vor der Aufnahme • Schwangere oder stillende Frauen oder Frauen, die planen, während der Studie oder innerhalb von bis zu 6 Monaten nach Studienende schwanger zu werden • Männer oder Frauen, die nicht zu konsequenten Verhütungsmaßnahmen mit einer zuverlässigen Methode während der Studie und bis zu 6 Monate nach dem Ende der Studie bereit oder in der Lage sind • Gleichzeitige Teilnahme an einer klinischen Studie innerhalb von 30 Tagen vor Einschluss in die Studie • Vorheriger oder aktueller Drogenmissbrauch • Andere begleitende antineoplastische Therapie • Schwere gleichzeitige Erkrankungen, einschließlich neurologischer oder psychiatrischer Störungen (einschließlich Demenz und unkontrollierter Anfälle), aktiver, unkontrollierter Infektionen, aktiver, disseminierter Gerinnungsstörung • Klinisch signifikante Herz-Kreislauf-Erkrankung (inkl. Myokardinfarkt, instabile Angina pectoris, symptomatische Herzinsuffizienz, schwere unkontrollierte Herzrhythmusstörung) ≤ 6 Monate vor der Aufnahme • Vorherige oder gleichzeitige Malignität ≤ 3 Jahre vor Aufnahme in die Studie (Ausnahme: Nicht-Melanom- Hautkrebs oder Zervixkarzinom FIGO Stadium 0-1), wenn der Patient kontinuierlich krankheitsfrei ist • Bekannte allergische Reaktionen auf Studienmedikamente • Bekannter Mangel an Dihydropyrimidin-Dehydrogenase • Psychologische, familiäre, soziologische oder geografische Bedingungen, die möglicherweise die Einhaltung des Studienprotokolls und des Nachsorgeplans beeinträchtigen (diese Bedingungen sollten vor der Registrierung in der Studie mit dem Patienten besprochen werden).
Therapie	Im Kontrollarm (siehe die Abbildung unten) erhalten die Patienten eine Kurzzeit-Bestrahlung mit 5 x 5 Gy, gefolgt von 9 Zyklen einer Konsolidierungschemotherapie (mFOLFOX6) oder alternativ 6 Zyklen CAPOX, gefolgt von einer erneuten Restaging in der 24. Woche wie durch die RAPIDO-Studie etabliert. Der experimentelle Arm beginnt mit einer RCT auf Fluorpyrimidin / Oxaliplatin-Basis (1,8 Gy bis 45 Gy; Erhöhung des Primärtumors um 9 Gy), gefolgt von einer Konsolidierungschemotherapie mit 6 Zyklen mFOLFOX6 oder alternativ 4 Zyklen CAPOX, gefolgt von einer erneuten Restaging in der 24. Woche. In beiden Armen wird für Patienten, die eine klinisch komplette Remission (cCR) erreichen, die durch klinische Untersuchungen, Endoskopie und MRT strikt beurteilt wird, eine W & W-Option mit engmaschiger Nachsorge- Intervallen empfohlen. Bei nicht vollständigem Remission ist eine sofortige TME-Operation vorgesehen.



Translationale Forschung	Ein umfangreiches translationales Forschungsprogramm wird implementiert, um die molekulare Prognose und prädiktive Profilerstellung weiter zu verfeinern und schließlich Untergruppen für die Stratifizierung der Behandlung und konservative chirurgische Eingriffe zu identifizieren.
Patientenzahl und Begründung	Die Probengröße wird durch die primäre Wirksamkeit der Organerhaltung bestimmt. Die Rekrutierung dauert 5 Jahre und alle Patienten werden mindestens 3 Jahre nachbeobachtet, sofern sie nicht vorher sterben. Daraus resultiert ein maximaler Nachsorgezeitraum von 8 Jahren. Wir gehen bei der Planung dieser Studie davon aus, dass Event- Times“ und „Times to study withdrawal“ einer exponentiellen Verteilung folgen und unabhängig voneinander sind. Wir rechnen mit einem geringen Ausscheiden von Patienten aus der Studie (5% über einen Zeitraum von 3 Jahren). Die Organerhaltung nach 3 Jahren wird im Kontrollarm mit 30% angenommen und im Versuchsarm um 10% erhöht auf 40% angenommen. Eine Stichprobengröße von 351 Patienten pro Gruppe ergibt daher eine Potenz von 90% bei einem zweiseitigen Signifikanzniveau von 5%. Bei einer Organerhaltung nach 3 Jahren von 38,5% im experimentellen Arm ergibt diese Probengröße eine Leistung von 80%. Insgesamt planen wir 702 Patienten zu randomisieren.

Biostatistik	Alle primären Analysen folgen dem ITT- Prinzip, d. h. Alle randomisierten Patienten werden in die Analysen und in die Behandlungsgruppen einbezogen, in die sie randomisiert wurden. Für das primäre Wirksamkeitsergebnis wird der Organerhalt durch Cox-Regression proportionaler Gefahren mit Behandlungs- und Stratifikationsvariablen der Randomisierung (Zentrum und Tumorabstand vom Analrand (<vs.> = 6 cm)) als Faktoren analysiert. Der Behandlungseffekt wird als Hazard Ratio mit 95% -Konfidenzintervallen und p-Wert angegeben, wobei die Nullhypothese getestet wird, dass die Hazard Ratio gleich 1 ist. Patienten, die sich aus der Studienbehandlung zurückziehen, werden auf die Endpunkte hin untersucht. Der Rückzug aus der Studie wird in der Primäranalyse als unabhängige Rechtszensur behandelt. Wenn der Rückzug aus der Studie erheblich ist und zwischen den Behandlungsgruppen unterschiedlich, werden in unterstützenden Analysen die Auswirkungen der unabhängigen Zensurannahme unter Verwendung gemeinsamer Gebrechlichkeitsmodelle untersucht. Der primäre Endpunkt sowie andere Ergebnisse bis zum Ereignis wie das krankheitsfreie Überleben oder das Gesamtüberleben werden von der Behandlungsgruppe als Kaplan-Meyer-Kurven mit 95% -Konfidenzbanden angezeigt. Die Analysen der Ergebnisse der Zeit bis zum Ereignis unter den sekundären Endpunkten warden wie die Analysen des primären Endpunkts durchgeführt.
Geplante Interimanalysen	Die Untersuchungen zur Sicherheit werden von einem unabhängigen „Data Safety Monitoring Committee „durchgeführt
Teilnehmende Zentren	Ca. 80 Zentren der German Rectal Cancer Study Group
Studiendauer	Start der Vorbereitung: Q2/2019 Start der Rekrutierung: Q3/2020 Geplante Beendigung der Rekrutierung: Q3/2025 Geplante Beendigung der Nachsorge: Q1/2029 Schlussbericht: Q2/2029

AIO-KRK-0319: Preoperative FOLFOX versus postoperative risk-adapted chemotherapy in patients with locally advanced rectal cancer and low risk for local failure: A randomized phase III trial of the German Rectal Cancer Study Group (ACO/ARO/AIO-18.2)

AIO-Studie	
Studiennummer/-Code:	AIO-KRK-0319 – ACO/ARO/AIO-18.2
Status:	in Rekrutierung
Rekrutierung:	geplant: ab Q3 2020 bis Q3 2025
Anzahl Patienten:	geplant: 818 randomisiert: 17
Anzahl Zentren:	geplant: 80-100 initiiert: 53 rekrutierend: 49
Weitere Zentren:	Interessierte Zentren wenden sich bitte an: ralf.hofheinz@umm.de
Letzte Aktualisierung	Okt. 2021

Sponsor	University of Heidelberg
Study Chairman (LKP)	Prof. Dr. Ralf-Dieter Hofheinz, Mannheim, for the German Rectal Cancer Study Group (ACO/ARO/AIO)
Contact	Prof. Dr. R.-D. Hofheinz Interdisziplinäres Tumorzentrum Mannheim Universitätsmedizin Mannheim Theodor-Kutzer Ufer 1-3, 68167 Mannheim ralf.hofheinz@umm.de Fon: +49 621 383 2855, Fax: +49 621 383 2488
Rationale	Patients with locally advanced rectal cancer are generally treated with preoperative 5-FU- or capecitabine-based chemo-radiotherapy (CRT) and total mesorectal excision (TME) surgery in order to decrease the rate of local failure. In patients with low risk for local failure in the middle third of the rectum (cT3a/b, N-) as determined with quality controlled MRI, the German S3 guidelines and the ESMO clinical practice guidelines state that neoadjuvant radiotherapy may be omitted. However, distant failure rate is still substantial in the range of 20-25% in these patients highlighting the need for more effective systemic treatment. The hereby proposed ACO/ARO/AIO-18.2 randomized trial incorporates three novel aspects: (1) patient selection relies on strict and quality controlled MRI features and therefore identifies a cohort without imminent need for radiotherapy, (2) the sequence of chemotherapy and surgery is changed in a way that chemotherapy is administered preoperatively to increase the rate of patients treated with chemotherapy, and (3) three months of neoadjuvant FOLFOX or XELOX (instead of up to 6 months adjuvant chemotherapy) are used as a sole perioperative treatment in order to administer effective doses of the presumably most effective perioperative treatment at an early time point during the course of disease. Thus, patients with locally advanced rectal cancer but low risk for local failure (cT1/2N+ in all thirds of the rectum, cT3a/b N- in the middle third, and cT3-4 Nany in the upper third) will be included and randomized between three months of neoadjuvant FOLFOX/XELOX in Arm A and primary resection of the tumor followed by risk (i.e. stage) adapted chemotherapy in Arm B.
Study type and study design	Investigator-driven, multicenter, open-label, randomized phase III study
Primary endpoint	The primary endpoint of this trial is disease-free survival, defined as the time from randomisation to one of the following events: no surgery or non-radical (R2) surgery of the primary tumour, locoregional recurrence after R0/1 resection of the primary tumour, second primary colorectal or other cancer, metastatic disease or progression, or death from any cause, whichever occurred first.

	We hypothesize that the 3-year DFS probability would improve from 78% in the standard arm to 85% in the investigational arm (hazard ratio of 0.65). With a power of 90% at a two-sided significance level of 5%, the sample size required to obtain a statistically significant difference is 818 patients (233 events) in total.
Secondary endpoints	• Acute and late toxicity assessment according to NCI CTCAE version 5.0 • Compliance (completion rate) of chemotherapy • Surgical morbidity and complications • Pathological UICC-staging, including pCR (ypT0N0) rate • R0 resection rate; negative circumferential resection rate (CRM > 1mm) • Tumor regression grading according to Dworak in the experimental arm • Rate of sphincter-sparing surgery • Rate of W&W with or without local regrowth • Cumulative incidence of local and distant recurrences • Overall survival • Quality of life and functional outcome based on treatment arm, and surgical procedures • Translational / biomarker studies (to be determined)
Inclusion criteria	• Male and female patients with histologically confirmed diagnosis of rectal adenocarcinoma localized 0 – 16 cm from the anal verge as measured by rigid rectoscopy (i.e. lower, middle and upper third of the rectum), depending on MRI-defined inclusion criteria (see below). • Staging requirements: High-resolution, thin-sliced (i.e. 3mm) magnetic resonance imaging (MRI) of the pelvis is the mandatory local staging procedure. • Transrectal endoscopic ultrasound (EUS) is used to help discriminate between T1/2 and early T3 tumors. • MRI-defined inclusion criteria: i. Lower third (0-6 cm): cT1/2 with clear cN+ based on defined MRI criteria, provided CRM- and EMVI- ii. Middle third (≥ 6-12 cm): cT1/2 with clear cN+ provided CRM- and EMVI-; cT3a/b, i.e. evidence of extramural tumor spread into the mesorectal fat of ≤ 5 mm provided N-, CRM-, and EMVI- iii. Upper third (≥ 12-16 cm): cT1/2 with clear cN+ provided CRM- and EMVI-; any cT3-4 irrespective of nodal status. • Spiral-CT of the abdomen and chest to exclude distant metastases. • Aged at least 18 years. No upper age limit. • WHO/ECOG Performance Status ≤1. • Adequate hematological, hepatic, renal and metabolic function parameters: • Leukocytes ≥ 3.000/mm³, ANC ≥ 1.500/mm³, platelets ≥ 100.000/mm³, Hb > 9 g/dl • Serum creatinine ≤ 1.5 x upper limit of normal • Bilirubin ≤ 2.0 mg/dl, SGOT-SGPT, and AP ≤ 3 x upper limit of normal. • Informed consent of the patient.
Exclusion criteria	• Distant metastases (to be excluded by CT scan of the thorax and abdomen). • Prior antineoplastic therapy for rectal cancer. • Prior radiotherapy of the pelvic region. • Major surgery within the last 4 weeks prior to inclusion. • Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.

	• Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 6 months (male or female) after the end of treatment (adequate: oral contraceptives, intrauterine device or barrier method in conjunction with spermicidal jelly). • On-treatment participation in a clinical study in the period 30 days prior to inclusion. • Previous or current drug abuse. • Other concomitant antineoplastic therapy. • Serious concurrent diseases, including neurologic or psychiatric disorders (incl. dementia and uncontrolled seizures), active, uncontrolled infections, active, disseminated coagulation disorder. • Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 6 months before enrolment. • Chronic diarrhea (> grade 1 according NCI CTCAE). • Prior or concurrent malignancy ≤ 3 years prior to enrolment in study (Exception: non-melanoma skin cancer or cervical carcinoma FIGO stage 0-1), if the patient is continuously disease-free. • Known allergic reactions on study medication. • Known dihydropyrimidine dehydrogenase deficiency. • Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule (these conditions should be discussed with the patient before registration in the trial).
Treatment	In the standard arm B, patients undergo surgical resection of the primary tumor followed by stage- (risk-)adapted adjuvant chemotherapy 4-8 weeks after surgery according to recommendations of the S3 guidelines in analogy to colon cancer. Details of the recommended protocols are provided in the protocol. The experimental arm A starts with 6 cycles of mFOLFOX or 4 cycles of XELOX. Surgery is scheduled four or six weeks after day 1 of the last mFOLFOX or XELOX cycle, respectively. No postoperative chemotherapy is planned.
Translational research	A translational research program, including monitoring by imaging, is implemented in order to further refine prognostic and predictive profiling, and eventually identifying subgroups for treatment stratification and conservative surgical procedures.
Sample size and justification	The sample size is driven by the primary efficacy outcome disease-free survival. Recruitment will be over 5 years and all patients will be followed up for at least 3 years, unless the patient dies beforehand, resulting in a maximum follow-up of 8 years. For the planning of the study we assume that the event times and times to study withdrawal follow exponential distributions and are independent. Withdrawal from the study is expected to be low; we adjust here for withdrawal of 5% over 3 years. Disease related treatment failure free survival at 3 years is assumed to be of 78% in the control and 85% in the experimental arm, respectively. Hence, a sample size of 409 patients per group yields a power of 90% at a two-sided significance level of 5%. With disease-free survival at 3 years of 84% in the experimental arm this sample size yields a power of 80.1%. In total we aim to randomize 818 patients.
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. For the primary efficacy outcome disease-free survival will be analyzed by Cox proportional hazards regression with treatment and stratification variables of the randomization (center und tumor distance from

	anal verge, i.e. <12 vs. ≥ 12cm) as factors. The treatment effect will be reported as hazard ratio with 95% confidence intervals and p-value testing the null hypothesis that the hazard ratio is equal to 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. If withdrawal from study is substantial and differential between the treatment groups, supporting analyses will explore the impact of the independent censoring assumption by use of shared frailty models. The primary endpoint as well as other time-to-event outcomes such as recurrence-free survival or overall survival 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.
Interim analyses; data safety monitoring board	No planned interim analyses are foreseen. Safety follow-up will be conducted by a data safety monitoring board (DSMB) on a regular basis which will be defined in a DSMB Charta.
Estimated number of sites	approximately 80-100 centers
Study duration	Start of preparation: Q2 2018 Start of recruitment: Q2 2019 Planned termination of recruitment: Q2 2024 Planned termination of follow-up: Q4 2027 Final study report: Q1 2028

Registerstudien

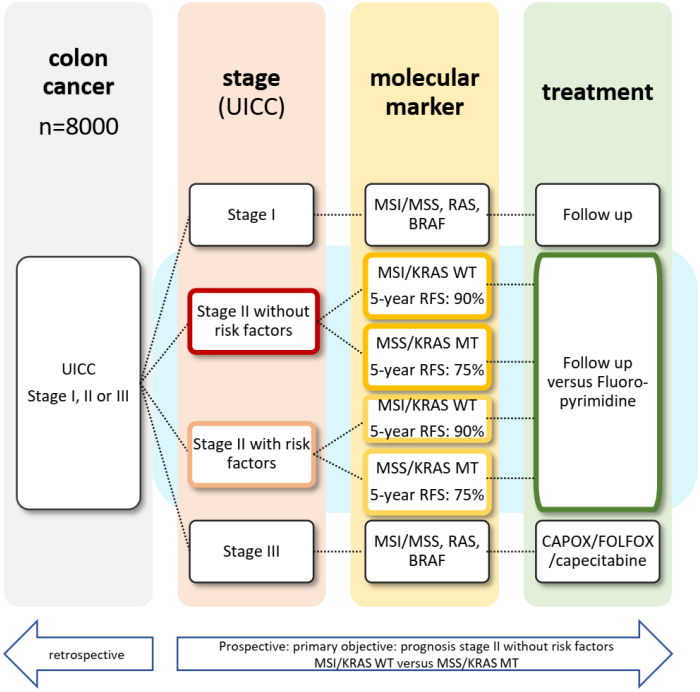
AIO-KRK-0413/ass: Retro- und prospektive Erfassung der Rolle von MSI und KRAS für die Prognose beim Kolonkarzinom im Stadium I, II + III sowie prospektiv bei hochsitzendem Rektumkarzinom im Stadium I, II + III (COLOPREDICT PLUS 2.0 - Register)

AIO-assoziierte Studie

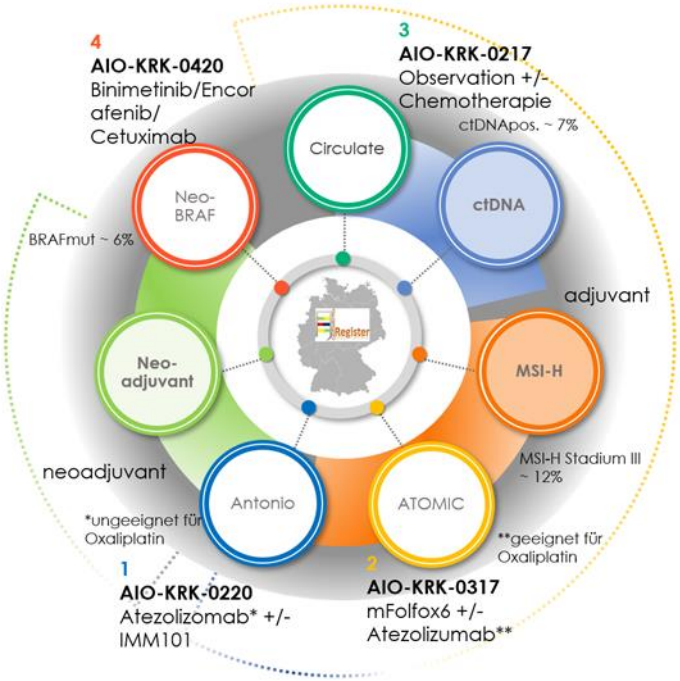
Studiennummer/-Code:	AIO-KRK-0413/ass - COLOPREDICT PLUS 2.0
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 – 2023
Weitere Zentren:	sind erwünscht
Zentren:	geplant: 200 initiiert: 181
Patienten:	geplant: 8000 aktuell eingeschlossen: 7300
Letzte Aktualisierung	August 2021 Addendum 1: 01-September 2020 (Kooperation Circulate, LKP G. Folprecht, NCT04120701) Addendum 2: 30-August-2021 (Kooperation BNT-001 Studie; NCT04813627)

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

	Abteilung für Hämatologie, Onkologie und Palliativmedizin St. Josef-Hospital Bochum Klinikum der Ruhr-Universität Tel.: 0234-509-3591, Fax:-Nr.: 0234-509-3592 E-Mail: onkologie@klinikum-bochum.de
Kontaktadresse/ Kontaktperson	Institut für Pathologie der Ruhr-Universität Bochum Bürkle-de-la-Camp-Platz 1, 44789 Bochum Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809 Ansprechpartner: S. Westphal(0234-302-4924, stephanie.westphal@pathologie-bochum.de) Klinischer Ansprechpartner: Dr. med.C. Lugnier (0234-509-2398, celine.lugnier@rub.de)
Studienziele	Primäres Studienziel: Im Rahmen des Colopredict Plus Registers sollen retrospektiv und prospektiv Patienten mit Kolonkarzinomen im Stadium I, II und III sowie prospektiv für hochsitzende Rektumkarzinome 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). Sekundäre Studienziele: • Rolle von MSI und KRAS auf die Prognose von Patienten mit Kolonkarzinomen sowie hochsitzenden Rektumkarzinomen im Stadium II mit Risikofaktoren inkl. RFS, DFS, OS im Stadium II • Prognose von Patienten im Stadium III A, B und C (UICC 7. Auflage) unter Standardchemotherapie inkl. RFS, DFS und OS im Stadium III Explorativ: 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 Aufbau einer Screening Plattform zur Identifikation von Patienten in klinischen und/oder molekularen Subgruppen für interventionelle Studien • Kooperation mit Circulate (EudraCT 2018-003691-12, Prof. Folprecht, Dresden) • Kooperation mit der epidemologischen Studie BNT000-001; NCT04813627 • Kooperation mit ATOMIC (EudraCT-Nr.: 2019-003562-40, Prof. Reinacher-Schick, Bochum) • Kooperation mit NeoBRAF (PD Dr. Stein, Hamburg) • Weitere kooperative Projekte zur (neo-)adjuvanten Therapie in Planung
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. 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. Es werden zusätzlich 800 Patienten mit hochsitzendem Rektumkarzinom (12-16cm ab ano) eingeschlossen dessen Behandlung gemäß S3-Leitlinie analog zum Kolonkarzinom erfolgt. Da die meisten interventionellen Studien beim Kolonkarzinom diese Patientengruppe einschließen, wurde das Protokoll durch ein Addendum vom 11.09.2020 temporär angepasst, um auch Patienten mit hochsitzenden Rektumkarzinomen für Therapiestudien über CPP 2.0 erfassen zu können.
Anzahl eingeschlossene Patienten	Aktuell 7300, Rekrutierungsziel: 8000
Flow-Chart	
Anzahl teilnehmende Zentren	Die Registerstudie soll vor allem, aber nicht ausschließlich innerhalb der Darmkrebszentren der DKG durchgeführt werden. 25 Stadium I/II/III Patienten pro Zentrum pro Jahr, 200 Zentren sollten rekrutiert werden. 3 Jahre Rekrutierungszeit.
Start des prospektiven Registers • Amendment 3.2 • Temporäres Addendum	September 2013 August 2018 September 2020 August 2021

• Temporäres Addendum	
Haupt-Einschlusskriterien	Patienten, die sich in den Behandlungskontext des teilnehmenden Zentrums begeben haben und die folgende Kriterien erfüllen: Prospektiver Patienteneinschluss: • männliche und weibliche Patienten mit der Diagnose eines Kolonkarzinoms im Stadium I, II oder III • männliche und weibliche Patienten mit der Diagnose eines hochsitzenden Rektumkarzinoms im Stadium I, II und III Bereitschaft der mit dem Studienzentrum kooperierenden Pathologie, Gewebeblöcke gemäß der Protokollanforderungen für die wissenschaftlichen Analysen zur Verfügung zu stellen • Alter ≥ 18 Jahre und in Besitz der Fähigkeit, die Anforderungen des Registers und die Aufklärung dazu zu verstehen, zu hinterfragen und zu bemessen • gemäß ICH-GCP unterschriebene Einwilligungserklärung zur Teilnahme an dem Register • unterschriebene Schweigepflichtsentbindung der behandelnden Ärzte für die Zwecke der Studienerhebungen Retrospektiver Patienteneinschluss (nur Kolonkarzinom) • Erstdiagnose ab dem 1.1.2006 • übrige Einschlusskriterien siehe Protokoll 5.1.1
Haupt-Ausschlusskriterien	Patienten, die • die Einschlusskriterien nicht erfüllen • 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.
Zielparameter	Primär: • 5-Jahres Rückfall-freies Überleben von MSI/KRAS WT Patienten versus MSS/KRAS MT Patienten im Stadium II ohne RF Sekundär: • 5-Jahres Rückfall-freies Überleben von MSI/KRAS WT Patienten versus MSS/KRAS MT Patienten im Stadium II mit RF • OS, DFS im Stadium II • RFS, DFS und OS im Stadium III Explorativ. • Identifizierung einer Prognosesignatur für Patienten im Stadium II ohne RF • Identifizierung von Patienten für mögliche Therapiestudien über bestimmte genetische oder andere molekulare Tumoreigenschaften (fakultativ) 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. Für die explorative Beurteilung anderer prognostischer Faktoren/molekularer Marker werden explorative Subgruppenanalysen durchgeführt.

Chart „Screening Plattform interventional trials (active and planned)“	
Addendum 1	01-September-2020 (Kooperation Circulate Trial, LKP G. Folprecht, NCT04120701)
Addendum 2	30-August-2021 (Kooperation epidemiological trial BNT000-001-study; NCT04813627)

AIO-KRK/YMO-0520/ass: CancerCovid - „Ressourcenallokation für die Krebsmedizin im Kontext von SARS-CoV-2. Nationale Studie zur Auswirkung der Pandemie mit SARS-CoV-2 auf die Versorgung von Patienten mit Tumorerkrankungen (Kolorektales Karzinom)”

Subprojekt 2 Onkologie: *“Quantitative Analyse der Auswirkungen von Allokation verfügbarer Ressourcen auf Patienten mit kolorektalem Karzinom (KRK).”*

AIO-assoziierte Studie	
Studiennummer/-Code:	AIO-KRK/YMO-0520/ass - CancerCovid
Status:	Datenerhebung wurde begonnen
Rekrutierungszeitraum	Zeitraum der Datenerhebung 01.01.2019 bis 31.12.2020
datenerhebende Zentren:	erwünscht
Zentren:	AIO- und Darmzentren
Daten:	retro- und prospektive Erhebung von Behandlungs- und Versorgungsdaten
Letzte Aktualisierung	Oktober 2021

Verantwortlicher Studienleiter	Prof. Dr. med. Anke Reinacher-Schick Abteilung für Hämatologie, Onkologie und Palliativmedizin St. Josef-Hospital Bochum Klinikum der Ruhr-Universität Tel.: 0234-509-3591, Fax-Nr.: 0234-509-3592 E-Mail: onkologie@klinikum-bochum.de

	Prof. Dr. med. Andrea Tannapfel Institut für Pathologie der Ruhr-Universität Bochum Zentrale Gewebebank Bürkle-de-la-Camp-Platz 1, 44789 Bochum Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809 E-Mail: andrea.tannapfel@rub.de
Weitere Mitarbeiter SP 2	Dr. med. Celine Lugnier, YMO, celine.lugnier@rub.de Dr. med. Anna-Lena Kraeft, anna-lena.kraeft@rub.de Eleni Kourti, YMO, e.kourti@klinikum-bochum.de Abteilung für Hämatologie, Onkologie und Palliativmedizin St. Josef-Hospital Bochum Klinikum der Ruhr-Universität Tel.: 0234-509-3591, Fax-Nr.: 0234-509-3592
Förderung	BMBF, Förderkennzeichen 01KI20521C
Mitglieder des Konsortiums	Prof. Dr. med. Jan Schildmann (*Koordination*; SP 1 Ethik) Institut für Geschichte und Ethik der Medizin Martin Luther Universität Halle-Wittenberg Magdeburger Str. 8 06112 Halle (Saale) Prof. Dr. med. Jochen Schmitt (SP 3 Versorgungsforschung) Zentrum für Evidenzbasierte Gesundheitsversorgung Universitätsklinikum Carl Gustav Carus Dresden Fetscherstr. 74 01307 Dresden
Kooperationspartner	KRK-Leitgruppe der AIO • Prof. Dr. med. Ralf-Dieter Hofheinz • Prof. Dr. med. Sebastian Stintzing AOK Sachsen Plus Prof. Dr. med. Stephan Herpertz; Klinik für Psychosomatische Medizin und Psychotherapie, Ruhr-Universität Bochum Prof. W. Knauf BNHO; Dr. V. Heidt WINHO R. Reichelt Onkotrakt AG
Studienziele	Primäres Studienziel des Konsortiums: Das Gesamtziel des Vorhabens ist die Entwicklung einer Handlungsempfehlung zur Priorisierung und Allokation von Ressourcen bei der Versorgung von Tumorpatienten unter der Sars-CoV-2 Pandemie. Die Beurteilungsgrundlage stützt sich auf eine empirisch untersuchte und ethisch informierte Beurteilungsgrundlage. Die quantitativen Daten, die der Analyse zugrunde liegen, sollen erhoben werden aus einem bundesweit etablierten Netzwerk aus Darmzentren, AIO-Zentren und den Daten aus der gesetzlichen Krankenversicherung AOK Plus Sachsen. Zusätzlich werden die ethischen und psychosozialen Belastungen von Patienten und Beschäftigten des Gesundheitssystems während der Pandemie untersucht. Durch ein Delphiverfahren werden diese Inhalte in eine Empfehlung eingebracht, welche klinische und gesundheitspolitische Aspekte berücksichtigt. Die Diskussion der Ergebnisse erfolgt mit Entscheidungsträgern aus Onkologie und Gesundheitspolitik.

	Studienziele Subprojekt Onkologie: Das Subprojekt Onkologie trägt zur Beantwortung der Fragestellung durch die Erhebung von aussagekräftigen Daten über national organisierte Tumornetzwerke bei, die an der Versorgung von Patienten mit Kolonkarzinomen in Deutschland wesentlich beteiligt sind. Die Auswertung von Kennzahlen der Colopredict Plus 2.0 Registerstudie und der AIO-Zentren sollen zur Beurteilung von Ausmaß und Auswirkung der Allokation, eine umfassende Beurteilungsgrundlage schaffen.
Datenerhebung	Erfasst werden Daten der Versorgung von Patienten mit kolorektalen Karzinomen aller Stadien sowie Vorsorgeuntersuchungen zum kolorektalen Karzinom. Ausschlaggebend ist hier der Zeitpunkt der Diagnose bzw. der Therapie um Versorgungsdaten aus den Quartalen 1-4 2020 unter der Corona-Pandemie mit korrespondierenden Daten vor der Pandemie (Quartal 1-4 2019) vergleichend zu analysieren. Daten der sog. „zweiten Welle“ werden mit erfasst.
erhobene Parameter	Anzahl der Erstdiagnosen Koloskopien (Vorsorge / Nachsorge) Tumorstadium Operationen (Primärtumor, Metastasen) Qualitätskriterien Darmkrebszentren (durchgeführte Tumorkonferenzen, erfolgte psychoonkologische Beratungen, Sozialdienstberatungen) Chemotherapie (erfolgte Zylen, intravenös, oral, kompex) Studieneinschlüsse Palliativkomplexbehandlung
Datenerhebung: Quelldaten	Ziel ist eine möglichst flächendeckende und repräsentative Erfassung der Versorgungsdaten unter der Pandemie sowie im Vergleichszeitraum. 1. Institut für Pathologie der Ruhr-Universität Bochum (Eingangszahlen) 2. Daten aus der Colopredict Plus 2.0 Registerstudie 3. AIO-Zentren 4. Daten der ambulanten Versorgung der WINHO 5. Daten der Onkotrakt AG zur ambulanten Chemotherapie
Anzahl teilnehmende Zentren	Anfrage an AIO und Darmzentren aus der ColoPredict Plus 2.0 Registerstudie sowie die Eingangsdaten des Instituts für Pathologie der Ruhr-Universität Bochum.
Laufzeit	07/2020 bis 12/2021, kostenneutrale Laufzeitverlängerung bis 30/04/2022 beantragt
Statistik	Alle dokumentierten Daten zur Beschreibung des Patientenkollektivs in Bezug auf Diagnostik, Therapie und Versorgung werden mittels statistischer Standardverfahren deskriptiv ausgewertet.
Die kostenneutrale Laufzeitverlängerung wurde genehmigt.	

AIO-YMO/ZNS/KRK-0219: Prospektive Sammlung von Patienten- und Tumordaten sowie von Tumorgewebe und Liquid Biopsies (Blut und/oder Liquor) bei Patienten mit mKRK und ZNS-Metastasen (GECCObrain)

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)
Studiennummer/-Code:	AIO-YMO/ZNS/KRK-0219 - GECCObrain
Status:	in Vorbereitung
Rekrutierungszeitraum:	2019 - 2024
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	31.10.2020

STUDY TYPE	Register mit Biobank
PRINCIPAL INVESTIGATOR	PD Dr. Marlies Michl Medizinische Klinik und Poliklinik III und CCC München[LMU] Klinikum der Universität München – Großhadern Marchioninistr. 15 81377 München
TRIAL OFFICE	Studiensekretariat der AG Onkologie Medizinische Klinik und Poliklinik III und CCC München[LMU] Klinikum der Universität München – Großhadern Marchioninistr. 15 81377 München
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe ZNS-Tumoren/Meningeosis	

Arbeitsgruppe Kopf-Hals-Tumoren

Operable Kopf-Hals Tumoren

AIO-KHT-0220/ass - Window of opportunity study of preoperative immunotherapy with atezolizumab (Tecentriq in local squamous cell carcinoma of the head and neck – an imCORE Study - PIONEER

AIO-Studie

Studiennummer/-Code:	**AIO-KHT-0220/ass - PIONEER**
Status:	rekrutierend
Rekrutierungszeit:	von: Q3/2021 bis: Q1/2023
Anzahl Zentren:	geplant: 3 aktuell initiiert: 1 (Essen) aktiv rekrutierend: 1
Weitere Zentren:	(z.B.) sind leider nicht möglich
Anzahl Patienten:	geplant: 20 aktuell eingeschlossen: 2
Letzte Aktualisierung	08.10.2021

STUDY TYPE	phase II
PRINCIPAL INVESTIGATOR	Prof. Dr. med. Stefan Kasper-Virchow Address: Department of Medical Oncology West German Cancer Center University Hospital Essen Hufelandstr. 55 45147 Essen Germany Phone: +49 (0)201-7233449 Fax: +49 (0)201-7235549 Email: stefan.kasper-virchow@uk-essen.de
TRIAL OFFICE	Universitätsmedizin Essen – Studienzentrum GmbH Hufelandstraße 55 45147 Essen Tel.: +49 (0)201 723-77411 Email: katrin.appel@uk-essen.de www.umesz.de
SPONSOR	University Hospital Essen Hufelandstraße 26 45147 Essen
CONDITION	Histologically proven resectable squamous cell carcinoma of the head and neck (SCCHN)
DESIGN	International, open-label, multicenter, single arm non-randomized window of opportunity study
INDICATION	Resectable squamous cell carcinoma of the head and neck (SCCHN)
OBJECTIVE(S)	**Primary objectives** • Effect of atezolizumab on tumor-infiltrating immune cells in resectable SCCHN • Feasibility of preoperative short time immunotherapy
INTERVENTION(S)	▪ atezolizumab 1200 mg intravenously (i.v.) on day 1

	Resection will be perfomed on day 21 to 28.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	**Secondary objectives** • Safety of preoperative short time immunotherapy and assessment of postoperative complication rates • To assess dynamics in tumor immunity • Exploratory analyses of predictive biomarker by gene and protein expression to establish correlation with pathological response • Characterization of changes in frequency and numbers of circulating immune cells • Resectability after immunotherapy • Influence of immunotherapy on histo-morphological assessment • (optional) set up of a registry for follow up of patients and subsequent documentation of relapse free survival (RFS) rate • and overall survival (OS) rate **Exploratory objectives** • Clinical response • Pathological regression
BACKROUND/RATIONALE	In patients with SCCHN, the time period between primary biopsy and resection represents an ideal window for neoadjuvant therapeutic studies. Furthermore, SCCHN tumors amenable to surgical resection with curative intent can yield large quantities of tissue, far beyond the requirements for pathological analysis and clinical staging, providing an invaluable resource for translational research, which would not be possible with the limitations of small biopsies from patients with metastatic disease. Window of opportunity studies assessing the potential anti-tumoral biological effects of novel therapeutic agents administered for a short-duration (2 – 4 weeks) in the preoperative setting constitute an efficient proof of concept strategy, allowing to rapidly evaluate and prioritise novel CIT. Pharmacodynamic and correlative studies on tumor tissue obtained pre-, on- and post-treatment can provide important insights into the mechanisms of action, differences in activity and potential predictors of response and resistance to define the optimal patient population. While a considerable number of immunotherapiesare currently in clinical development in SCCHN, most studies lack a thorough translational research program that would allow to better understand the dynamics of immune cell populations leading to an effective antitumor response. The relatively large volume of tissue available at resection allows performing a standardized series of assays with state-of-the-art technologies to interrogate the immunological consequences of immunotherapies in SCCHN. In addition, serial analyses of peripheral immune cell populations will assess the impact on systemic immune responses. This study will assess the importance of targeting mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination.
KEY EXCLUSION CRITERIA	**Exclusion criteria** 1. Evidence of metastatic disease 2. Prior treatment with immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies

	3. Treatment with investigational therapy within 28 days prior to initiation of study treatment 4. Any anti-cancer therapy, including chemotherapy or hormonal therapy, within 4 weeks prior to initiation of study treatment 5. Bilateral pleural effusion 6. Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to Day 1, Cycle 1. Note: The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e. for adrenal insufficiency) and mineralocorticoids (e.g. fludrocortisone) is allowed 7. Treatment with a live-attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study, and for 5 months after the last dose of atezolizumab 8. Treatment with systemic immuno-stimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment 9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins; known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or to any component of the atezolizumab formulations 10. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study 11. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab 12. Uncontrolled tumor-related pain. Patients requiring narcotic pain medication must be on a stable regimen at study entry 13. Pregnant and lactating women 14. Acute toxicities from previous therapy that have not resolved to Grade ≤ 1, except for alopecia 15. Infections a. Positive human immunodeficiency virus (HIV) test Known HIV+ patients may be included but must have: A stable regimen of highly active anti-retroviral therapy (HAART) No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests b. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening followed by a negative HBV DNA test, are eligible for the study. The HBV DNA test will be performed only for patients who have a positive total HBcAb test. c. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV ribonucleic acid (RNA) test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test. d. Active tuberculosis

	e. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia f. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment g. Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study. 16. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 12.1 for a more comprehensive list of autoimmune diseases and immune deficiencies) with the following exceptions: - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) may be eligible provided that they meet the following conditions: – Rash must cover less than 10% of the body surface area. – Disease is well controlled at baseline and only requires low potency topical steroids. – There are no acute exacerbations of underlying condition within the last 12 months (e.g., not requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids) 17. Adverse events (AE) related to any previous radiotherapy, chemotherapy, targeted therapy or surgical procedure that have not reolved to Grade ≤1, except alopecia (any grade) and Grade 2 neuropathy 18. Prior allogeneic stem cell or solid organ transplantation 19. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computer tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 20. Active malignancy or a prior malignancy within the past 3 years. Patients with completely resected basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and patients with isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study. 21. Any Grade ≥ 3 hemorrhage or bleeding event within 28 days of Day 1 of Cycle 1 22. Increased corrected QT (QTc) interval (QTc > 470 ms) 23. Family history of long QT syndrome or other risk factors for torsades de pointes 24. History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1 25. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within

	6 months prior to Cycle 1 Day 1, severe cardiac arrhythmia requiring medication or severe conduction abnormalities, unstable arrhythmias, acute coronary syndromes (including unstable angina), or history of coronary angioplasty/stenting/bypass grafting within past 6 months. a. Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded b. patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate 26. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications 27. Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety Participation in another clinical study within the last 3 months prior to inclusion or simultaneous participation in other clinical studies with an exception of studies evaluating radiological imaging.
KEY INCLUSION CRITERIA	**Inclusion criteria** 1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent has to be obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening examinations and laboratory results must have been obtained within 14 days before first study drug administration (initial tumor imaging: within 28 days before first study drug administration). 2. Only patients for whom sufficient tumor material to be judged by the local investigator and which is of adequate quality can be included into the trial. Please refer to section 6.5 for further details on quantity and quality of tumor samples. 3. Histologically or cytologically proven SCCHN (cT1-4a, cN0-3, cM0) that is amenable to surgical resection with curative intent based on the decision of the local multidisciplinary tumorboard. 4. Patients with relapse after primary radio(chemo)-therapy are allowed if a salvage surgery is possible (maximum 20% in each arm). Patients should have recovered from the effects of radiation: AE/sequelae should resolves to ≤ grade 2 (no minimum recovery period required). 5. Male or female, 18 years of age or older on day of signing informed consent 6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 7. Life expectancy >12 weeks 8. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment: • Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without granulocyte colony-stimulating factor support • Lymphocyte count $\geq 0.5 \times 10^9$/L • Platelet count $\geq 100 \times 10^9$/L without transfusion • Hemoglobin ≥ 90 g/L

	○ Patients may be transfused to meet this criterion but patients in need of chronic or repeated RBC transfusion should be discussed with the sponsor before. • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN) • Serum bilirubin ≤ 1.5 × ULN with the following exception: ○ Patients with known Gilbert disease: direct serum bilirubin level ≤ ULN for patients with total bilirubin levels>1.5 ULN. • Serum creatinine ≤ 1.5 × ULN or Creatinine clearance ≥30 mL/min (calculated using the Cockcroft-Gault formula) • Serum albumin ≥ 2.5 g/dL • International normalized ratio (INR) or activated Partial Thromboplastin Time (aPTT) ≤ 1.5 × ULN (This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low−molecular weight heparin or warfarin) should be on a stable dose 9. Women of childbearing potential: • Should have a negative urine or serum pregnancy test within 14 days prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. • Agreement to remain abstinent (refrain from heterosexual intercourse) or use a non-hormonal contraceptive method with a failure rate of < 1% per year during the treatment period and for at least 5 months after last study drug administration • A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state (≥ 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, and copper 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 post-ovulation methods) and withdrawal are not acceptable methods of contraception. For men: with female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 5 months after the last dose in arm A and B to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
OUTCOME(S)	**Primary variables** • Percentage of patients with at least 2-fold increase of GzmB+/CD8+ T cells by immunohistochemistry (IHC) after 1 administration of atezolizumab between pre-treatment biopsy specimens and post-treatment resection specimens Number of patients with completion of pre-operative immunotherapy and resection of SCCHN

<table>
<tr><td>STATISTICAL ANALYSIS</td><td>At least 20 consecutive patients will be included in the study.Interims analysis for safety will be done after 6 patients were resected. In addition if the first 3 patients will have a delay in surgery for more than 3 weeks an additional safety analysis will be done in these patients and the study will be temporarily paused. All primary and secondary analyses are based on pre-vs. post-treatment comparisons.
The primary objective of this study is to determine the change in tumor infiltrating GzmB+/CD8+ T cells after 1 cycle of preoperative atezolizumab.
The fold-change (FC) of the immune cells between pre-treatment biopsy and post-treatment resection specimens is the primary observable. It appears reasonable to assume log(FC) to be normally distributed (Wei et al. 2004). A change of the mean value of FC by one unit of its a-priori unknown distribution width, i.e. an effect of size 1, is deemed to be a minimum result size we would like to capture with a probability of 80% (power = 0.8). For this study we deem a significance level of α = 0.05 to be appropriate.
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Summary of the parameters:
<table><tr><th>Parameter</th><th></th></tr><tr><td>effect size</td><td>1</td></tr><tr><td>α</td><td>5%</td></tr><tr><td>β</td><td>20%</td></tr><tr><td>power (1- β)</td><td>80%</td></tr><tr><td>test</td><td>two-sided, one group</td></tr></table>
The primary endpoint will be positive if the 2-fold increase of GzmB+/CD8+ T-cells is observed in ≥30% of patients..

The sample size calculation for these parameters gives a minimum of n = 17 evaluable study participants in each arm, in order to detect a true effect of size one with 80% probability and only a 5% chance of a signal to be false positive. Assuming 10% attrition and non-evaluability, we estimate our need to enroll at least 20 patients to ensure 17 evaluable patients.

Patients could be included after prior radio-(chemo) therapy in case of salvage surgery. A maximum of 20% of patients with previous radio-(chemotherapy) will be included in each arm.

Co-primary endpoint will be the feasibility of a pre-operative short time immunotherapy in patients with resectable SCCHN. The endpoint will be positive if 15 out of 17 evaluable patients (>85%) have completed the pre-operative immunotherapy and have been resected.

All other parameters and secondary endpoints will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If any p values are calculated (e.g. in subgroup comparisons), they are considered to be descriptive and will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error.</td></tr>
<tr><td>SAMPLE SIZE</td><td>20</td></tr>
<tr><td>TRIAL DURATION</td><td>For the individual patient:
Approximately 3 months (up to 2 weeks screening, 3 weeks study therapy and follow up visit / end of study visit 37±10 days after standard of care surgery. An optional registry study will be launched for additional follow up (up to 36 months after last study drug administration)

Planned study schedule</td></tr>
</table>

	First Patient In	Q3/2021
	Last Patient In	Q2/2023
	Last Patient EoT	Q2/2023
	LPLV	Q4/2023
	DBL	Q2/2024
	End of study	Q2/2024
PARTICIPATING CENTERS	Two centres in Germany (University Medicine Essen, West German Cancer Center, National Center for Tumor Diseases (NCT) Heidelberg) and one center in The Netherlands (Netherlands Cancer Institute, Antoni Van Leeuwenhoek Hospital Amsterdam)	
FURTHER CENTERS DESIRED?	no	
NUMBER of PATIENTS	20	
CURRENT NUMBER of PATIENTS	2	

Arbeitsgruppe Lebensqualität und PRO – Patient Reported Outcomes

Inoperable metastatic or locally advanced solid tumors, parenteral nutrition

AIO-LQ-0119/ass: Open-label, randomized, multicenter, phase IV trial comparing parenteral nutrition using Eurotubes® vs. traditional 2/3-chamber bags in subjects with metastatic or localized solid tumors requiring parenteral nutrition (PEKANNUSS)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-LQ-0119/ass - PEKANNUSS		
Status:	rekrutierend		
Rekrutierungszeit:	von: Nov. 2019	bis: Nov. 2022	
Zentren:	geplant: 50	aktuell initiiert: 18	rekrutierend: 13
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant: 350	aktuell eingeschlossen: 103	
Letzte Aktualisierung	01.10.2021		

STUDY TYPE	Open-label, randomized, multicenter, investigator-initiated phase IV trial
PRINCIPAL INVESTIGATOR	Prof. Dr. med. Salah-Eddin Al-Batran
TRIAL OFFICE	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main, Germany
SPONSOR	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main, Germany
CONDITION	Patients with metastatic or localized solid tumors who have an indication for parenteral nutrition
DESIGN	This is an open-label, randomized, multicenter, investigator-initiated, phase IV trial. Patients with metastatic or localized solid tumors who fulfil the eligibility criteria and who have an indication for parenteral nutrition will be enrolled. Patients will be stratified according to ECOG (0-1 vs. 2 vs. 3), the modified Glasgow Prognostic Score (mGPS) (0-1 vs. 2) and whether the patient receives concurrent systemic anti-tumor treatment (e.g. chemotherapy, targeted therapy, immunotherapy) or not. In a first step, patients will be randomized in a 2:1 ratio to Arm A or Arm B: **Arm A: Standard Parenteral Nutrition using Eurotubes®.** or **Arm B: Standard Parenteral Nutrition using 2/3-chamber bags.** Patients randomized to Arm B will receive PN according to the routine used by the participating site. Patients in Arm A will be stratified again by the same criteria as listed above and randomized in a 1:1 ratio to Arm A-1 or Arm A-2: **Arm A-1: Standard Low Glucose Parenteral Nutrition using Eurotubes®** Patients randomized to Arm A and in a second randomization to treatment Arm A-1 receive standard PN reduced in glucose in Eurotubes®. or **Arm A-2: Standard Parenteral Nutrition using Eurotubes®.**

	Patients randomized to Arm A and in a second randomization to treatment Arm A-2 will receive standard PN in Eurotubes®. Patients will be recruited during regular consultation visits. At screening and at all regular visits during the HPN treatment period (one visit per four-week interval after randomization for a maximum of 12 months) the ECOG performance status and body weight will be determined. Additionally, physical examinations and laboratory assessments including CRP, albumin and total protein levels will be performed. The HPN therapy plan and any modifications and adjustments to this plan during the course of HPN treatment will be recorded from visit 1 onwards. Anti-cancer treatment at the time of screening and during the course of the HPN treatment period (e.g. type of treatment) will be documented. Monitoring of Adverse Events and medical device deficiencies will be performed at every visit. AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. During the study the patient will maintain a study diary to document details of the administration of the HPN. A QoL questionnaire will be completed during regular study visits until EOT. After completion of study treatment, patients will enter the follow-up period. During this period, they will be followed approximately every 3 months for survival, which can be done by phone.
INDICATION	Patients with metastatic or localized solid tumors requiring parenteral nutrition
OBJECTIVE(S)	<u>Primary Objectives</u> *Co-Primary objective Catheter Related Infections (CRI)* • To compare the incidence of catheter related infections. *Co-Primary objective patient autonomy* • To compare the frequency of self-administered parenteral nutrition at home (HPN). <u>Secondary Objectives</u> • To compare the efficacy of parenteral nutrition (PN) in terms of body weight, C-reactive protein (CRP) and albumin levels, and overall survival (OS) • To compare the Quality of life (QoL) by use of the modified HPN-PROQ questionnaire • To determine the frequency and duration of visits by the nursing service • To compare the safety in terms of the incidence of other catheter related complications, severe, common toxicity criteria (CTC) grade 3-5 infections, and PN-related Adverse Events (AEs) <u>Secondary Objectives (Arm A-1 vs. A-2)</u> • To compare the incidence of catheter related infections (CRI). • To compare the efficacy of PN in terms of body weight, C-reactive protein (CRP) and albumin levels, and overall survival (OS) • To compare the Quality of life (QoL) by use of the MODIFIED HPN-PROQ questionnaire • To compare the safety in terms of the incidence of other catheter related complications, severe, common toxicity criteria (CTC) grade 3-5 infections, and PN-related Adverse Events (AEs)

INTERVENTION(S)	• **Arm A-1: Standard Low Glucose Parenteral Nutrition using Eurotubes®** Patients randomized to Arm A and in a second randomization to treatment Arm A-1 receive standard PN reduced in glucose in Eurotubes®. • **Arm A-2: Standard Parenteral Nutrition using Eurotubes®.** Patients randomized to Arm A and in a second randomization to treatment Arm A-2 will receive standard PN in Eurotubes®. • **Arm B: Standard Parenteral Nutrition using 2/3-chamber bags.** Patients randomized to Arm B will receive PN according to the routine used by the participating site.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	N/A (no translational research)
BACKROUND/RATIONALE	Cancer is often characterized by extensive invasion, early metastases, and, in many cases, a rapidly occurring marked cachexia leading to a very poor prognosis especially in the metastatic situation. Cachexia is a strong and independent predictor of mortality, poor therapeutic response, diminished functional capacity, and reduced QoL. It is defined as the debilitating state of involuntary weight loss, often connected with anorexia, tissue wasting, malnutrition, and inability for natural nutrition intake. The combination of these symptoms is also named „cancer anorexia-cachexia syndrome" (CC). Approximately 50% of all cancer subjects suffer from CC and its severe impact on QoL and response to chemotherapy [Bossola et al., 2007]. Especially in the advanced stages, it cannot be fully cured by increased food intake or oral supplements and requires supportive or total parenteral nutrition. If needed, patients can live on PN for an unlimited time, the mean administration period depends much on the underlying disease, the ability to eat and the patient's general condition. However, data has shown that PN is accompanied by an increased risk of blood stream infections (BSI) [Dissanaike et al., 2007] and is an independent risk factor for both catheter-related bloodstream infections (CRBSI) and central line-associated bloodstream infections (CLABSI) [Beghetto et al., 2005]. BSI represent 15% of all nosocomial infections and are associated with increased mortality and other serious medical conditions such as severe sepsis or septic shock [Pontes-Arruda et., 2012]. In addition to the safety aspect, BSIs lead to longer hospital stays and hence, additional costs [Turpin et al., 2011]. Although most PN related BSI are caused by the intravenous catheter, numerous manipulations on the infusion unit may multiply the hazard of extrinsic contaminations [Didier et al., 1998]. To reduce this well-known risk, the relevant phases of PN (production, adding of supplements, administration) are subject to highest standards of hygiene in order to minimize the contamination risk. Industrial PN is manufactured following the guidelines of Good Manufacturing Practice (GMP) and under clean room conditions which reduces the contamination hazard significantly. Data indicate advantages of industrially manufactured PN compared to pharmacy-compounded PN formulations in terms of safety, however the limited data do not allow a definite conclusion [Turpin et al., 2012; Canada et al., 2009]. Furthermore, the change from oral food intake to PN is associated with many changes in the subject's everyday life that lead to restriction of autonomy and flexibility. CC patients are often unable to perform the PN procedure correctly on their own, especially when supplements need to be added. The nursing services need to visit the subject daily to perform the PN administration. The infusion takes around 12 to 14 hours to finish and is typically administered in the evening to be infused overnight. The subjects' daily life is highly determined by the appointments of the nursing service, overnight stays away are nearly impossible and the dependency on outside assistance can diminish

	the patients' self-esteem and QoL. The extent to which these limitations to the subject's self-determination can diminish the QoL is currently poorly studied and needs further investigation. Subsequently, it is of high interest to assess if the QoL shows to be higher in subjects performing the PN administration autonomously without nursing service assistance. Blood glucose levels and ketogenic diets are a contentious issue and subject of controversial discussion among oncologists. In the 1920s, Nobel laureate Otto Warburg observed that unlike healthy body cells, cancer cells strongly upregulate the glucose intake to produce energy preferably via glycolysis, instead of the much more efficient way of oxidative phosphorylation [Liberti and Locasane, 2016]. This phenomenon is known as the Warburg-Effect. Data hint that carbohydrate restriction and ketogenic diets possibly obstruct cancer growths [Klement and Kaemmerer, 2016], however, too little data is available to come to a definite conclusion. Thus, it will be another goal of the trial to collect data from patients with solid tumors receiving glucose-reduced PN and to examine if potential benefits regarding survival and other efficacy endpoints such as body weight can be observed.
KEY EXCLUSION CRITERIA	Patients who meet any of the following criteria will be excluded from study entry: 1. > 4 weeks of consecutive (≥ 3 days per week) parenteral nutrition in the last 3 months prior to study enrolment 2. Participation in another interventional clinical trial that could influence the endpoints of this trial or planned participation in such a study at the same time as this study is active (participation in other trials is possible in the follow up time for OS). The study is active, if the patients receive study treatment (PN), did not discontinue the trial for other reasons, and is still within the 12 months active study period 3. Current catheter related infection at baseline in patients with a suspected/proven previous conservatively managed catheter-related infection, a negative pair of blood cultures drawn from the central catheter is required. 4. Pregnancy or breastfeeding 5. Known hypertriglyceridemia ≥ CTCAE grade 3 6. Unable or unwilling to provide written informed consent and to comply with the study protocol 7. Uncontrolled diabetes mellitus 8. Congestive heart failure NYHA ≥ 3 9. Renal insufficiency GFR < 30 ml/min 10. Uncontrolled infection 11. Liver insufficiency
KEY INCLUSION CRITERIA	Patients* must meet the following criteria to be eligible for the study: 1. Age ≥ 18 years 2. Histologically confirmed metastatic or localized solid tumor. Perioperative setting of HPN is allowed if HPN is planned for a duration of ≥ 2 months 3. ECOG performance status of 0, 1, 2 or 3 4. Indication for PN (the subject needs a PN independent of the trial) 5. PN planned for 3 or more days per week 6. Negative pregnancy test in women of childbearing potential 7. Willingness to perform double-barrier contraception during study for women of childbearing potential 8. Willingness to maintain a study diary 9. Life expectancy > 3 months 10. Written informed consent

	*There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently.
OUTCOME(S)	**Primary endpoints** Co-Primary endpoint catheter related infections (CRI) Defined as the presence of bacteraemia originating from the intravenous (port) catheter – Bacteraemia must be confirmed through a blood culture according to study site-specific routine, preferably through paired quantitative blood cultures or a culture of the catheter if the catheter is removed – OR any infections originating from the intravenous (port) catheter, requiring intravenous antibiotics OR infections in the intravenous (port) catheter, requiring intravenous antibiotics or antibiotics delivered to the catheter itself or catheter removal. For the diagnostic procedures to be done to confirm CRI, investigators are recommended to follow the DGHO guidelines. Co-Primary endpoint patients' autonomy The rate of self-administered parenteral nutrition at home (autonomy rate), defined as administration without nursing service assistance, as documented within the patient's study diary and calculated as the number of patients with autonomy divided by the total number of patients in the respective arm. Autonomy – as relevant for the primary endpoint – is achieved if the patient self-administers 50% or more of her/his total administrations (Note: Help of family members or other personal caregivers accounts for self-administration). **Secondary endpoints** Efficacy endpoints • Relative weight change determined at baseline and during study visits approx. every four weeks after enrolment; • Relative change of albumin and CRP levels measured at baseline and during regular study visits; • Overall survival (OS) defined as the time from randomization to death from any cause. Quality of Life endpoints • Quality of Life (QoL) through the MODIFIED HPN-PROQ questionnaire; • Frequency of PN-related visits by nursing service (as documented in the patients' diary). Safety endpoints • Catheter related complications such as line occlusions of catheter-related central venous thrombosis; • Severe, NCI-CTC common toxicity criteria version 5.0 grade 3-5, infections including fever of unknown origin and other Adverse Events according to NCI-CTC common toxicity criteria version 5.0; • PN-Related Adverse Events (AEs) and hospitalizations during therapy
STATISTICAL ANALYSIS	The primary analysis will compare patients randomized to Arm A (Standard Parenteral Nutrition using Eurotubes®) with those randomized to Arm B (Standard Parenteral Nutrition using 2/3-chamber bags) regarding the CRI rate and the objective patient autonomy and will be based on the ITT population. All secondary analyses, excluding safety endpoints analyses, which will be based on the safety population, will be based on the ITT population. The parameters will be evaluated in an explorative manner, providing means, medians, ranges, standard deviations and/or confidence intervals. Rates will be compared using fisher's exact test and continuous variables using t-test. For the time-to-event variable OS, the Kaplan-Meier method will be used, and treatment groups will be compared using a log rank test. All resulting p-values for secondary endpoints will be considered descriptive and will be presented explicitly without referring to hypotheses or a significance level. Usually, no p-value adjustment for multiple-testing will be performed. Thus, the p-values will

	reflect the comparison-wise error and not the experiment-wise error. All p-values will be two-sided if not stated otherwise.
SAMPLE SIZE	For both co-primary endpoints statistical significance is assessed using a fisher's exact test at a two-sided alpha level of 0.04 for the catheter related infections (CRI) rate and 0.01 for the objective patient autonomy, respectively. The power calculation was carried out using the Power Procedure in SAS version 9.4 (method: Walters normal approximation for unbalanced groups): Considering the 2:1 randomization, 226 patients must be included in Arm A (Standard Parenteral Nutrition using Eurotubes®) and 113 patients in Arm B (Standard Parenteral Nutrition using 2/3-chamber bags) to detect an improvement of the CRI rate from 25% (Arm B) to 10% (Arm A) with 90% power, resulting in a sample size of 339 patients. Concurrently, only 333 patients (222 in Arm A and 111 in Arm B) are needed to ensure 90% power to detect an improvement of the objective patient autonomy from 5% with traditional 2/3-chamber bags to 20% with Eurotubes®. Therefore, the patients' autonomy endpoint can be neglected for the sample size calculation. Assuming a dropout rate of about 3% it is planned to include 350 patients.
TRIAL DURATION	Patients will be observed for a maximum of 12 months of their PN starting from the date of randomization (except for OS which may be updated after the 12 months prior to data base closure). Physicians are free to continue PN after end of the observational period if they believe that PN is in the best interest of the patients, but this is done outside the study and is captured in the eCRF as post-discontinuation therapy. Recruitment is expected to occur over 3 years. The expected total study duration is 4.5 years.

Arbeitsgruppe Mammakarzinom und Gynäkologische Tumoren

Registerstudie: Mammakarzinom, 1st-line

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

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-MAM-0218/ass // OPAL	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 – 2021	
Weitere Zentren:	erwünscht	
Zentren:	geplant: ca. 200	initiiert: 227
Patienten:	geplant: 2000 (ABC)	aktuell eingeschlossen: 1795
	3000 (EBC)	aktuell eingeschlossen: 406
Letzte Aktualisierung	06.10.2021	

STUDY TYPE	National, observational, open, prospective, longitudinal, multicenter cohort study
PRINCIPAL INVESTIGATOR	Steeringboard: Prof. Dr. med. Thomas Decker, Prof. Dr. med. Nadia Harbeck, 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, Ellen-Gottlieb-Str. 19, 79106 Freiburg, Germany
CONDITION	Early breast cancer (EBC), Advanced breast cancer (ABC)
DESIGN	National, observational, open, prospective, longitudinal, multicenter cohort study
INDICATION	Early Breast cancer, Advanced breast cancer
OBJECTIVE(S)	To describe treatment reality (systemic treatments and sequential treatments) applied in German routine practice. EBC: To assess effectiveness of systemic treatment with cytotoxic, endocrine and targeted substances by various outcome parameters such as response rate (including pCR), event-free survival, overall survival; to assess effectiveness of therapy in distinct subgroups. ABC: To assess effectiveness of systemic treatment with cytotoxic, endocrine and signaling pathway inhibitors by various outcome parameters such as response rate, progressionfree survival, overall survival; to assess effectiveness of therapy in distinct subgroups
INTERVENTION(S)	Non-interventional
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Patients will be asked to give additional informed consent agreeing that their pre-existing 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 effectiveness of different treatments for EBC and ABC 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 (cytotoxic, endocrine, or targeted) for EBC or ABC • Patient who do not receive any systemic therapy for EBC or ABC

KEY INCLUSION CRITERIA	EBC cohort
	• Female and male patients with early breast cancer (stage I-III defined as breast cancer that has not spread beyond the breast or the axillary lymph nodes)
	• Patients at the start of their initial systemic treatment for EBC, i.e. at start of neoadjuvant treatment for patients receiving neoadjuvant therapy or start a adjuvant treatment if no neoadjuvant therapy is given. Treatment can be cytotoxic, endocrine, or targeted substances, whatever was given.
	
	ABC cohort
	• Female and male patients with advanced breast cancer (stage IV defined as synchrone or metachrone diagnosis of distant metastases at inclusion)
	• 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
	• Written informed consent
	  • Patients participating in the PRO module: signing of informed consent form and completion of baseline questionnaire before start of initial systemic treatment for EBC or systematic first-line treatment for ABC
	  • Patients not participating in the PRO module: within six weeks after start of initial systemac teratment for EBC or systemic first-line treatment for ABC

OUTCOME(S)	Response rate, event/progression free survival, overall survival
STATISTICAL ANALYSIS	Descriptive
SAMPLE SIZE	EBC cohort: 3000 patients (1500 Hormonreceptor-positive and Her2-negative, 750 Her2-positive, 750 triple negative) ABC cohort: 2000 patients (1000 Hormonereceptor-positive, Her2-negative, 500 Her2-positive, 500 triple-negative)
TRIAL DURATION	9 years (ABC) 8 years (EBC)

Registerstudie

AIO-DIG-MAM-0221/ass - DEfenseCOVID-19 – Ein deutschlandweites Register für alle Krebspatientinnen und Krebspatienten zur Erfassung der Auswirkungen der COVID 19 Pandemie

AIO-assoziierte-Studie

Studiennummer/-Code:	**AIO-DIG-MAM-0221/ass - DEfenseCOVID-19**	
Status:	in Rekrutierung	
Rekrutierungszeit:	von: 12/2020	bis: 12/2021
Anzahl Zentren:	monozentrisch; Einschluss deutschlandweit über e-consent	
Weitere Zentren:	keine, Unterstützer machen Patient*innen auf die Studie aufmerksam	
Anzahl Patienten:	aktuell eingeschlossen: 274	
Letzte Aktualisierung	18.05.2021	

Projektleiter	Prof. Dr. Peter A. Fasching Universitätsklinikum Erlangen Frauenklinik Universitätsstraße 21/23 91054 Erlangen
Leitung Projekt-management	Dr. Lena A. Wurmthaler Universitätsklinikum Erlangen Frauenklinik Universitätsstraße 21/23 91054 Erlangen
Kontaktperson	Prof. Dr. Peter A. Fasching: peter.fasching@uk-erlangen.de Stellvertretend: Dr. Lena A. Wurmthaler: lena.wurmthaler@uk-erlangen.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Digitalisierung.	

Arbeitsgruppe Neuroendokrine Tumoren/ Karzinoide

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

Studiennummer/-Code:	AIO-NET-0117/ass – RamuNET-Trial	
Status:	Genehmigung erfolgt – Initiierung der ersten Zentren im April 2019	
Rekrutierungszeitraum:	voraussichtliches Rekrutierungsende Q4/2022	
Patienten:	geplant: 45	aktuell eingeschlossen: 26
Zentren:	geplant: 8	initiiert: 7
Weitere Zentren:	Interessierte Zentren wenden sich bitte an Prof. Michl	
Letzte Aktualisierung	Oktober 2021	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Patrick Michl Universitätsklinikum Halle Universitätsklinik für Innere Medizin I Ernst-Grube-Straße 40 06120 Halle (Saale) Phone: +49 (0) 345 - 557 2661 Fax: +49 (0) 345 - 557 2253 E-Mail: patrick.michl@uk-halle.de
CONDITION	Pancreatic neuroendocrine tumors (pNET)
OBJECTIVE(S)	The aim of this study is to investigate whether ramucirumab in combination with 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. • 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. • Allergy against dacarbazine or ramucirumab • Current enrolment or participation within the last 4 weeks in a clinical drug trial • 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. • 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. • Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management • 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

	• Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy. • 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 • 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 • History of gastrointestinal perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation. • 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. • 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-G3 differentiated PNET excluding neuroendocrine carcinomas (NEC). Both non-functional and functional NET can be included. • Age: 18-75 years • Measurable disease (RECIST 1.1) • 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. • If the tumor biopsy is older than 6 months in progressive disease a rebiopsy is mandatory • ECOG 0-1 • Life expectancy > 12 weeks • 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). • 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) • Adequate bone marrow function (absolute neutrophil count >1,500/mm^3, platelets >100,000/mm^3, hemoglobin>9 g/dL) • 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. • Pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices) • 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. • Written informed consent
OUTCOME(S)	<u>Primary endpoint</u> • Disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria <u>Secondary endpoints</u> • Objective tumor response (ORR) • progression-free survival (PFS) • overall survival (OS)

	• toxicity • biochemical response (tumor marker chromogranin A; in cases of functional NET: gastrin, insulin etc.) • QoL (EORTC QLQ-C30 questionnaire) • 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. Primary endpoint is the disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria The sample size calculation follows an exact binomial single-stage design (A'Hern 2001) H_0: $p<=p_0=60\%$ versus H_1: $p>=p_1=80\%$, alpha=0.05, beta=0.1 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%. 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 Treatment per patient: until disease progression or intolerable toxicity Follow-up per patient: 24 months after begin of treatment. First patient in to last patient out (months): 36 Duration of the entire trial (months): 42 months Intended start date: 1st quarter 2018 Expected end of the study: 3rd quarter 2021
PARTICIPATING CENTERS	- UK Halle - UKE Hamburg - Zentralklinik Bad Berka - Charité - UKGM Standort Marburg - UK Ulm - 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

Studiennummer/-Code:	AIO-NET-0417/ass – COMPETE-Trial	
Status:	in Rekrutierung	
Rekrutierungszeitraum:		
Weitere Zentren:		
Zentren:	geplant: 59	initiiert: 59
Patienten:	geplant: 300	aktuell randomisiert: 267
Letzte Aktualisierung	Oktober 2021	

APPLICANT/ COORDINATING INVESTIGATOR	ITM Solucin GmbH/ Prof. Dr. Wolfgang Weber Technische Universität München
CONDITION	Well-differentiated neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET), with positive SSTR expression
OBJECTIVE(S)	**Primary objective** progression-free survival (PFS) **Secondary objectives** 1. overall survival (OS)
INTERVENTION(S)	- Slow intravenous infusion/injection (IV) of ^{177}Lu-edotreotide, - 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: 1. Known hypersensitivity to edotreotide or everolimus 2. Known hypersensitivity to DOTA, lutetium-177, or any excipient of edotreotide or everolimus or any other Rapamycin derivative 3. Prior exposure to any peptide receptor radionuclide therapy (PRRT) 4. Prior therapy with mTor inhibitors 5. Prior EFR (extended field radiation) to GEP-NET lesions within 90 days before randomisation or radioembolisation therapy 6. Therapy with an investigational compound and/or medical device within 30 days prior to randomisation 7. Indication for surgical lesion removal with curative potential 8. Planned alternative therapy (for the period of study participation) 9. Serious non-malignant disease 10. Clinically relevant renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments 11. Pregnant or breast-feeding women. 12. 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: 1. Histologically 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) 2. Measurable disease per RECIST 1.1Somatostatin receptor positive ($SSTR^+$) disease 3. Progressive disease based on RECIST 1.1. criteria as eviden-ced by two morphological imaging examinations made with the same imaging method (either CT or MRI)
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 prospective, randomised, controlled, 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).
SAMPLE SIZE	300
TRIAL DURATION	PFS will be assessed individually per patient from date of randomization until the date of first documented progression, assessed up to 30 months.

Interdisziplinäre Arbeitsgruppe Nierenzellkarzinom

Nierenzellkarzinom, 1st-line

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

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-NZK-0117/ass - SUNNIFORECAST	
Status:	Aktiv, in Rekrutierung	
Rekrutierungszeitraum	11/2017 – 12/2022	
Zentren:	geplant:	initiiert: ~25
Patienten:	geplant: 306	eingeschlossen: 273
Weitere Zentren:	Interessierte Zentren können sich melden	
Letzte Aktualisierung	September 2021	

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Lothar Bergmann Universitätsklinikum Frankfurt Medizinische Klinik II Theodor-Stern-Kai 7 60590 Frankfurt
Studienziele	**Primäres Studienziel:** OS Rate nach 12 Monate **Sekundäre Studienziele:** OS Rate nach 6 und 12 Monaten Dauer der Response (DOR) Progressionsfreie Überleben (PFS) Mediane Gesamtüberleben (mOS) Ojektive Responserate (ORR) Sicherheit und Tolerabilität der Therapien
Patientenzahl	Geplant: 306, Rekrutierend Teilnehmende Zentren (>30): Deutschland, Frankreich, Belgien, Niederlande, UK, Spanien, Tschechien).
Haupt-Einschlusskriterien	**Inclusion:** a) Subjects must have signed and dated an IRB/IEC approved written informed consent form i accordance with regulatory and institutional guidelines. This must be obtained before the pernformance of any protocol related procedures that are not part of normal subject care. b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study. 2. Target Population a) Histological confirmation of non-clear RCC with at least 50% non-clear cell component according to actual WHO classification36 b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC c) Karnofsky > 70% (See Appendix 2, 14.2) d) Measurable disease
Haupt-Ausschlusskriterien	**1. Target Disease Exceptions**

	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. b) Tumors with a clear-cell component of $\underline{\geq}$ 50% **Medical History and Concurrent Diseases** c) 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. d) 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. e) 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. f) 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. g) Uncontrolled adrenal insufficiency. h) 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 $QTcF = QT / 3\sqrt{RR}$ i) Poorly controlled hypertension (defined as systolic blood pressure (SBP) of $\geq$ 150 mmHg or diastolic blood pressure (DBP) of $\geq$ 90 mmHg), despite antihypertensive therapy. 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. k) History of cerebrovascular accident including transient ischemic attack within the past 12 months. l) History of deep vein thrombosis (DVT) unless adequately treated with low molecular weight heparin 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. n) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months. o) Serious, non-healing wound or ulcer. p) Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 30 days. q) Any requirement for anti-coagulation, except for low molecular weight heparin. r) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

	s) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). t) Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection. 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. v) Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug. 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. x) Receiving concomitant CYP3A4 inducers or strong CYP3A4 inhibitors y) Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the Standard of Care agent (eg, malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection). z) Hypersensitivity to Standard of Care agent or any of the excipients aa) Patients who were vaccinated with a live vaccine 2 weeks prior to the start of the CT **2. Physical and Laboratory Test Findings** a. Left ventricular ejection fraction (LVEF) less than the LLN as assessed by echocardiography or multigated acquisition (MUGA) scan. b. Any of the following laboratory test findings: 2. WBC < 2,000/mm^3 3. Neutrophils < 1,500/mm^3 4. Platelets < 100,000/mm^3 5. AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present) 6. Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL) 7. Serum creatinine > 2.5 x upper limit of normal (ULN) or creatinine clearance < 20 mL/min (measured or calculated by Cockroft-Gault formula): $\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$ $\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$ **3. Allergies and Adverse Drug Reaction** a) History of severe hypersensitivity reaction to any monoclonal antibody. **4. Other Exclusion Criteria** Subjects who are **incompetent** to understand and sign the informed consent.
Tumorevaluierung Criteria for evaluation	Tumor assessment with CT/MRT according to RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria and immune-related response criteria (irRECIST)
Rationale	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. Standard of Care (SOC) 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 or a combination of pembrolizumab + axitinib or avelumab + axitinib in first line therapy [PREPARE 2.0]

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-NZK-0115/ass - PREPARE	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 - 2023	
Zentren:	geplant: 100	initiiert: 41
Patienten:	geplant: 430	aktuell eingeschlossen: **48**
Weitere Zentren:	erwünscht	
Letzte Aktualisierung	Oktober 2021	

Study Type	Open-label, randomized, observational phase III study
Coordinating investigator (LKP)	Prof. Dr. med. Viktor Grünwald Univ.-Prof. für interdisziplinäre Uroonkologie Westdeutsches Tumorzentrum Innere Klinik (Tumorforschung) und Klinik für Urologie Universitätsklinikum Essen, Hufelandstr. 55 45147 Essen Telefon: +49 0201-723 85584 E-Mail: Viktor.Gruenwald@uk-essen.de
Sponsor:	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, info@aio-studien-ggmbh.de
Objectives	Primary objective: To determine the impact of a 24 weeks concomitant coaching on patient reported outcomes of patients receiving standard first-line treatment for mRCC with sunitinib or a combination of checkpoint inhibitor (CPI) + axitinib. Secondary objectives: Assessment of the impact of a 24 weeks concomitant coaching on additional QoL measures, patient compliance, efficacy and safety. Exploratory objectives: Assessment of inflammatory markers in tumor samples and serum.

Endpoints	<u>Primary endpoint:</u> QoL assessment during sunitinib treatment: Rate of responders to concomitant coaching assessed by the FKSI-15 questionnaire <u>Secondary endpoints:</u> • ORR according to RECIST 1.1 criteria • OS • PFS • Duration of treatment • Dose density of sunitinib • Rate of hospitalization irrespective of TEAEs • Treatment beyond progression • Further cancer treatment and time to first subsequent therapy (TFST) • 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) • Treatment Emergent Adverse Events according to CTC 4.03: • Frequency/incidence, severity, percentage reduction, time-to-event of ADRs, SAEs and specific TEAEs (e.g. hand-foot syndrome, diarrhea, stomatitis, fatigue, hypertension) • Reduction of grade 3/4 ADRs • Health related Quality of Life (FACT-G, EQ-5D) • Time to improvement or deterioration measured by HRQoL • Assessment of comorbidities by Charlson Comorbidity Index (CCI) and social status
Number of patients	N=430 total Currently recruited: **48**
Start date	Q1/2017
More centres?	Target number: 100 / Yes (currently **35** 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. **2.** Age ≥ 18 years at time of study entry. **3.** Advanced or metastatic renal cell carcinoma, not amendable to surgery with curative intent, rendering the patient eligible for 1st-line systemic treatment. **4.** Intended first-line treatment with sunitinib, with pembrolizumab plus axitininb or with avelumab plus axitinib. **5.** Documented progressive disease within 6 months prior to study inclusion. **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. **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. **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. 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, axitinib, pembrolizumab and avelumab for mRCC (except palliative radiotherapy). **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]. **3.** CNS metastases, unless local therapy has been for at least 3 month and patient does not require the use of steroids. **4.** Chronic liver disease with Child-Pugh B or C score **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). **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. **7.** Participation in another clinical study with an investigational product during the last 30 days before inclusion. **8.** Any previous treatment with a tyrosine kinase inhibitor or checkpoint inhibitor for metastatic disease. Adjuvant or neoadjuvant therapy for localized disease is permitted, provided that relapse occurred at least 6 months after last exposure. **9.** Previous enrollment or randomization in the present study (does not include screening failure). **10.** Involvement in the planning and/or conduct of the study (applies to both Pfizer staff and/or staff of sponsor and study site). **11.** Patient who might be affiliated or otherwise dependent on the sponsor, site or the investigator. **12.** Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities [§ 40 Abs. 1 S. 3 Nr. 4 AMG]. 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 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 offtreatment [4/2 schedule; total cycle length = 6 weeks]. or • avelumab: recommended dose of avelumab incombination with axitinib is 800 mg administered intravenously over 60 minutes every 2 weeks and recommended dose of axitinib 5 mg orally taken twice daily. or • pembrolizumab: recommended dose of pembrolizumab as part of combination therapy is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes and recommended dose of axitinib is 5 mg orally taken twice daily. 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. Concomitant coaching [primary intervention]: The corner stones of the pro-active coaching are as follows: • Patient education ○ Information on nature and severity of treatment emergent AEs ○ Information about remedies for TEAEs ○ Propagation and explanation of tests and treatment decisions

<table>
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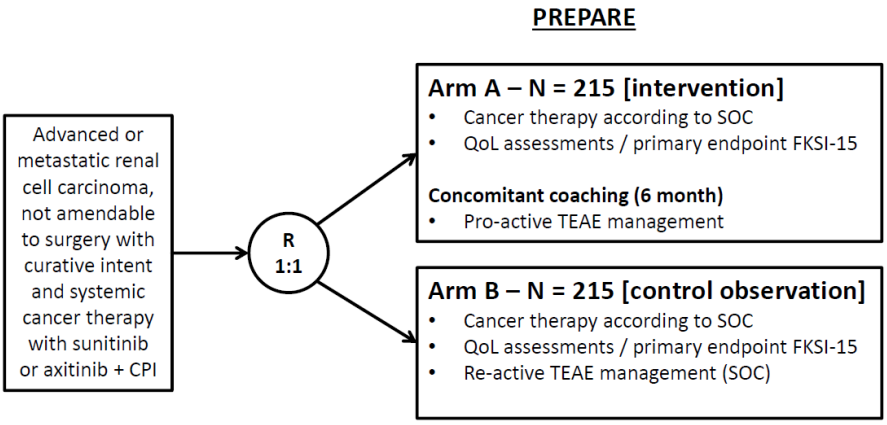
Patient instruction on self-care and preventive measures

Preemptive AE treatment strategies

Proactive assessment of treatment emergent AEs with emphasis on predefined ADRs of special interest (fatigue, diarrhea, stomatitis, skin toxicities, hypertension)

Supervision of reported ADR severity, ADR mitigation strategies and cancer treatment modification by treating physician
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)
Availability of coach for unscheduled contacts by phone (during normal business hours)



</td></tr>
<tr><td>Criteria for tumor evaluation</td><td>RECIST 1.1</td></tr>
<tr><td>Rationale</td><td>Clinical outcome has improved since the introduction of targeted therapies and the recent addition of immune-checkpont inhibitors 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. Sunitinibis associated with a response rate of approx. 30% (Motzer et al., 2013). However, 10-20% of patients are not able to tolerate treatment and stop early because of treatment-related toxicity (Motzer et al., 2013; 2007). For patients dropping-off therapy for intolerance, clinical outcome remains poor (Grünwald et al., 2013).

Recently, new 1st-line treatment strategies for advanced RCC combining the VEGFR inhibitor axitinib with immune checkpoint inhibitors (CPI) have emerged. Results of the Javelin renal 101 trial demonstrate that treatment efficacy of the avelumab + axitinib combination was superior to that of sunitinib, while toxicity profiles of the two regimens are very similar in terms of adverse event types and incidence (Motzer et al., 2019). Similar results have been reported for the combination of pembrolizumab + axitinib from the Keynote-426 study (BI et al., 2019).
As single agent CPI therapies have become a routine treatment in several tumor entities in recent years, immune-related adverse events (irAE) have become a part ofclinical reality. But importantly, irAE require management strategies that differ from AE caused by TKIs. When combining CPI with axitinib, the overlap of toxicities between both may mask irAE and may lead to delayed management, thereby furthering the risk of severe toxicity.

Proactive treatment has been shown to impact time to event and severity of adverse events (AE) in cancer patients treated by EGFR inhibition plus chemotherapy (Lacouture et al., 2010), justifying a structured approach to manage treatment-emergent adverse events (TEAEs) proactively. To date, prospective data for management of irAE is scarce, but type and severity of TEAEs render a proactive intervention of putative benefit.</td></tr>
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	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. 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.

Arbeitsgruppe Ösophagus-/ Magen-Karzinom

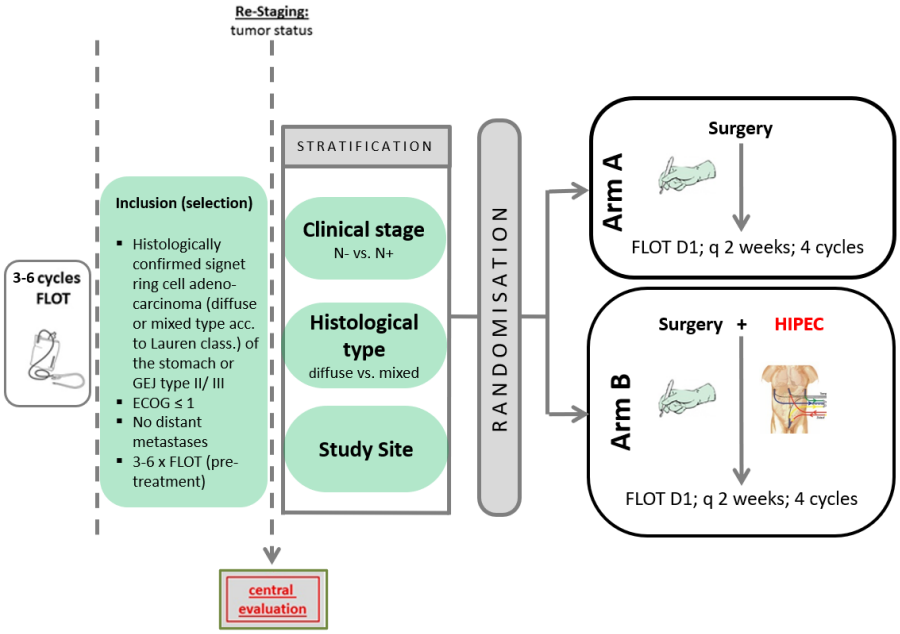
Lokal fortgeschrittenes Adenokarzinom des gastroösophagealen Übergangs oder Magens, perioperativ

AIO-STO-0319/ass: Preventive HIPEC in combination with perioperative FLOT versus FLOT alone for resectable diffuse type gastric and gastroesophageal junction Typ II/III adenocarcinoma - A phase III trial of the AIO/CAOGI/ACO (FLOT-9)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-STO-0319/ass - FLOT-9	
Status:	rekrutierend	
Rekrutierungszeitraum:	Studienstart 2020, 3,5 Jahre Rekrutierung	
Weitere Zentren:	auf Anfrage	
Zentren:	geplant: 20	initiiert: 17
Patienten:	geplant: 200	aktuell eingeschlossen: 15
Letzte Aktualisierung	08.10.2021	

STUDY TYPE	Multicenter, randomized, open label phase III study
PRINCIPAL INVESTIGATOR	Priv.Doz. Dr. med. Thorsten Oliver Götze Institute of Clinical Cancer Research (IKF) UCT- University Cancer Center Frankfurt Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Tel.: +49 69 7601-4187; Fax -3655 Email: goetze.thorsten@khnw.de
TRIAL OFFICE	IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
SPONSOR	Institut für klinisch-onkologische Forschung (IKF) Krankenhaus Nordwest gGmbH Steinbacher Hohl 2-26 60488 Frankfurt/Main
CONDITION	gastric and gastroesophageal junction Typ II/III
DESIGN	This is a multicenter randomized controlled and open-label study including patients with localized and locally advanced diffuse type adenocarcinoma of the stomach and Type II/ III GEJ scheduled to receive perioperative chemotherapy combined with intraoperative HIPEC procedure. The scope of the trial is to evaluate the efficacy as well as the safety and tolerability of the combination of perioperative chemotherapy combined with an intraoperative HIPEC for resectable diffuse and mixed type gastric and GEJ (types II/III) adenocarcinoma. Intraoperative hyperthermic chemotherapy is summarized under the abbreviation HIPEC in the following. Patients with localized and locally advanced diffuse type adenocarcinoma of the stomach and Type II/ III GEJ (i.e. ≥cT3 any N or any T N-positive) with exclusion of distant metastases and after receiving neoadjuvant FLOT-therapy will be included in this trial after a central review. All enrolled patients will have had diagnostic laparoscopy prior to start of FLOT and received 3-6 pre-operative cycles (de-escalation or dose modification allowed) 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) in the preoperative treatment phase. After completion of neoadjuvant FLOT-therapy followed by pre-operative tumor assessment, patients without disease progression (expected to be approximately 90% of the patients) will be included into the trial, stratified by initial clinical stage, histological type of tumor (mixed vs. diffuse) and HIPEC-center. They will be randomized 1:1 to receive either postoperative FLOT (Arm A) or postoperative FLOT + intraoperative HIPEC (Arm B).  The phase III design starts with a safety run-in phase. After 20 patients had curatively intendend resection in Arm B, an interim safety analysis is performed that shows feasibility, safety, and tolerability of Arm B. It is not planned to discontinue recruitment for the interim safety analysis.
INDICATION	resectable diffuse type gastric and gastroesophageal junction Type II/III adenocarcinoma
OBJECTIVE(S)	• To compare PFS in both trial arms • To compare OS in both trial arms • To compare the rates of peritoneal relapse after 2 and 3 years in both arms • To determine the safety of perioperative FLOT + HIPEC: Safety Objectives To evaluate the safety and tolerability of intraoperative HIPEC + perioperative FLOT compared with perioperative FLOT alone in patients with diffuse type adenocarcinoma of the stomach and Type II/ III gastroesophageal junction (GEJ), focusing on surgical serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities • To evaluate the perioperative morbidity and mortality of the regimens described above
INTERVENTION(S)	**Arm A (FLOT)** Surgery in Arm A is planned to occur 4 to 6 weeks after d1 of last FLOT. Surgery is carried out in kind of gastrectomy, transhiatal extended gastrectomy. Patients will receive 4 additional post-operative cycles (8 weeks)

	of FLOT in the post-operative treatment phase. Post-operative treatment should start 6 to 8 weeks, but at maximum 12 weeks after surgery. **Arm B (FLOT/ HIPEC)** Surgery in Arm B is planned to occur 4 to 6 weeks after d1 of last FLOT. Surgery is carried out in kind of gastrectomy, transhiatal extended gastrectomy. In the HIPEC group, an omentectomy (Standard in Gastrectomy procedure) and resection of the round ligament will be performed. Surgery will be combined with an intraoperative Hyperthermic IntraPEritoneal Chemotherapy (HIPEC). HIPEC itself can be performed in open- or closed-abdomen procedure (techniques are further defined in the protocol, section 13.5. After positioning of inflow catheter and drains intraabdominal cisplatin solution (75mg/m2 in NaCl 0.9%) will be administered at a temperature of 42°C for 90 minutes. Perfusion with cisplatin at a dose of 75 mg per square meter and at a flow rate of 1 liter per minute will be then initiated (with 50% of the dose perfused initially, 25% at 30 minutes, and 25% at 60 minutes). The perfusion volume will be adjusted such that the entire abdomen is exposed to the perfusate. The HIPEC procedure takes 120 minutes in total, including the 90-minute perfusion period. To prevent heat trauma to normal tissue the temperature of the silicon drain will not be increased over 42° C. 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. In both of the arms, tumor assessments (CT or MRI) and diagnostic laparoscopy are performed before randomization and prior to surgery, and then every 3 months (radiological tumor assessment) thereafter until progression/relapse, death or end of follow-up. A change from CT into MRI in the follow up period is possible at any time. During treatment, clinical visits (blood cell counts, detection of toxicity) occur prior to every treatment dose. Safety of FLOT/ HIPEC will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.
BACKROUND/RATIONALE	The main reason for treatment failure after curative surgical resection of gastric cancer is intra-abdominal spread. The main ways of dissemination of gastric cancer (GC) are the peritoneal fluids and haematic circulation. It has been demonstrated as peritoneal dissemination is more frequent than haematogenous metastases. The most common cause of tumor progression in advanced gastric cancer is peritoneal carcinosis (PC). Even following potentially curative surgery PC is frequent, and the prognosis of patients with PC from GC is extremely poor even. (Coccolini et al., 2016) In 40- 50% of these cases, a peritoneal seeding is the primary localization of recurrence. The likelihood for a peritoneal relapse is even much more common in the diffuse type, and ranges between 60 and 70%. (M. Jansen) On the other hand, intestinal type tumors tend to spread via hematogenous routes and show only a peritoneal seeding rate of 20-30%. Therefore, the outcome of diffuse type gastric cancer in particular remains unsatisfactory. This type is associated younger age; usually affects the body of the stomach, and presents shorter duration and worse prognosis compared with the intestinal type. Moreover, the response of peritoneal metastases to systemic chemotherapy is poor, mainly due to the presence of the “Peritoneal-plasma barrier” which isolates the peritoneal cavity from the effects of intravenous chemotherapy (Seshadri & Glehen, 2016). Systemic chemotherapy improves median survival in advanced and/or metastatic GC to not more than 12 months (Coccolini et al., 2015). The same

	gain in term of survival has not been described with macroscopic PC (Coccolini et al., 2015) due to the inadequate diffusion of systemic chemotherapy into the abdominal cavity (Coccolini et al., 2015). Taken together, it is clear that considerable investigation is still required to improve especially perioperative protocols in curative intend, particularly the postoperative component, in this aggressive subgroup of gastric cancer.
KEY EXCLUSION CRITERIA	1. Patients without neoadjuvant therapy or those who received a neoadjuvant therapy other than FLOT 2. Known hypersensitivity against 5-FU, leucovorin, oxaliplatin, or docetaxel 3. Other known contraindications against, 5-FU, leucovorin, oxaliplatin, or docetaxel 4. Clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV 5. Clinically significant valvular defect 6. Past or current history of other malignancies not curatively treated and without evidence of disease for more than 3 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix 7. Criteria of primary unresectability, e.g.: • Radiologically documented evidence of major blood vessel invasion or invasion of adjacent organs (T4b). • Patients with involved retroperitoneal (e.g. para-aortal, paracaval orinteraortocaval lymph nodes) or mesenterial lymph nodes (distant metastases!) 8. Other severe internal disease or acute infection 9. The patient has undergone major surgery within 28 days prior to enrollment. 10. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or ascites. 11. On-treatment participation in another interventional clinical study in the period 30 days prior to inclusion and during the study 12. Subject pregnant or breast feeding, or planning to become pregnant 13. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) 14. Any other concurrent antineoplastic treatment including irradiation 15. Known intraabdominal adhesion situs 16. Pre existing peritoneal seeding
KEY INCLUSION CRITERIA	1. Histologically confirmed, medically operable, resectable diffuse or mixed type (according to Lauren's classification) adenocarcinoma of the gastroesophageal junction (AEG II-III) or the stomach (uT3, uT4a, any N category, M0), or any T N+ M0 patient 2. Patient has received 3 to 6 cycles of neoadjuvant FLOT (de-escalation or dose modification allowed) 3. No preceding cytotoxic or targeted therapy other than neoadjuvant FLOT therapy 4. No prior partial or complete tumor resection 5. Female and male patients ≥ 18 and ≤ 70 years. Patients in reproductive age must be willing to use adequate contraception during the study (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 6. ECOG ≤ 1 7. 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 8. Laparoscopic exclusion of peritoneal carcinomatosis (in case of ascites, peritoneal masses, or if otherwise suspected clinically!) 9. Hematological, hepatic and renal function parameters adequate to allow surgical procedure and HIPEC at investigator´s discretion.

	10. Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures
OUTCOME(S)	**Primary efficacy endpoint** • PFS as evaluated by log rank test using KM-curves **Secondary efficacy endpoints** • OS, defined as the time from randomization to death from any cause, referring to the total number of enrolled and eligible patients of neoadjuvant chemotherapy with FLOT +/- HIPEC in diffuse type gastric and esophagogastric adenocarcinoma Type II/ III. • Rate of patients with peritoneal relapse at 2 and 3 years in both arms • PFS rates at 2, 3 & 5 years • OS rates at 3 & 5 years • Safety analysis of the combination of perioperative chemotherapy combined with intraoperative HIPEC • OS and PFS (medians and rates) according to subgroup (diffuse vs. mixed and gastric vs. GEJ type II/ III) • Quality of life (QoL) – EORTC QLQ C30 and EORTC QLQ STO22 • Post-operative morbidity at day 30 after surgery acc. Clavien–Dindo classification • P.o. pain acc. EVA- scale
SAMPLE SIZE	A total of n = 200 [HR 0.65] patients with diffuse type adenocarcinoma of the stomach and GEJ Type II/ III will be included in the study. The sample size was based on the data of the phase III results of the FLOT 4 trial.
TRIAL DURATION	Recruitment period will last 42 months (approximately 40 patients per year). Total study duration is 66 months (42 months recruitment plus 24 months follow up after last patient in). The study can be analyzed earlier or later depending on the number of events observed.
PARTICIPATING CENTERS	Up to 20 sites in Germany
FURTHER CENTERS DESIRED?	yes
NUMBER of PATIENTS	N=200

Lokal fortgeschrittenes, resektables Adenokarzinom des gastroösophagealen Übergangs, neoadjuvant

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

Studiennummer/-Code:	AIO-STO-0118 // RACE	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2020 bis voraussichtlich 2023	
Zentren:	geplant: 40	initiiert: 31
Patienten:	geplant: 340	aktuell eingeschlossen: 110
Weitere Zentren:	sind möglich	
Letzte Aktualisierung	Oktober 2021	

STUDY TYPE	Multicenter randomized phase III
PRINCIPAL INVESTIGATOR	Prof. Dr. Ralf-Dieter Hofheinz TagesTherapieZentrum am Interdisziplinären Tumorzentrum Universitätsmedizin Mannheim der Universität Heidelberg Theodor-Kutzer Ufer 1-3, Haus 9, 68167 Mannheim Tel: +49 621 383 2855 Email: ralf.hofheinz@umm.de
TRIAL OFFICE	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt/Main Martin Walker Tel: +49 69 / 7601-4571 Email: walker.martin@ikf-khnw.de
SPONSOR	Ruprecht-Karls Universität Heidelberg Represented by the chancellor Dr. Holger Schroeter Seminarstraße 2, 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) 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) Arm B (experimental arm)

	Two cycles of neoadjuvant induction chemotherapy with FLOT (5-FU 2600 mg/m2 d1, folinic acid 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)
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. 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). 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. In addition to addressing clinical questions, companion studies are foreseen: The study also aims at collecting tissue and liquid biopsies including circulating tumor cells, for translational research. Additional substudies will address questions of biomarker use and genomic alterations complimenting the well annotated clinical information and follow up data from the clinical trial. This could be a first step towards finding molecular predictors of response to different neoadjuvant therapies and potentially offer a molecular method of stratifying which patients will benefit the most from specific neoadjuvant therapies.
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 • Staging according to TNM classification assessed by endoscopic ultrasound, spiral computed tomography of the chest and abdomen • Patients must be surgical candidates as determined by the treating surgeon • ECOG performance status 0-1 • Age 18 years and above • Adequate hematologic and liver and renal function • Consent to biomarker analyses on tumor tissue and blood
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)

	• Known hypersensitivity /contraindications against 5-FU, folinic acid, oxaliplatin or docetaxel • Clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV • Clinically significant valvular defect • 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 • Other severe disease or acute infection • Peripheral polyneuropathy > NCI Grade II according to CTCAE version 4.0 • Participation in another clinical trial in the period 30 days prior to inclusion and during the study • Subject pregnant or breast feeding • Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) • Any other concurrent antineoplastic treatment including irradiation
OUTCOME(S)	• Progression-free survival • Overall survival including survival rates after 1, 3 and 5 years • R0 resection rate • Number of harvested lymph notes • Site of tumor relapse. • Perioperative complication and mortality rate • Safety/toxicity as assessed by NCI CTC criteria • Quality of life (QoL) by using the EORTC QLQ- C30 and the esophagogastric module Oes24
STATISTICAL ANALYSIS	Efficacy/test accuracy: The primary aim is to compare PFS between both study groups. Description of the primary efficacy/test accuracy analysis and population: PFS will be compared between both study groups using a logrank test stratified for tumor site on a two-sided level of significance of 5% following the intention-to-treat principle. Kaplan-Meier curves will be shown and the hazard ratio will be calculated. Safety: Absolute and relative frequencies of adverse events will be presented for both treatment groups and for relevant subgroups. Estimation of confidence intervals for event probabilities; Fisher's exact test for group comparisons. Secondary endpoints: Descriptive statistics; 95% confidence intervals for relevant quantities and effect sizes; analysis of overall survival as described for PFS; stratified Chi-squared tests for comparison of categorical measures (response rate, R0 resection rate); linear regression for comparison of continuous outcomes (QoL scores)

Limitiert metastasiertes Adenokarzinom des Magens oder gastroösophagealen Übergangs, 1st-line

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

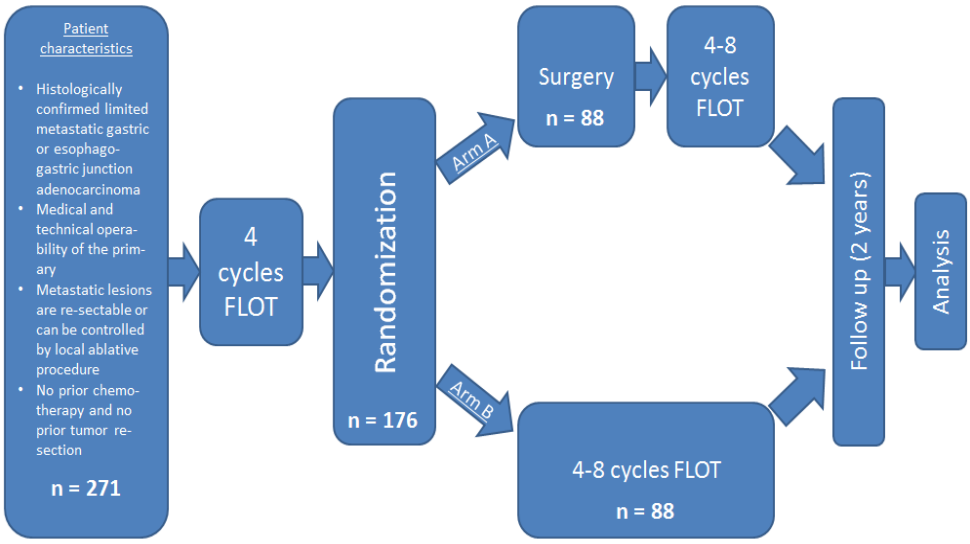
AIO-Studie

Studiennummer/-Code:	AIO-STO-0215 - RENAISSANCE / FLOT5	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2016 - 2021	
Zentren:	geplant:	initiiert:
Patienten:	geplant: 176 randomisierte Patienten aktuell eingeschlossen: 151 aktuell randomisiert: 111	
Weitere Zentren:	Weitere Zentren auf Anfrage	
Letzte Aktualisierung	30.09.2021	

Trial type	Prospective, randomized, multicentre, open label, phase III trial
Coordinating investigators	Prof. Dr. med. Salah-Eddin Al-Batran (LKP) Institut für Klinisch-Onkologische Forschung (IKF) Krankenhaus Nordwest UCT – Universitäres Centrum für Tumorerkrankungen Frankfurt Steinbacher Hohl 2-26, 60488 Frankfurt Tel. 069/7601-4420, Fax 069/7601-3655, albatran.salah@khnw.de Prof. Dr. med. Stefan P. Mönig Hôpitaux Universitaires de Genève, Service de Chirurgie viscéral stefan.moenig@hcuge.ch
Sponsor of the Study according to AMG	Institute of Clinical Cancer Research (IKF) Krankenhaus Nordwest gGmbH Steinbacher Hohl 2-26 60488 Frankfurt/Main
Study Management	Ulli S. Bankstahl Dr. Claudia Pauligk Institute of Clinical Cancer Research (IKF) UCT- University Cancer Center Frankfurt, Krankenhaus Nordwest Steinbacher Hohl 2-26, 60488 Frankfurt am Main Tel.: +49 69 7601-4596, -3906; Fax -3655 Email: bankstahl.ulli@khnw.de; pauligk.claudia@khnw.de
Medical condition	Limited metastatic adenocarcinoma of the stomach or esophagogastric junction (modified Flot3 arm B trial population)
Objective(s)	The aim of the study is to investigate whether induction chemotherapy followed by resection of the primary tumor (and eventually the metastases) prolongs overall survival with maintained quality of life compared to chemotherapy alone (the current standard) in previously untreated patients with synchronously limited metastatic esophagogastric adenocarcinoma. The primary endpoint is overall survival.
Intervention(s)	Experimental intervention/index test: 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. Control intervention/reference test: Arm B: Patients will receive 8 to 12 cycles of FLOT for palliation (current standard). Follow-up per patient: Survival status will be assessed every 3 months for up to 5 years after randomization. Duration of intervention per patient: Basically, a total treatment of 8-12 cycles FLOT (16 to 24 weeks) will be administered. Experimental and/or control off-label or on-label in Germany: not applicable
Key inclusion and exclusion criteria	Key inclusion criteria: - Histologically confirmed limited metastatic gastric or esophagogastric junction adenocarcinoma. - Medical and technical operability of the primary (central evaluation). - 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. - No prior chemotherapy and no prior tumor resection. Key exclusion criteria: - Medical inoperability. - Inability to understand the study and/or comply with the protocol procedures. - Extensive metastatic status or cM0. - Secondary malignancy < 3 years ago.
Outcome(s)	Primary efficacy endpoint: Overall survival (OS) 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 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 Duration of the entire trial (months): 72 Recruitment period (months): 48
Anzahl eingeschl. Pat.	141 eingeschlossen, 108 randomisiert (Stand 23.10.2020)

Study-Design: FLOT5



Lokal fortgeschrittenes oder metastasiertes Adenokarzinom

AIO-STO-0417: Modified FOLFOX plus/minus Nivolumab and Ipilimumab vs. FLOT plus Nivolumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction – A randomized phase 2 trial. [MOONLIGHT]

AIO-Studie		
Studiennummer/-Code:	AIO-STO-0417 - MOONLIGHT	
Status:	Rekrutierung Arm A/B und A1/A2 abgeschlossen Rekrutierung Arm C seit 09/2021 geöffnet	
Rekrutierungszeitraum	2018 - 2022	
Weitere Zentren:	Nicht benötigt	
Zentren:	geplant: 30	initiiert: 27
Patienten:	geplant: 257	aktuell eingeschlossen: 218
Letzte Aktualisierung	Oktober 2021	

Study type	Randomized, open labelled, multicenter phase II trial followed by a non-randomized arm
Lead Coordinating Investigator	Prof. Dr. Salah-Eddin Al-Batran Krankenhaus Nordwest, Institut für Klinisch-Onkologische Forschung, Steinbacher Hohl 2-26 60488 Frankfurt am Main Tel.: +49 69 7601-4420; Fax -3655 Email: albatran@khnw.com
Deputy Lead Coordinating Investigator	Prof Dr. Sylvie Lorenzen Klinikum rechts der Isar III. Medizinische Klinik des Klinikums rechts der Isar Ismaninger Str. 22 81675 München

	Tel.: +49 89 / 4140-9696; Fax -4879 Email: Sylvie.Lorenzen@mri.tum.de
Sponsor Project Management Sponsor	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Sabine Junge Tel: +49 69 / 76 01-4186 Email: junge.sabine@ikf-khnw.de
Objectives / Endpoints (efficacy, safety)	Primary endpoint: PFS based on the ITT population for patients treated with mFOLFOX plus Nivolumab plus Ipilimumab (Arm A) vs. patients treated with mFOLFOX alone (Arm B) and progression-free survival rate (PFS@6) for Arms A2 and C. Secondary endpoints: • Progression Free Survival acc. to RECIST v1.1 for Arms A1, A2 and C • Progression Free Survival rate at 6 months (PFS@6) for Arms A and B • Overall Response Rate (ORR) according to RECIST v1.1 • Duration of response and disease stabilization • Overall survival (OS) • Subgroup analysis including PFS and OS by PD-L1 expression status • Safety (according to NCI-CTCAE V 4.03) and tolerability • Quality of life (EORTC QLQ-C30). The QoL analyses will include QoL mean values, QoL response and time to symptom deterioration (TTSD) • 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	Rationale for the currently recruiting FLOT arm: Emerging data from recent phase III trials indicate that immune checkpoint inhibitors such as Nivolumab and Pembrolizumab prolong OS and PFS when added to the doublet chemotherapy. However, the extent of improvement regarding PFS is smaller than expected and if administered as monotherapy, there is an increased early mortality with the checkpoint inhibitors as compared with chemotherapy (crossing survival curves) (Tabernero et al. 2019; Janjigian et al. 2021, Kato et al. 2020). This is most likely explained by the fact that patients need time to establish antitumoral immunity, while some patients with aggressive disease experience early disease progression and death. This provides a rationale to test whether the intensification of chemotherapy using a triplet (mFOLFOX plus Docetaxel = FLOT) instead of the doublet, while reducing immunotherapy to Nivolumab instead of Nivolumab and Ipilimumab would be more beneficial and safer. Therefore, Arm C is designed to evaluate the efficacy of the combination of FLOT plus Nivolumab in the same patient group of the other study arms and descriptively compare this treatment with mFOLFOX plus Nivolumab plus Ipilimumab (Arm A) and with mFOLFOX alone (Arm B). As our study generally aims at gaining insights into the potentially most optimal chemo-immunotherapy regimen (therapy optimization) for a future trial, the implementation of Arm C fits well into the concept of the trial. With Arm C our trial evaluates three variations for the concept of immunochemotherapy: chemotherapy doublet plus immunotherapy doublet administered in parallel, chemotherapy doublet plus immunotherapy doublet administered sequentially, and chemotherapy triplet plus immune monotherapy administered in parallel. Because Arms A and B are fully recruited, it is not possible to perform a randomized comparison for Arm C. However, using the patients from Arms A and B as a comparator is still better than historical controls as these patients

	are treated by the same centres, under the same therapeutic and diagnostic guidelines, and in a close time period. It is important to note that FLOT is a well-established standard of care triplet regime in both, the neoadjuvant and metastatic settings. Accordingly, according to current S3 guidelines, docetaxel-containing triplet therapy such as FLOT can be considered for patient treatment, based on numerous studies on this field (e.g. van Cutsem et al., 2006 and Wagner et al., 2017). Approximately 20-30% of patients with mGC in the US (Davis et al NCCN Network Annual Conference and Abrams, ESMO GI 2016# PD-034) and a comparable proportion of patients in Germany receive a taxane-containing triplet as first-line therapy. Rationale for this in most cases is an expected faster and more frequent treatment response, which is crucial for the therapy choice especially for patients with a high remission pressure.
Population	Patients with advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction are eligible for this study.
Inclusion/exclusion criteria	Inclusion Criteria: 1. All subjects must have inoperable, advanced or metastatic GC or GEJ adenocarcinoma. 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. 3. Subject must be previously untreated with systemic treatment given as primary therapy for advanced or metastatic disease. 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. 5. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization. 6. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D). 7. ECOG performance status score of 0 or 1 (Appendix B). 8. Life expectancy > 12 weeks 9. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03): a. WBC ≥ 2000/uL b. Neutrophils ≥ 1500/µL c. Platelets ≥ $100x10^3$/µL d. Hemoglobin ≥ 9.0 g/dL e. Serum creatinine ≤ 1.5 x ULN f. AST ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastases are present) g. ALT ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastases are present) h. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN) 10. Males and Females* ≥ 18 years of age *There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently. 11. 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. 12. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study. 13. 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. 14. 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. 15. 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) 2. 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. 3. 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. 4. 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. 5. 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. 6. 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. 7. > Grade 1 peripheral neuropathy according to CTCAE version4.03 8. Known Dihydropyrimidine dehydrogenase (DPD) deficiency 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. 10. Ascites which cannot be controlled with appropriate interventions. 11. Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry; congestive heart failure NYHA grade 3 and 4 12. Significant acute or chronic infections including, among others: a. Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

	b. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection. 13. History of allergy or hypersensitivity to study drugs or any constituent of the products 14. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 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].
Investigational and control drugs	Study drugs: Nivolumab and Ipilimumab Study treatment: FOLFOX + Nivolumab and Ipilimumab; sequential therapy with FOLFOX + Nivolumab and Ipilimumab; FLOT + Nivolumab
Investigational and Control Arm, Dose, regimen, treatment cycle	**Treatment: Arm A/A1*** (this therapy arm is already closed) 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 2400 mg/m² IV continuous infusion over 44 hours (day1+2) every 2 weeks until disease progression or inacceptable toxicity or end of study treatment. Chemotherapy can also be administered per local standard. + Nivolumab 240mg “Flatdose” i.v. d1 every 2 weeks + Ipilimumab 1mg/kg i.v. d1 every 6 weeks **Treatment: Arm A2 (“sequential”)** (this therapy arm is already closed) Three cycles of induction chemotherapy with FOLFOX: Oxaliplatin 85 mg/m², leucovorin 400 mg/m2 and fluorouracil 400 mg/m² administered IV on Day 1 followed by fluorouracil 2400 mg/m² IV continuous infusion over 44 hours of each treatment cycle. Cycles are repeated every 2 weeks. Chemotherapy can also be administered per local standard. Followed by immunotherapy consisting of 4 administrations of Nivolumab at 240mg “Flatdose” i.v. d1 every 2 weeks and 2 administrations of Ipilimumab at 1mg/kg i.v. d1 every 6 weeks Repetition of chemotherapy and immunotherapy: The above described therapy sequence consting of 3 cycles of FOLFOX followed by immunotherapy may be repeated starting two weeks after last administration of immunotherapy once, or, if medically reasonable, for an unlimited number of repetitions upon investigator decision. However, repetition of chemotherapy after the first 3 cycles is optional and may be skipped. After completion or discontinuation of chemotherapy, immunotherapy will be continued consisting of: Nivolumab at 240mg “Flatdose” i.v. d1 every 2 weeks and Ipilimumab at 1mg/kg i.v. d1 every 6 weeks **Standard Treatment Arm B** (this therapy arm is already closed) 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 2400 mg/m² IV continuous infusion over 44 hours (day1+2) every 2 weeks until disease progression or inacceptable toxicity or end of study treatment. Chemotherapy can also be administered per local standard. **Treatment Arm C**** (currently recruiting) Nivolumab 240mg “Flatdose” i.v. d1 every 2 weeks + FLOT: Docetaxel 50mg/2, Oxaliplatin 85 mg/m², leucovorin 200 mg/m² on day 1 and fluorouracil 2600 mg/m² IV continuous infusion over 24 hours of each treatment cycle. Cycles are repeated every 2 weeks until disease progression or inacceptable toxicity or end of study treatment. After completion or discontinuation of chemotherapy, immunotherapy may be continued consisting of:

	Nivolumab at 240mg “Flatdose” i.v. d1 every 2 weeks Chemotherapy can also be administered per local standard. Therapy can also be splitted, administering nivolumab on day one and FLOT starting at day two of the cycle. Duration of treatment Treatment with each of the components FOLFOX, FLOT, 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. If one component of the treatment is stopped for any cause, the other components can be continued. *Arm A1 is identical to Arm A. Patients are randomized concurrently with Arm A2 after recruitment of the first 118 patients into Arm A and B is completed. A1 will comprise 30 patients. ** Arm C will recruit 50 patients.
Statistical considerations	Arm A vs. B: PFS analysed according to the ITT principle is the primary efficacy endpoint. The expected median PFS in the standard arm is 5.5 months; the expected median PFS in the experimental arm is 8.5 months. We hypothesize that the experimental therapy is associated with clinically relevant improvement according to a HR of 0.68. In the frame of a phase II testing, the use of a one-sided significance level of 10% is justified. Based on this, 118 randomized subjects (59 in the control and 59 in the experimental treatment group) will be enrolled to provide 80% power for detecting an average HR of 0.68 using the log rank test at a one-sided type I error of 10% and assuming a 5% drop out rate. The sample size calculation is based on 2 years recruitment time and 1 year follow up time after last patient-in. So the minimum follow-up time is 3 years. 1:1 Randomization will be performed according to the following stratification criteria: • ECOG PS (0 vs 1) • Tumor status (prior resection vs. no prior resection) Arm A1 vs. A2 To evaluate if a sequential treatment of mFOLFOX plus Nivolumab plus Ipilimumab (Arm A2) is less toxic but equally effective as parallel treatment of mFOLFOX plus Nivolumab plus Ipilimumab (Arm A and A1) 57 patients are needed using a one-stage Fleming design (Fleming 1982) with following assumptions: • The sequential therapy would be rated as unacceptable, if the actual PFS rate at 6 months (PFS@6) was only 47% or lower (corresponding to the median PFS of Arm B of 5.5 months) • The sequential therapy would be considered to be a promising candidate for further development, if the true PFS@6 amounted to 61% or higher (corresponding to the expected median PFS of Arm A of 8.5 months) • Probability to accept the sequential therapy as effective, in spite of a true PFS@6 of <47%: 10% (type I error) • Probability to reject the sequential therapy as ineffective (<47%), although the true PFS@6 is promising (>61%): 20% (type II error, corresponding to a power of 80%) Allowing for two non-informative drop-outs, 59 patients have to be recruited into Arm A2. 30 patients are to be allocated to the reference arm A1, according to the 1:2 randomization. The same stratification factors (ECOG PS and tumor status) as in the randomization of arms A and B are applied. The final conclusion for the sequential treatment will depend on the definite PFS rate and its confidence interval, the respective findings in the reference arm, as well as the information on type, frequency and severity of toxicities.

<table>
<tr><td></td><td>Arm C:
Based on emerging data from recent phase III trials, immune checkpoint inhibitors such as Nivolumab and Pembrolizumab added to the doublet chemotherapy prolong OS and PFS, but the extent of improvement regarding PFS is smaller than expected and if administered as monotherapy, there is a an increased early mortality (crossing survival curves) with the checkpoint inhibitors as compared with chemotherapy (Tabernero et al. 2019; Janjigian et al. 2021; Kato et al. 2020). This is most likely explained by the fact that patients need time to establish antitumoral immunity, while some patients with aggressive disease experience early disease progression and death. This provides a rationale to test whether the intensification of chemotherapy using a triplet (mFOLFOX plus Docetaxel = FLOT) instead of the doublet, reducing immunotherapy to Nivolumab instead of Nivolumab and Ipilimumab would be more beneficial and safer. Therefore, Arm C is designed to evaluate the efficacy of the combination of FLOT plus Nivolumab in the same patient group and descriptively compare this treatment with mFOLFOX plus Nivolumab plus Ipilimumab (Arm A) and with mFOLFOX alone (Arm B). The sample size is chosen according to clinical reasoning. No statistical hypothesis testing is planned. A sample size of 50 patients to be treated with FLOT plus Nivolumab is regarded sufficient to get a first sight into the efficacy and to obtain data on the feasibility, safety and toxicity of the the study treatment.
As our study generally aims at gaining insights into the potentially most optimal chemo-immunotherapy regimen (therapy optimization) for a future trial, the implementation of Arm C fits well into the concept of the trial. With Arm C our trial evaluates three variations for the concept of immunochemotherapy: chemotherapy doublet plus immunotherapy doublet administered in parallel, chemotherapy doublet plus immunotherapy doublet administered sequentially, and chemotherapy triplet plus immune monotherapy administered in parallel.
Because Arms A and B are fully recruited, it is not possible to perform a randomized comparison for Arm C. However, using the patients from Arms A and B as a comparator is still better than historical controls as these patients are treated by the same centres, under the same therapeutic and diagnostic guidelines in a close time period.
The KEYNOTE-062 study (Tabernero et al. 2019) reported a median PFS of 6.9 months for the combination of Pembrolizumab plus chemotherapy while the Checkmate 649 (Janjigian et al. 2021) reported a median PFS of 7.7 months for the combination of Nivolumab plus mFOLFOX. Therefore, we expect the true median PFS of FLOT plus Nivolumab to be between 8 and 9 months corresponding to PFS rates at 6 months of about 59% and 63%.
The final conclusion for the combination of FLOT plus Nivolumab will depend on the definite PFS rate at 6 months (and its confidence interval), the respective findings in the arms A and B, as well as the information on type, frequency and severity of toxicities. The precision of the estimation of the PFS@6 is provided by confidence intervals (CIs) in the following table, for different actual PFS@6 findings:
<table>
<tr><th>PFS@6</th><th>Exact 95% CI</th></tr>
<tr><td>29/50 (58%)</td><td>43.2% … 71.8%</td></tr>
<tr><td>30/50 (60%)</td><td>45.2% … 73.6%</td></tr>
<tr><td>31/50 (62%)</td><td>47.2% … 75.4%</td></tr>
<tr><td>32/50 (64%)</td><td>49.2% … 77.1%</td></tr>
</table>
</td></tr>
<tr><td>Key dates</td><td>FPFV: Q2 2018
Planned time for recruitment: 45 months
Follow-up: every 2 months for up to 1 year after last patient-in.</td></tr>
</table>

AIO-STO-0121/ass – Phase IIA trial of short-term chemotherapy and pembrolizumab, followed by Pembrolizumab and OLaparib as firstline therapy in Her-2 negative gastric/gastroESophageal-juncTion (GEJ) AdenocaRcinoma POLESTAR

AIO-assoziierte Studie	
Studiennummer/-Code:	**AIO-STO-0121/ass - POLESTAR**
Status:	in Vorbereitung
Rekrutierungszeitraum	Geplant: 2022 - 2023
Weitere Zentren:	Nicht benötigt
Zentren:	geplant: 10
Patienten:	geplant: 31
Letzte Aktualisierung	Oktober 2021

Study type	Interventional, single-arm, open-label, multicenter phase II trial
Lead Coordinating Investigator	PD Dr. med. Georg Martin Haag Nationales Centrum für Tumorerkrankungen Universitätsklinikum Heidelberg Im Neuenheimer Feld 460 69120 Heidelberg
Sponsor Project Management Sponsor	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Dipl.-Biol Kristina Ihrig, Dr. Claudia Pauligk Tel: +49 69 / 76 01-3906 Email: Ihrig.kristina@ikf-khnw.de; pauligk.claudia@ikf-khnw.de
Objectives / Endpoints (efficacy, safety)	The primary objective of this phase II study is to assess the overall survival at 1 year. Secondary objectives are the assessment of the objective response rate, the best overall response, treatment feasibility rate along with safety and toxicity of the treatment. Primary endpoint • Overall survival (OS) rate at 1 year Secondary Endpoints • Progression-free survival, defined as time from enrollment to disease progression according to RECIST 1.1 and iRECIST. • Objective response rate (ORR), defined as the percentage of patients with complete response (CR) or partial response (PR) according to RECIST 1.1 and iRECIST. • Best overall response, defined as the best response recorded from enrollment to treatment discontinuation for any reason. • Feasibility rate, defined as 1 - severe toxicity/withdrawal rate before the fourth cycle of pembrolizumab/olaparib has been completed. • Safety and toxicity: Adverse events will be recorded and graded according to version 5.0 of National Cancer Institute Common Toxicity Criteria (NCI-CTC).
Background / Rationale	Pembrolizumab as monotherapy has shown non-inferiority in comparison to a platinum-based chemotherapy in Her-2 negative patients with a PD-L1 CPS ≥ 1. However, response rate and progression-free survival are inferior in comparison to a platinum-based chemotherapy. In addition, early mortality during the first year is higher with pembrolizumab than with chemotherapy. Early results from Checkmate 649 and Keynote 590 suggest a superior outcome of chemotherapy combined with a PD-1 inhibitor, however the

	optimal duration of chemotherapy is unknown, continued chemotherapy is associated with significant toxicity. HRD alterations are found in approximately 15-20% of patients with esophagogastric adenocarcinoma, providing a strong rationale for the use of a PARP inhibitor in this disease. Given the limited efficacy of these agents in patients with platinum-refractory disease, an early use in patients with platinum-sensitive disease should be preferred. Preclinical and clinical data suggest a synergism by combining a PARP inhibitor with a PD-l/PD-L1 inhibitor: • Impaired DNA repair induced by PARP inhibitors could generate DNA damage that leads to increase of the neoantigen load [Brown et al. 2018]. • DNA damages and DDR deficiencies induce the activation of cGAS–STING and NF-κB pathways, leading to inflammation and infiltration of tumors by immune cells across multiple types of cancers, a prerequisite of tumor-killing effect of ICI [Strickland et al. 2016]. PARP inhibitors lead to an upregulation of PD-L1 expression, which might improve activity of PD-1 inhibition [Jiao et al. 2017]. • The antitumor activity of PARPi has been observed in patients with platinum-sensitive tumors regardless of BRCA1/2 mutation or HRD status, suggesting an alternative mechanism unrelated to conventional lethal synthetic-mediated cytotoxic effects [Mirza et al. 2016]. As a consequence, there is a strong rationale for the combination of olaparib and pembrolizumab in patients with platinum-sensitive, Her-2 negative esophagogastric adenocarcinoma independent of PD-L1 CPS status. An initial short-term chemotherapy could be helpful to ensure an early disease control in patients with a high tumor load before efficacy of immunotherapy can be observed, thus avoiding a symptomatic deterioration during the first weeks of treatment.
Population	Patients with metastatic or locally unresectable, histologically confirmed Her-2 negative adenocarcinoma of the gastroesophageal junction (AEG I-III according to Sievert´s classification) or the stomach.
Inclusion/exclusion criteria	**Patients must meet all of the following <u>Inclusion Criteria</u> for trial participation:** 1. Metastatic or locally unresectable, histologically confirmed Her-2 negative adenocarcinoma of the gastroesophageal junction (AEG I-III according to Sievert´s classification) or the stomach. 2. Adjuvant/neoadjuvant or perioperative chemotherapy or chemoradiotherapy must have been finished at least 6 months before start of the study intervention. 3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. 4. Ability for oral intake of the study drug. 5. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of esophagogastric adenocarcinoma will be enrolled in this study. 6. Male participants: A male participant must agree to use a contraception as detailed in the protocol during the treatment period and for at least 6 months after the last dose of study intervention and refrain from donating sperm during this period. 7. Female participants: A female participant is eligible to participate if she is not pregnant , not breastfeeding, and at least one of the following conditions applies: a. Not a woman of childbearing potential (WOCBP) as defined in protocol OR b. A WOCBP who agrees to follow the contraceptive guidance as given in protocol during the treatment period and for at least 6 months after the last dose of study intervention. 8. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

9. Have measurable or evaluable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
10. Have provided archival tumor tissue sample. FFPE tissue blocks are preferred to slides.
11. Have adequate organ function as defined in the following table. Specimens must be collected within 14 days prior to the start of study intervention.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1500/µL
Platelets	≥ 100 000/µL
Hemoglobin	≥ 9.0 g/dL or ≥ 5.6 mmol/L[a]
Renal	
Measured or calculated[b] creatinine clearance	≥ 50 mL/min
Hepatic	
Total bilirubin	≤ 1.5 ×ULN OR direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN (≤ 5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.
[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within the last 2 weeks.
[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Patients who meet at least one of the following Exclusion Criteria are not eligible for trial participation:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to start of study intervention. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137). Has received any previous treatment with a PARP inhibitor, including Olaparib.
3. Has received prior systemic anti-cancer therapy for metastatic or locally advanced (irresectable) disease. A prior neoadjuvant or adjuvant chemotherapy is allowed (see inclusion criterion 2)
4. Persistent clinically relevant toxicities, CTCAE Grade > 2 caused by previous cancer treatment.
5. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.
6. Participant received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 28 days prior to the first dose of study intervention.
7. Participant is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption.

	8. Major surgery within 2 weeks of starting study intervention and patients must have recovered from any effects of any major surgery. 9. Participant is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 2 weeks. *Note: a current list of strong/moderate inhibitors of CYP3A4 can be found at the following website:* https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers 10. Participant is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (eg. bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents. *Note: a current list of strong/moderate inducers of CYP3A4 can be found at the following website:* https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers 11. Concomitant use of drugs inhibiting DPD activity (including sorivudine, brivudine), the required wash out phase is 4 weeks before start of the study intervention. 12. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation > 500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome. 13. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed. 14. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention. 15. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. 16. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. 17. Participant has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML. 18. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously completely resected brain metastases may participate if there is no sign of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention. 19. Has severe hypersensitivity (≥ Grade 3) to FOLFOX or CAPOX-based chemotherapy, olaparib, pembrolizumab and/or any of its excipients. 20. Known DPD deficiency. Patients with a reduced DPD activity (CPIC activity score of 1.0-1.5) might participate in the study and receive a reduced dosage of 5-FU/capecitabine after discussion with the coordinating investigator and sponsor [https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/] 21. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g.,

	thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. 22. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. 23. Has an active infection requiring systemic therapy. 24. Has a known history of Human Immunodeficiency Virus (HIV) infection (known HIV1/HIV2 antibodies positive). 25. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA is detected) infection. 26. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan, previous allogenic bone marrow/blood transplantation or any psychiatric disorder or substance abuse that prohibits obtaining informed consent. 27. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 6 months after the last dose of study intervention. 28. Has had an allogenic tissue/solid organ transplant.
Investigational and control drugs	Study drugs: Pembrolizumab, Olaparib Study treatment: modified FOLFOX-6 or CAPOX plus Pembrolizumab, followed by Pembrolizumab and Olaparib
Investigational and Control Arm, Dose, regimen, treatment cycle	<u>Chemotherapy pre-phase plus Pembrolizumab:</u> <u>Pembrolizumab+mod FOLFOX-6:</u> • Pembrolizumab 200 mg 30 min. day 1 and day 22 • modified FOLFOX-6 regimen (3 cycles, starting day 1, 15, 29): Oxaliplatin 85 mg/m² 2h day 1, 15, 29 Leucovorin* 400 mg/m² 2h day 1, 15, 29 5-FU 400 mg/m² bolus, followed by 2.400 mg/m² 46h day 1, 15, 29 (*) Note: Leucovorin can be replaced by sodium folinate that is given according to local guideline. On day 1, Pembrolizumab has to be applied before chemotherapy. or <u>Pembrolizumab+CapOx:</u> • Pembrolizumab 200 mg 30 min. day 1 and day 22 • CapOx regimen (2 cycles starting day 1, 22): Oxaliplatin 130 mg/m² 2h day 1, 22 Capecitabine 1.000 mg/m² bid. day 1-14, 22-35 Pembrolizumab has to be applied before chemotherapy. See protocol for dose adjustments in patients with a reduced DPD activity. <u>Pembrolizumab and Olaparib:</u> • q21d: Pembrolizumab 200 mg day 1 30 min. and Olaparib 300 mg bid. cont. day 1 to 21 (up to 35 cycles)
Statistical considerations	Platinum-based chemotherapy alone leads to a one-year survival rate of about 45%, the same survival rate has been observed with pembrolizumab monotherapy in patients with PD-L1 CPS ≥ 1 [18]. Assuming a higher efficacy of the combination of pembrolizumab and olaparib among patients with HR mutations, the one-year survival rate in the cohort with HR alterations is

	expected to be 75%, whereas the expected one-year survival rate for patients without HR mutations is 65%. Considering a prevalence rate of 20% for patients with one of the predefined HR alterations an overall one-year survival rate of 67% is expected in the total trial population. Using a one-stage design for pilot studies according to Fleming [51] with an alpha of 5% and a power of 80%, 31 patients are required based on the assumptions that the experimental therapy would be rated as unacceptable, if the actual one-year survival rate was only 45% or lower, or that on the other hand, the therapy regimen would be considered to be a promising candidate for further development, if the true one-year survival rate amounted to 67% or more. There is no full interim analysis planned for this study, due to the small sample size and the relatively short recruitment period.
Key dates	FPFV (planned): Q4 2021 max. 56 months from FPI to LPO consisting of: 12 months recruiting (FPI to LPI) + max. 26 months of treatment (LPFT to LPLT) + max 18 months FU for OS after LPLT
Number of patients, and location	Total number of patients: 31 Location of sites: Germany
Number of enrolled pts.	0, trial in preparation
Participating centers	10 in total

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

Studiennummer/-Code:	AIO-STO-0415 - RAMIRIS
Status:	in Rekrutierung
Rekrutierungszeitraum	2019 - 2023
Weitere Zentren:	erwünscht
Zentren:	geplant: 48 in Deutschland, 12 weitere in Österreich und Italien. initiiert: 45 in Deutschland
Patienten:	geplant: Phase II: 111/Ph III: 318 aktuell eingeschlossen: 111 Phase II, 102 Phase III
Letzte Aktualisierung	Oktober 2021

Study type	Randomized, multicenter phase II/III trial
Principal Investigator	Prof. Dr. med. Sylvie Lorenzen Klinikum rechts der Isar der Technischen Universität München, Abteilung für Hämatologie und Onkologie, Ismaningerstr. 22, 81675 München Tel. 089/41409969; Fax 089/4140-3654822 sylvielorenzen@gmx.de
Sponsor	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest

Project Management Sponsor	Steinbacher Hohl 2-26 60488 Frankfurt am Main Dipl.-Biol. Kristina Ihrig, Dr. Claudia Pauligk Tel: +49 69 / 76 01-4281, -3906 Email: kristina.ihrig@ikf-khnw.de; pauligk.claudia@ikf-khnw.de
Objectives / Endpoints (efficacy, safety)	**Objectives for phase III portion** Primary Efficacy Objectives: • To compare overall survival (OS) in patients with locally advanced, inoperable or metastatic esophagogastric adenocarcinoma receiving FOLFIRI with ramucirumab versus paclitaxel with ramucirumab as second line therapy in patients who failed prior taxane-containing therapy in the intent to treat population (ITT) and where OS is defined as the time from randomization to death from any cause • To compare Objective Overall Response Rate (ORR) in the groups as described above and where ORR is defined as the proportion of patients with complete or partial remission according to RECIST 1.1 Secondary Efficacy Objectives: To compare the treatment arms in terms of • Disease Control Rate (DCR) as defined as proportion of patients with complete or partial remission or stable disease (CR, PR, SD) according to RECIST 1.1 • Progression free survival (PFS) defined as the time from randomization to disease progression or death from any cause • Quality of life (QoL) as measured by EORTC-QLQ-C30 during treatment and follow-up (until d30 after EOT) and/or until progression, or start of new anticancer therapy. **Safety Objective (phase II and III):** • To evaluate the safety and tolerability of ramucirumab plus FOLFIRI or paclitaxel in patients with locally advanced, inoperable or metastatic esophagogastric adenocarcinoma, defined as incidence, frequency and severity of adverse events and serious adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE V 4.03), discontinuation rate and dose adjustment rate **Endpoints for phase II** **Primary endpoint:** OS rate after 6 months, based on an ITT population. The experimental therapy (FOLFIRI + Ramucirumab) would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true OS rate amounted to 65% or more, as this corresponds to the efficacy of the standard Ramucirumab-Paclitaxel regimen according to the RAINBOW (Wilke et al., 2014) study in the western population. **Secondary endpoints:** To compare treatment arms with respect to • Progression-free survival • Objective response rate (CR + PR) • Tumor control rate (CR, PR, SD) • Safety (according to NCI-CTCAE V 4.03) and tolerability • Assessment of quality of life during treatment and follow-up. **Exploratory endpoints (optional):** Translational research analysis in serum samples, e.g.: Chemokines and angiogenic factors in plasma (e.g. sCAIX, PGE2, Tryptase, PlGF, GM-CSF, G-CSF, S100A8, S100A9) **Endpoints for phase III**

	Co-primary endpoints of the phase III portion: • Overall Survival and Objective Overall Response Rate (ORR) **Secondary endpoints of the phase III portion:** • Treatment efficacy in terms of Disease Control Rate (DCR; CR, PR, SD) and progression free survival (PFS) • Quality of life during treatment and follow-up (until d30 after EOT) and/or until progression or start of new anticancer therapy. • Safety (according to NCI-CTCAE V 4.03) and tolerability
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 standard 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. 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. 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. In colorectal cancer FOLFIRI was tolerable together with ramucirumab (Tabernero et al., Lancet Oncol 2015). 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 FOLFIRI (standard treatment) with ramucirumab compared to the standard treatment of ramucirumab plus paclitaxel. This trial aims to investigate the efficacy and safety of ramucirumab plus FOLFIRI (investigational arm A) compared to paclitaxel plus ramucirumab (control arm B). Since the initiation of the RAMIRIS trial, the landscape of the treatment of gastric and gastroesophageal adenocarcinoma has changed. More and more patients are treated with a taxane-based regimen in the perioperative or 1st line metastatic setting. For patients with locally advanced, potentially operable gastroesophageal cancer, perioperative FLOT is the new accepted treatment standard with an improvement of 15 months in overall survival vs. ECX/F in the FLOT4 trial (Al-Batran et al, Lancet, in press). For patients with an esophageal or gastroesophageal junction cancer, neoadjuvant radiochemotherapy according to the CROSS – trial (41Gy plus Carboplatin AUC 2 + Paclitaxel 50mg/m²) is an alternative treatment option recommended in the guidelines (Van Hagens et al, NEJM 2012). In addition, the Japanese JACCRO GC-07 trial showed an improvement of the 3- year relapse-free survival by > 15% with the addition of docetaxel to S-1 for resected patients with a pStage III gastric cancer (Kodera et al, ASCO 2018). These rapid developments will lead to a very large group of patients who are taxane-pretreated and need a second-line therapy. For patients with taxane-pretreatment, the benefit of a combination of ramucirumab and paclitaxel is still unclear, and many physicians prefer the use of an irinotecan-based regimen as second line treatment. Therefore, at the time of the RAMIRIS phase II trial initiation, there was a great need to generate data on an

	irinotecan-based regimen together with ramucirumab. Now the situation has changed and there is very high need to definitely answer the question about the optimal backbone regimen for ramucirumab in patients who had received a taxane. Moreover, the pre-planned safety interims analysis of the phase II RAMIRIS trial did not reveal any unexpected safety issues after the inclusion of 58 patients (36 patients treated with FOLFIRI + Ramucirumab and 22 patients treated with Paclitaxel + Ramucirumab). In addition, the estimated OS rate in the standard Arm B after 6 months (n=22) was 62% (95% CI 43% - 89%). This was well in accordance with the rate of 65%, as anticipated at the planning phase of the trial. Therefore, the AIO investigators implement a phase III portion of the ongoing RAMIRIS phase II trial. Of note, the phase III portion will not utilize the patients enrolled into the phase II portion. The phase III portion of the RAMIRIS trial will evaluate whether the combination of FOLFIRI with ramucirumab (investigational arm A) is superior in terms of OS and ORR compared to the standard treatment of ramucirumab plus paclitaxel (control arm B) in patients who had received a prior taxane (docetaxel or paclitaxel) and can lead to a new standard of care in this particular group of patients by changing the national and international guidelines.
Population	Patients with advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction are eligible for this study.
Inclusion/exclusion criteria	**Inclusion** 1. Signed written informed consent 2. Male or female* ≥ 18 years of age; Patients in reproductive age must be willing to use adequate contraception (that results in a failure rate of <1% per year) 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 (including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants, intrauterine devices (IUDs) and intrauterine hormone-releasing system (IUS)), nonhormonal IUDs and complete abstinence). Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start. Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start. * There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. Histologically proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction 4. Metastatic or locally advanced disease, not amenable to potentially curative resection 5. Phase II only: 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. 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 one line. OR Phase III only: Radiological or clinical disease progression during or after the last dose of a first-line platinum, fluoropyrimidine-containing therapy. Patients must also have received a taxane with the first-line or during their adjuvant or neoadjuvant therapy or both. Neoadjuvant/adjuvant platinum containing therapy is permitted and is counted as first-line therapy if progression occurs <12 months after completion of the treatment. If progression occurred ≥12 months after completion of neoadjuvant/adjuvant therapy, the therapy is not counted as a treatment line. At decision of the investigator, different regimens can be considered as one line of prior treatment, in case these were administrated as a sequential or alternating therapy. 6. Measurable or non-measurable but evaluable disease

	7. ECOG performance status 0-1 8. Life expectancy > 12 weeks 9. Adequate hematological, hepatic and renal functions: • Absolute neutrophil count (ANC) ≥ 1.5 x 109/L • Platelets ≥ 100 x 109/L • Hemoglobin ≥9 g/dL (5.58 mmol/L) • Total bilirubin ≤ 1.5 times the upper normal limit (UNL) • AST (SGOT) and ALT (SGPT) ≤ 3.0 x UNL in absence of liver metastases, or ≤ 5 x UNL in presence of liver metastases; AP ≤ 5 x UN • Serum creatinine ≤ 1.5 x upper limit of normal, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed) • 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) • 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 therapy). Patients receiving warfarin/ phenprocoumon must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy. 10. Ability to comply with scheduled assessments and with management of toxicities **Exclusion** Patients with any of the following will not be eligible for participation: 1. Other tumor type than adenocarcinoma (e.g. leiomyosarcoma, lymphoma) or a second cancer except in patients with squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been effectively treated. Patients curatively treated and disease-free for at least 5 years will be discussed with the sponsor before inclusion 2. Squamous gastric cancer 3. Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol 4. Phase II only: Previous therapy with paclitaxel or FOLFIRI Phase III only: Previous therapy with FOLFIRI 5. Current treatment with any anti-cancer therapy ≤ 2 weeks prior to study treatment start unless rapidly progressing disease is measured 6. Concurrent treatment with any other anti-cancer therapy 7. Previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study 8. Patient has undergone major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to first dose of protocol therapy. The patient has elective or planned major surgery to be performed during the course of the clinical trial 9. Grade 3-4 GI bleeding within 3 months prior to enrollment 10. History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) during the 3 months prior to first dose of protocol therapy 11. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis. 12. Known brain or leptomeningeal metastases 13. Known allergic/ hypersensitivity reaction to any of the components of the treatment 14. Contraindications to the use of atropine

	15. Other serious illness or medical conditions within the last 12 months prior to study drug administration 16. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol 17. The patient has uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management 18. Active uncontrolled infection 19. Current history of chronic diarrhea 20. Active disseminated intravascular coagulation 21. Any other serious concomitant disease or medical condition that in the judgment of the investigator renders the subject at high risk of treatment complication or reduced the probability of assessing clinical effect 22. Known Dihydropyrimidine dehydrogenase (DPD) deficiency 23. Prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation. 24. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy 25. The patient is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted 26. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to treatment start or at the same time as this study 27. 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 < 1. Note: Neuropathy due to prior chemotherapy is allowed if not > NCI Grade II according to CTCAE version 4.03 28. Subject pregnant or breast feeding, or planning to become pregnant within 3 months after the end of treatment 29. Subject (male or female) is not willing to use highly effective methods of contraception (per CTFG-Guideline) during treatment and for 3 months (male or female) after the end of treatment 30. Patients known to have a HER 2 positive Cancer who have not been treated already with a HER 2 targeting agent. 31. 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 1:1 Each Cycle: either: • Experimental Treatment: Arm A (FOLFIRI + Ramucirumab) Ramucirumab 8 mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle Plus 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) or • Standard Treatment: Arm B (Paclitaxel + Ramucirumab) Ramucirumab 8mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle Plus Paclitaxel 80 mg/m^2 on day 1, 8, 15 Each cycle will be repeated after 28 days (from day 1) until the patient experiences progress (*) Note: Leucovorin can be replaced by sodium folinate that is given according to local guideline.
Sample size calculation	**Phase II portion:**

	According to these parameters, and using a standard single-stage phase II design by FLEMING (1981), n = 67 patients evaluable for efficacy have to be recruited in the R-FOLFIRI arm. About n = 34 patients are to be allocated to the reference R-Pac arm, according to the 2:1 randomization. The final conclusion of the phase II trial will depend on the definite OS rate (and its confidence interval), the respective findings in the R-Pac reference arm, as well as the information on type, frequency and severity of toxicities. Thus, a total number of about 67 + 34 = 101 evaluable patients is required. Assuming a 10% drop out rate we are planning to include 111 pts **Phase III portion:** Based on results of the RadPAC Trial (Lorenzen …Al-Batran et al, ASCO Annual meeting 2017 Abstract No:4027) as well as on interim results from the control arm of the phase II part of the RAMIRIS trial (taxane-pretreated subgroup), the median OS in the standard arm is assumed to be about 6 months. An increase to 8.6 months (corresponding to a hazard ratio of HR=0.70) in the experimental arm seems to be a reasonable aim, and is unequivocally considered to be a major, clinically relevant advantage. In order not to miss such an improvement by the R-FOLFIRI treatment (if it actually exists) with a high level of confidence (power = 80%), a total of n = 264 events have to be observed, based on a α error rate of 0.020 (one-sided). Under the following assumptions • recruitment period: 18 months • minimum the follow-up time of the last recruited patient: 1 year • exponential distribution of the survival curves • 5% drop-out rate, likewise following an exponential distribution over 2½ years 318 eligible patients (i.e. about 159 per arm) should be randomized to achieve the required number of events. (In case the event count is not reached within the time frame described above, a prolongation of follow-up for up to three months may be considered.) The following calculations are performed with respect to the co-primary endpoint ORR: A total of 298 patients, i.e. about 149 per arm, ensure 80% power to significantly detect an ORR improvement from 10% to 25% based on a one-sided α error level of 0.005.
Key dates	FPFV: Q4 2019 Follow-up: every 2 months for up to 1 year
Number of patients and location	<u>Phase II portion:</u> Total number of patients: 111 (Arm A 67+ Arm B 34, recruitment completed) <u>Phase III portion</u>: Total number of patients: 318 (Arm A 159 + Arm B 159) Location of sites: Germany; Austria and Italy (planned) Note: Patients randomized in the phase II part of RAMIRIS are not included in the total number of patients for phase III. The 318 patients of phase III will be enrolled in addition to the 111 patients in phase II.

Lokal fortgeschrittenes oder metastasiertes Adenokarzinom des Magens oder gastroösophagealen Übergangs – palliativeTherapie, 3rd-line

AIO-STO-0221/ass - Randomized Phase III Controlled Trials of Regorafenib containing regimens versus standard care in Refractory Advanced Gastro-Oesophageal Cancer (AGOC) - INTEGRATE IIb

AIO-assoziierte-Studie

Studiennummer/-Code:	**AIO-STO-0221/ass - Integrate IIb**
Status:	in Vorbereitung
Rekrutierungszeit:	von: Jan 2022 bis: ca. Jan 2024
Anzahl Zentren:	geplant: 26 (s.u.) aktuell initiiert: 0 aktiv rekrutierend: 0
Weitere Zentren:	sind erwünscht (Details siehe unten)
Anzahl Patienten:	geplant: 80 (in Europa) aktuell eingeschlossen: 0
Letzte Aktualisierung	30.09.2021

STUDY TYPE	A multicenter, randomized phase III, open label trial with 2:1 (RegoNivo: standard chemotherapy)
PRINCIPAL INVESTIGATOR	Prof. Dr. Markus Möhler Leitung Gastrointestinale-Onkologische Ambulanz, Oberarzt, Johannes Gutenberg-University Mainz, Germany, Universitätsmedizin Mainz, I.Medizinische Klinik und Poliklinik, Langenbeckstraße 1, 55131 Mainz Telefon: +49 (0) 6131-176076, Telefax: +40 (0) 6131-176472 E-Mail: markus.moehler@unimedizin-mainz.de
TRIAL OFFICE	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
SPONSOR	Sponsor global: Australasian Gastro-Intestinal Trials Group (AGITG) Level 6, 119-143 Missenden Road Camperdown NSW 2050, Australia Local sponsor, Europe: Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main, Germany
CONDITION	Refractory Advanced Gastro-Oesophageal Cancer
DESIGN	A randomised phase III, open label, trial with 2:1 (RegoNivo:standard chemotherapy) randomisation and stratification by: • Geographic region (Asia vs. Rest of World) • Prior VEGF inhibitors (Y vs N) • Prior immunotherapy (Y vs N)
INDICATION	Refractory Advanced Gastro-Oesophageal Cancer. The study will include patients, who have failed or been intolerant to a minimum of 2 lines of prior anti-cancer therapy for recurrent/metastatic

	disease which must have included at least one platinum agent and one fluoropyrimidine analogue. **Note**: Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy will be considered as first line treatment where people have relapsed or progressed within 6 months of completing treatment; Radiosensitising chemotherapy given solely for this purpose concurrent with palliative radiation will not be considered as a line of treatment. Ramucirumab monotherapy, or immunotherapy with a checkpoint inhibitor, will be considered a line of treatment.
OBJECTIVE(S)	Primary Objective (Endpoint): To determine the effect of RegoNivo on overall survival (OS) (death from any cause) in the overall study population and in the Asian sub-population. Secondary Objectives (Endpoints): To determine the effect of RegoNivo on: • Progression free survival (PFS)(disease progression or death) • Objective tumour response rate (OTRR)((partial or complete response (PR or CR)) according to Response Evaluation Criteria in Solid Tumours (RECIST) version. 1.1, and iRECIST • Quality of life (QoL)(scores from participant-completed questionnaires) • Safety (rates of adverse events) Tertiary/Correlative Objectives: • To identify prognostic and predictive biomarkers (tissue and circulating) for study endpoints (relating to survival, response and safety) • To evaluate regorafenib PK in patient populations from different geographical regions (regorafenib levels).
INTERVENTION(S)	Study Treatments: Participants in the RegoNivo arm will self-administer 90mg (3x30mg) of regorafenib days 1-21 of each 28-day treatment cycle and receive intravenous nivolumab 240 mg day 1 of 14 days until disease progression or prohibitive adverse events as per protocol. After 2 months, patients whose disease is controlled may have nivolumab administered 480 mg every 28 days. Participants in the control arm will receive investigator choice chemotherapy with any of the following agents: taxane, irinotecan or oral trifluridine/tipiracil (TAS102). Both treatment groups will receive Best Supportive Care (BSC).
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	The trial incorporates translational studies (biomarker research) in the trial design. Planned biomarker analyses may include but are not limited to: • Investigation of VEGF-related biomarkers including VEGF, VEGF polymorphisms, circulating VEGF isoforms (VEGF A short isoforms), VEGF family receptors (VEGFR-1, 2, 3) and other proteins downstream of VEGFR, as prognostic and/or predictive markers for those study endpoints relating to survival, response and safety • Other biomarkers relating to angiogenesis and/or tumourigenesis in blood and tumour including FGF pathway, PDGF, vWF, Tie1 and 2. • Evaluation of the prevalence and distribution of the four proposed molecular phenotypes of gastric cancer proposed by the Cancer Genome Atlas Research Network (2014), and their association with angiogenic biomarkers and regorafenib activity. • Regorafenib pharmacokinetics in patients from different geographical regions. • Associations between circulating tumour DNA and clinical outcomes • Associations between autoimmunity and clinical outcomes • Immunoprofiling including: immune cell infiltration, expression of immune checkpoint molecules including PD-1 and PD-L1

	• Tumour mutational burden (TMB) • Cellular and molecular signatures associated with immune-related adverse events. Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.
BACKROUND/RATIONALE	Advanced Gastro-oesophageal Carcinoma (AGOC) has a poor prognosis, and there is no established standard treatment following failure of first- and second-line chemotherapy. Regorafenib (BAY 73-4506) is an investigational oral multi-targeted tyrosine kinase inhibitor (TKI) which targets angiogenic (VEGF, TIE-2), stromal (PDGF-β), and oncogenic (RAF, RET and KIT) receptor tyrosine kinases, and has shown activity in other solid tumours. Regorafenib was shown to prolong PFS across all regions/subgroups in INTEGRATE The INTEGRATE II trial is currently a randomised phase III, controlled trial aiming to determine if regorafenib improves overall survival in refractory AGOC. Immune checkpoint inhibitors enhance anti-tumour T-cell activity through the inhibition of immune checkpoints such as the programmed death-1 (PD-1) receptor. Nivolumab is a fully human IgG4 monoclonal antibody inhibitor of PD-1, shown to be effective in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens in the ATTRACTION-2 study. Biologic rationale exists for synergy between anti-angiogenic therapy (anti-VEGF and others) and anti-PD-1/PD-L1 therapy through changes in the tumour microenvironment. The regorafenib and nivolumab combination (RegoNivo) showed manageable toxicity and encouraging activity in patients with refractory advanced gastric cancer in a Phase Ib trial, including in patients having received prior nivolumab. Current practice in countries participating in INTEGRATE IIb has evolved to use chemotherapy in 3rd and subsequent lines of therapy in fit patients. Agents with demonstrated activity in the 2nd line setting (vs Best supportive Care alone) are utilised, including taxanes (paclitaxel and docetaxel), irinotecan, and oral trifluridine/tipiracil (TAS 102). With the shift in practice in AGOC resulting in use of multiple lines of therapy, the use of new immunotherapy agents, and the promising activity of RegoNivo, this amended trial is proposed to compare the effectiveness of RegoNivo in pre-treated patients with AGOC to the current standard therapy (i.e.: chemotherapy).
KEY EXCLUSION CRITERIA	○ Prior anti-VEGF targeted therapy using small molecule VEGF TKIs. Prior anti- VEGF targeted monoclonal antibody therapies (e.g. bevacizumab and ramucirumab) are permitted. ○ Any prior use of more than one immune checkpoint inhibitor ○ Treatment with any previous drug therapy within 2 weeks prior to first dose of study treatment ○ Uncontrolled metastatic disease to the central nervous system ○ History of another malignancy within 2 years prior to randomization ○ Patients who require high dose systemic corticosteroids < 14 days prior to randomization ○ Pregnancy, lactation, or inadequate contraception.
KEY INCLUSION CRITERIA	○ Adult patients with metastatic or locally recurrent gastro-oesophageal cancer that **a.** has arisen in any primary gastro-oesophageal site; and **b.** is of adenocarcinoma or undifferentiated carcinoma histology; and **c.** is evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1); and

	d. has failed or been intolerant to a minimum of 2 lines of prior anti-cancer therapy (at least one platinum agent and one fluoropyrimidine analogue) ○ ECOG Performance Status of 0 or 1 ○ Adequate bone marrow, renal and liver function
OUTCOME(S)	○ Overall Survival (OS) *(Death from any cause)* ○ Progression Free Survival (PFS) *(Disease progression or death)* ○ Objective Tumour Response Rate (OTRR) ○ Quality of Life (QoL) ○ Safety ○ Tertiary/Correlative
STATISTICAL ANALYSIS	A statistical analysis plan for INTEGRATE IIb will be prepared and finalised prior to database release for analysis. The primary analysis of efficacy endpoints will be performed on the analysis set comprising all randomised patients in accordance with the intention-to-treat analysis principle. The safety population will comprise all randomised participants who received at least one administration of study medication. Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis.
SAMPLE SIZE	A sample of 450 participants (globally; 80 patients in Europe) randomised in a 2:1 ratio (RegoNivo: chemotherapy) and followed until 380 deaths occur (e.g. over a 24 month recruitment period plus an additional follow-up period of at least 12 months) provides 90% power to detect a hazard ratio (HR) for OS of 0.70 with a 2-sided α of 0.05.
TRIAL DURATION	Globally: a 24-month recruitment period plus an additional follow-up period of at least 12 months.
PARTICIPATING CENTERS	Up to 26 sites in Germany and in other European countries.
FURTHER CENTERS DESIRED?	Yes
NUMBER of PATIENTS	450 randomized patients globally; 80 in the European countries.
CURRENT NUMBER of PATIENTS	Recruitment in the European countries has not started yet.

Register: Hepatozelluläres Karzinom / Gallengangskarzinom / Gallenblasenkarzinom / Pankreaskarzinom / Magen- und Speiseröhrenkarzinom – palliativ, 1st-line

AIO-HEP/STO-0219/ass: PLATON Pilot-StudyPlatform for Analyzing Targetable Tumor Mutations – PLATON (Pilot-Study) and The PLATON Network (Main-Study)

AIO-assoziierte Studie	
Studiennummer/-Code:	AIO-HEP/STO-0219/ass// PLATON (pilot-study)
Status:	recruiting
Rekrutierungszeitraum:	FPI 25.11.2020 LPI planned Q1-2022 N=120 of 200 patients recruited
Zentren	40 sites actively recruiting
Weitere Zentren:	The PLATON network is open for study sites
Letzte Aktualisierung	18.10.2021

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str 1, 30625 Hannover and Prof. Dr. med. Salah-Eddin Al-Batran Krankenhaus Nordwest Institut für Klinisch-Onkologische Forschung UCT- University Cancer Center Frankfurt Steinbacher Hohl 2-26, 60488 Frankfurt/Main
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Hepatobiliäre Tumoren	

Arbeitsgruppe Pankreaskarzinom

Pankreaskarzinom, metastasiert, 1st-line

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		
Studiennummer/-Code:	AIO-PAK-0317/ass - FOOTPATH	
Status:	In Rekrutierung	
Rekrutierungszeitraum:	Q1/2019 – Q2/2022	
Zentren:	geplant: 40	initiiert: 40
Patienten:	geplant: 270	aktuell eingeschlossen: 204
Weitere Zentren:	Nicht geplant.	
Letzte Aktualisierung	15.10.2021	

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

	• Liposomal irinotecan 80 mg/m^2 i.v. over about 90 minutes followed by • Folinic acid 400 mg/m^2 i.v. over about 30 minutes followed by • 5-FU 2400 mg/m^2 i.v. over about 46 h (pump) ***mFOLFOX6:*** On Day 1 of a 14-day cycle: • Oxaliplatin 85 mg/m^2 i.v. • Folinic acid 400 mg/m^2 i.v. followed by • 5-FU 2400 mg/m^2 i.v. over about 46 h (pump) Treatment is given until disease progression or the occurrence of unacceptable toxicity. ***Recommended second-line regimens:*** 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: **Arm A:** After failure of gemcitabine/*nab*-paclitaxel the recommended second-line treatment would be the NAPOLI regimen. **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 • Known DPD-deficiency (special screening test not required) • Symptomatic clinically significant ascites (expected indication for repeated paracentesis) • 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. • Previous palliative chemotherapy or other palliative systemic tumor therapy for metastatic disease of PDAC • 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 • Previous radiotherapy of PDAC • Any major surgery within the last 4 weeks before study entry • Clinical significant decrease in performance status within 2 weeks of intended first application of study medication (by medical history) • Severe tumor-related cachexia and/or known weight loss > 15% within one month before study enrollment • Pre-existing polyneuropathy ≥ grade 2 according to CTCAE version 4.03 • 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 • 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. • 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

	• Hypersensitivity to the study drugs or to any of the excipients or to compounds with similar chemical or biologic composition • 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. • Patient known to be homozygous for UGT111*28 or strongly suspected to be homozygous for the UGT111*28 allele • Requirement for concomitant antiviral treatment with sorivudine or brivudine • Continuing abuse of alcohol, drugs, or medical drugs • Pregnant or breast-feeding females or FCBPs unable to either perform highly effective contraceptive measures or practice complete abstinence from heterosexual intercourse • 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 • 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) • No option for surgical resection or radiation in curative intent • At least one unidimensionally measurable tumor lesion (according to RECIST 1.1) • ECOG performance status 0 - 1 • Life expectancy at least 3 months • Adequate hepatic, renal and bone marrow function, defined as: ▪ Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L ▪ Haemoglobin ≥ 9 g/dL ▪ Thrombocytes ≥ 100 x 10^9/L ▪ 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. ▪ AST/GOT and/or ALT/GPT ≤ 2.5 x ULN or in case of liver metastasis ≤ 5 x ULN) ▪ Serum creatinine within normal limits or creatinine clearance [1] ≥ 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. ▪ Acceptable coagulation studies defined as prothrombin time (or INR) and PTT ≤ 1.5 x ULN • 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 **and** 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. 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.

	• 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. • Signed and dated informed consent before the start of any specific protocol procedures Patient's legal capacity to consent to study participation
OUTCOME(S)	**Primary Endpoint:** • Progression free survival (PFS) **Secondary Endpoints:** • Overall survival (OS) • Objective response rate (ORR) • Disease control rate (DCR) • Duration of study treatment • Type, incidence, causal relationship and severity of adverse events according to NCI CTCAE version 4.03 • Quality of life as assessed by EORTC-QLQ-C30 • 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: H_0: PFS (arm B) ≤ PFS (arm A) H_1: PFS (arm B) > PFS (arm A) and H_0: PFS (arm C) ≤ PFS (arm A) H_1: PFS (arm C) > PFS (arm A) 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.
TRIAL DURATION	5 years

AIO-PAK-0219xx: Intensified treatment in patients with local operable but oligometastatic pancreatic cancer - multimodal surgical treatment versus systemic chemotherapy alone: a randomized controlled phase 3 trial [METAPANC]

AIO-Studie		
Studiennummer/-Code:	AIO-PAK-0219xx - ACO/AIO-19 - METAPANC	
Status:	Förderung durch DFG, vor Einreichung	
Rekrutierungszeitraum:	geplanter Beginn: I Q 2022 – geplantes Ende IV Q 2027	
Anzahl Patienten:	geplant: 400	aktuell randomisiert: noch nicht gestartet
Anzahl Zentren:	geplant: 25	aktuell initiiert: noch nicht gestartet
Weitere Zentren:	In Evaluation	
Letzte Aktualisierung	Nov. 2021	

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Medical condition	Patients with locally resectable but oligometastatic pancreatic cancer
Trial-Office	Johanna Kreutzer, M.A. (Study Coordinator); University Medical Center Göttingen, Trial Office of Dept. of General and Visceral Surgery; Robert-Koch-Str. 40, 37075 Göttingen, Germany; Tel. +49 551 67825, Fax +49 551 67861, email: studiensek-chirurgie@med.uni-goettingen.de
Hypothesis	Overall survival in patients with oligometastases in pancreatic cancer and intensified chemotherapy is superior after complete surgical resection compared to chemotherapy alone.
Participants / study population	Key inclusion criteria: Age ≥ 18 years and ≤ 75 years; histologically confirmed metastatic adenocarcinoma of the pancreas; medical and technical operability of the primary tumor defined tumor board assessment; limited metastatic status (≤ 3 resectable liver metastases); adequate hematological (WBC ≥3000/µL, absolute neutrophil count ≥1500 /µL, platelets ≥100.000/µL, hemoglobin ≥8 g/dL), hepatic (bilirubin ≤2.5 x mg/dl) and renal function (creatinine clearance >50ml/min) parameters; ECOG performance status ≤ 1; signed study-specific consent form prior to therapy; measurable disease according to RECIST v1.1. Key exclusion criteria: Unresectable pancreatic cancer; prior chemotherapy within 6 months or prior radiation therapy within 28 days; significant comorbidity (e.g. cardiovascular, pulmonary); peritoneal carcinomatosis or > three liver metastases or ~~non-~~

	extrahepatic metastasis; inability to understand the study and/or comply with the protocol procedures.
Trial type	Interventional trial: [X]
Treatments / procedures	Experimental intervention: Chemotherapy (modified FOLFIRINOX at least 8 cycles) followed by surgery followed by additive 5-FU-based chemotherapy for 3 months Control intervention: Chemotherapy (modified FOLFIRINOX at least 8 cycles) followed by 5-FU based maintenance therapy (FOLFIRI or capecitabine) for three months or until progression Follow-up per patient: minimum of 2 years from randomization. Duration of intervention per patient: approx. 8 months
Endpoint(s)	Primary endpoint: Overall Survival (OS, time from randomization to death from any cause) Secondary endpoint(s): Progression-free survival (time of randomization to cancer progression or death) according RECIST and clinical data; Quality of life (EORTC QLQ-C30, PAN-26, Q-TWIST); Exploratory/Translational: Tissue samples: Genetic profiling, molecular subtyping Liquid biopsy samples: Analysis of cell-free DNA/RNA/proteins Radiomics: machine-learning model to preoperative CT images for non-invasive subtype prediction and therapy response. Assessment of safety: Standard reporting for adverse events (AEs) and serious adverse events (SAEs). AEs and SAEs will be summarized by frequencies and percentage for each treatment group. AEs will be coded according to MedDRA, analyzed, and presented following ICH E3 Structure and Content of Clinical Study Reports. Events of special interest (e.g. toxicities, post-operative complications) will be summarized in the same manner.
Trial duration	First patient in to last patient out (months): maximum of 92 Duration of the entire trial (months): maximum of 98 Recruitment period (months): maximum of 60
Statistical analysis	Statistical methods used to compare groups for primary and secondary outcomes: The primary outcome survival will be analyzed by a Cox proportional hazards regression. The treatment effect will be reported as hazard ratio with 95% confidence intervals and p-value testing the null hypothesis of no effect. Patients withdrawing from study medication will be followed up for endpoints. Withdrawal from the study will be dealt with as independent right censoring in the primary analysis. If withdrawal from study is substantial and differential between the treatment groups, supporting analyses will explore the impact of the independent censoring assumption by use of shared frailty models for time to death and time to withdrawal from study. The analyses of the time-to-event outcomes among the secondary endpoints will follow the same lines as the analyses of the primary endpoint. Methods for additional analyses, such as subgroup analyses and adjusted analyses: Planned subgroup analyses include metastasis status (synchronous/metachronous), mGPS score. We will use an adaptive design. A sample size review verifying planning assumptions such as the overall event and dropout rate will be conducted. Furthermore, a futility analysis will be carried out.
Sample size	To be assessed for eligibility: (approx. n = 400, informed consent) To be assigned to the trial: (n = 272) To be analyzed: (n= 272 ITT, including 218 completers)

Participating sites	No. of cities to be involved (planned): 20 German (AIO/ACO group network), 5 Netherlands (from DPCG network), Finland, Norway No. of centres to be involved: approx. 25 high-volume centers in GER/NL//FIN/NOR Names of cities and centres: approx. 25/25

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

AIO-Studie

Studiennummer/-Code:	AIO-PAK-0118 - SEPION	
Status:	aktiv	
Rekrutierungszeitraum:	2020 – 2022	
Zentren:	geplant: 8 -10	initiiert: 9
Patienten:	geplant: 75	eingeschlossen:42
Weitere Zentren:	derzeit nicht möglich	
Letzte Aktualisierung	11/2021	

COORDINATING INVESTIGATOR	Prof. Dr. med. Jens Siveke
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CONDITION	Patients with metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (stage IV) and no prior chemotherapy for stage IV disease.
OBJECTIVE(S)	→ **Primary objective(s)** → 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 (Arm B) and/or Romidepsin (Arm A) in combination with nab-Paclitaxel/Gemcitabine in patients with advanced PDAC (Part 1a and 1b), followed by sequential immune targeting with PD-L1 blockade in combination with low-dose Lenalidomide (Part 2) in patients with controlled disease after 3 cycles (Part 1). → 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. → **Secondary objective(s)** → 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) → to show a promising clinical activity of the selected epigenetic and chemotherapeutic targeting approach from Part 1a with

	regard to the disease control rate (Part 1b) → 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) → to assess OS in all patients treated at the recommended dose and regimen **Exploratory Translational Sub-studies** 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. 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. 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. 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: Arm A • Absolute neutrophil count < 1 x 10^9/L for ≥7 days • Platelets < 50 x 10^9/L for ≥7 days (severe thrombopenia) • > Grade 2 non-hematologic toxicity, except alopecia Only if deemed related to Romidepsin: • Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion • ≥ Grade 2 non-hematologic toxicity, except alopecia Arm B • Absolute neutrophil count < 1 x 10^9/L for ≥7 days • Platelets < 50 x 10^9/L for ≥7 days (severe thrombopenia) • > Grade 2 non-hematologic toxicity Only if deemed related to Azacitidine: • unexplained reductions in serum bicarbonate levels to less than 20 mmol/l

	• unexplained elevations in serum creatinine or blood urea nitrogen to ≥ 2-fold above baseline values and above ULN Arm C • Absolute neutrophil count < 1 x 10^9/L for ≥7 days 1) • Platelets < 50 x 10^9/L for ≥7 days (severe thrombopenia) • ≥ Grade 2 non-hematologic toxicity, except alopecia Only if deemed related to Romidepsin: • Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion • ≥ Grade 2 non-hematologic toxicity, except alopecia Only if deemed related to Azacitidine: - unexplained reductions in serum bicarbonate levels to less than 20 mmol/l - unexplained elevations in serum creatinine or blood urea nitrogen to ≥ 2-fold above baseline values and above ULN 2) 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. 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. (but a maximum of 75 patients in total). 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 (PR, SD). Patients without DCR will enter a 12 month long-term follow-up. 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** 1. Patients who have had 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 2. Patients may not be receiving any other investigational agents 3. Patients who have previously received Romidepsin, Azacitidine, Lenalidomide or Durvalumab or any PD1 or PD-L1 inhibitor or pacticipate currently on an other clinical trial, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study 4. Patients with untreated or uncontrolled brain metastases or leptomeningeal disease 5. Presence of other active illnesses 6. Any known cardiac abnormalities such as: • Congenital long QT syndrome • QTc interval ≥ 470 milliseconds. Calculated from 3 ECGs using Fridericias Correction

	7. Myocardial infarction within 6 months prior to C1D1. Subjects with a history of myocardial infarction between 6 and 12 months prior to C1D1 who are asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event may participate 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) 9. Symptomatic coronary artery disease (CAD), e.g., angina Canadian Class II-IV. 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 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 MRI 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) 12. Concomitant use of any drug known to prolong QT interval 13. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) 14. Lactating, pregnant or breast feeding 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 16. Diagnosis of immunodeficiency or any condition that requires systemic steroid therapy or other forms of immunosuppressive therapy; 17. Prior thromboembolic events 18. History of other malignancies, except: • Malignancy treated with curative intent and with no known active disease present for ≥ 5 years before the first dose of study drug and felt to be at low risk for recurrence by investigator. • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. • Adequately treated carcinoma in situ without current evidence of disease (all treatment of which should have been completed 6 months prior to randomization) 19. Any uncontrolled active systemic infection 20. Major surgery within 4 weeks prior to first dose of study drug 21. 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 22. History of stroke or intracranial hemorrhage within 6 months prior to enrollment 23. History of interstitial lung disease, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis 24. 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 25. Concomitant use of warfarin or other Vitamin K antagonists 26. Known allergy or hypersensitivity to any study drug or any of the study drug excipients 27. 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 28. Current or prior use of immunosuppressive medication within 14 days (use 28 days if combining Durvalumab with a novel agent) before the first dose of Durvalumab. The following are exceptions to this criterion:

	• Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) • Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent • Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) 29. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], 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: • Patients with vitiligo or alopecia • Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement • Any chronic skin condition that does not require systemic therapy • Patients without active disease in the last 5 years may be included but only after consultation with the study physician • Patients with celiac disease controlled by diet alone 30. 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 • Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. • Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with Durvalumab may be included only after consultation with the Study Physician. 31. History of allogenic organ transplantation 32. 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 (HBV; known positive HBV surface antigen (HBsAg) result), hepatitis C (HCV), or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. These patients will be closely monitored for signs and symptoms of active HBV or VZV infection throughout therapy. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA 33. 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 34. Subject is an employee of GWT-TUD GmbH
KEY INCLUSION CRITERIA	**Principal inclusion criteria** Subjects must fulfill all of the following criteria before inclusion in the study: 1. Patients must have histologically confirmed PDAC 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) 3. Patients must not have received the following drugs before: Azacitidine, Romidepsin, any checkpoint-inhibitor or immunomodulating agents such as IMiDs (Lenalidomide) 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 5. Male or female, age ≥ 18 years 6. Body weight > 30 kg for inclusion into Part 2 (according to Durvalumab treatment) 7. ECOG performance status 0 or 1 8. Patients must have normal organ and marrow function as defined below • Leukocytes ≥ 2,5 x 10^9/L

	• Absolute neutrophil count ≥ 1,5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Haemoglobin ≥ 9 g/dL • Total 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 • Asparate aminotransferase/alanine aminotransferase (AST/ALT) (SGOT/SGPT) ≤ 2.5 x ULN and ≤ 5 in the case of liver metastasis • 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 9. Patients must be recovered from the effects of any prior surgery 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 11. All subjects must agree to refrain from donating blood while on study drug and for 90 days after discontinuation from this study treatment 12. All subjects must have a life expectancy of at least 12 weeks 13. All subjects must agree not to share medication 14. Females of childbearing potential (FCBP) must • Understand the potential teratogenic risk to the unborn child • Understand the need and agree to utilize two reliable forms of contraception simultaneously without interruption for at least 28 days before starting study drug, while participating in the study (including dose interruptions), and for at least 90 days after study treatment discontinuation • Understand and agree to inform the investigator if a change or stop of method of contraception is needed • Be capable of complying with effective contraceptive measures • 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 • Understand the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test • Understand the need and accept to undergo pregnancy testing based on the frequency outlined in this protocol • Acknowledges that she understands the hazards Lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of Lenalidomide • Females must agree to abstain from breastfeeding during study participation and for at least 90 days after study drug discontinuation 15. Males must • Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP • 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. • 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. • 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. 16. Females of non-childbearing potential: • 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: 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) 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)** The primary endpoint is the safety and tolerability of Azacitidine (Arm B) and/or Romidepsin (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). Safety and tolerability will be determined by the following parameters: • Clinical laboratory (clinical chemistry, hematology, urinalysis) • Performance status according to Eastern Cooperation Oncology Group (ECOG) • Recording of AEs and concomitant medication • Physical examination • ECG • ECHO (Echocardiography) or MUGA (Multiple-Gated-Acquisition-(MUGA)-Radionuclide-Imaging) • Vital signs (pulse, blood pressure, body temparature) 3) Moreover, in the dose escalating part of the study (Part 1a/Phase I), the recommended dose for RDE and 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	→ Descriptive analyses → Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by treatment group. Frequency tables for categorical data will be provided. Medical history findings will be summarized using MedDRA terms. → Safety examinations → 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. In summary, the trial design is based on the following assumptions: • 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. • 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. • 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) • 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%). 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.* Because of our aim to study a consolidation concept in the second part of the study, a sufficient number of patients with controlled disease after 3 cycles of therapy is needed based on the statistical considerations. Thus, in addition to the patients undergoing part 1a (Dose escalation) and part 1b (Dose Expansion), patients treated with nab-Paclitaxel/Gemcitabine alone will be additionally recruited in this study (so-called “standard arm”). The number of patients in the standard group may vary on the recruited number of patients in Parts 1a and 1b (total target number of patients for Part 1 including standard group = 75), so that 41 patients will be available for Part 2 given a presumed 60% DCR after 3 cycles in part 1 (Goldstein 2015) and a drop-out rate of 10%. 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:** → Maximum 4 months induction (part 1), 12 months consolidation (part 2), after that 12 months Follow Up starting after completion of the consolidation therapy (part 2) with subsequent long-term Follow Up for SPMs. → **Planned study schedule** → First Patient First Visit → Q1/2020 → Last Patient First Visit → Q1/2022 → Last Patient End of Trial → Q1/2023 → Last Patient Last Active Follow up → Q1/2024 → Last Patient Last Follow Up of SPMs → Q1/2026 → Final Study report (primary data) → Q4/2024 → Report of SPMs → Q2/2026
PARTICIPATING CENTERS	Prof. Dr. Jens Siveke, Universitätsklinikum Essen Prof. Dr. Volker Kunzmann, Universitätsklinikum Würzburg Prof. Dr. Thomas Seufferlein, Universitätsklinikum Ulm Prof. Dr. Stefan Böck, Ludwig-Maximilians-Universität München PD Dr. Marianne Sinn, Universitätsklinikum Hamburg-Eppendorf Dr. Gabriele Siegler, Klinikum Nürnberg, 5. Med. Klinik Prof. Dr. Jörg Trojan, Universitätsklinikum Frankfurt Dr. Alexander König, Universitätsmedizin Göttingen Dr. Dirk-Thomas Waldschmidt, Uniklinik Köln

AIO-PAK-0120/xx: MAintenance ThErapy vs. Observation in FOLFIRINOX treated metastatic Pancreatic ductal adenocarcinoma patients - A prospective, randomized multi-center phase II AIO trial (MATEO-Panc)

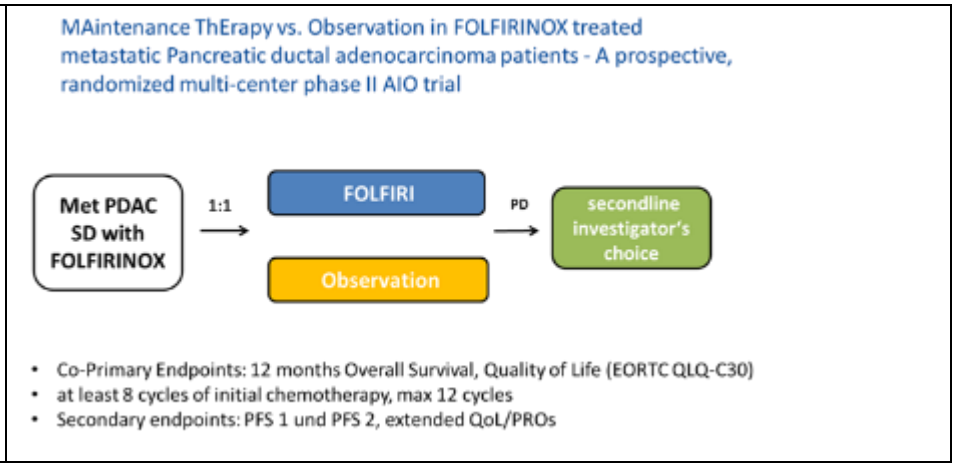
AIO-Studie

Studiennummer/-Code:	**AIO-PAK-0120/xx - MATEO-Panc**		
Status:	in Vorbereitung		
Rekrutierungszeit:	von:	bis:	
Anzahl Zentren:	geplant:	aktuell initiiert:	aktiv rekrutierend:
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant:	aktuell eingeschlossen:	
Letzte Aktualisierung	15.05.2020		

Study phase	Phase II
Study design	Randomized, multi-center Phase II designed to evaluate overall survival at 12-months and quality of life for maintenance treatment with FOLFIRI versus observation in metastatic pancreatic ductal adenocarcinoma (PDAC) after disease stabilization under FOLFIRINOX
Sponsor details	Universitätsklinikum Hamburg-Eppendorf Martinistraße 52 20246, Hamburg, Germany
Coordinating Investigator	**Marianne Sinn, PD Dr. med.** II. Department of Medicine University Medical Center Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg, Germany Tel: +49-40-7410-52960

	email: ma.sinn@uke.de
Study Coordinators	**Martin Schönlein and Joseph Tintelnot, Dr. med.** II. Department of Medicine University Medical Center Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg, Germany Tel: +49-40-7410-52960 email: ma.schoenlein@uke.de; j.tintelnot@uke.de
Countries	Germany
Centre(s)	n= 20-25
Planned sample size (N)	n= 265 tested, n=242 assigned
Planned study start/end dates	FPI: Q1/2021 LPI: Q4/2024 LPLT: Q2/2026 End of Follow up period after LPLT: Q2/2026
Rational and Objectives	The combination chemotherapy regimen FOLFIRINOX became standard of care in the treatment of metastatic PDAC since 2010 (Conroy, ASCO 2010; Conroy et al., 2011). About 50% of the herewith treated patients are expected to reach disease stabilization after 6 months of therapy (Conroy et al., 2011), but toxicity is high (e.g. grade 3/4 neutropenia 46%, sensory polyneuropathy 12%) and increasing over the time. Although in daily clinical practice, dose modifications will become necessary after 8-12 cycles in almost every patient, no concrete de-escalation or maintenance treatment strategy has been established so far. In principle, two different strategies are possible: Maintenance by de-escalation of chemotherapy or an observation/watch and wait-strategy, which means no further treatment until progression of disease with a reinduction of chemotherapy. De-escalation studies in colorectal cancer which compared a maintenance with a watch and wait strategy showed that the benefit of an improved progression free survival was not directly translated into an improved overall survival (Sonbol et al., 2019). However, PDAC must be considered as a very aggressive tumor type with a high risk of early disease progression and an associated deterioration of overall survival and general condition. Furthermore, maintenance treatment does not necessarily lead to diminished quality of life (Quidde et al., 2016). Interestingly, FOLFIRINOX even led – despite the above described side effects – to an increase in quality of life in comparison to a less intensive gemcitabine monotherapy due to symptoms related to tumor burden like pain or cachexia (Gourgou-Bourgade et al., 2013). Our combined co-primary endpoint of overall survival at 12 months and QoL will help to substantiate this question. No biomarker-driven therapy or treatment strategy could be implemented in the therapeutic algorithm of PDAC patients, so far. The trial concept will provide excellent conditions for a concomitant translational research program with the aim to implement prognostic and predictive biomarkers in with focus on three main strategies: 1) liquid biopsy: monitoring of circulating tumor cells and tumor DNA (ctDNA) to provide markers for early disease progression (Li et al., 2018; Rieser et al., 2018) 2) microbiome analysis: stool composition and its diversification during treatment to test for potential outcome related biomarkers (Riquelme et al., 2019) 3) tumor organoids: establishing ex vivo drug sensitivity tests using tumor organoids grown from re-biopsies taken at study inclusion on a voluntary basis
Primary Endpoints	**1. Primary endpoint:** 12 months overall Survival (OS) **2. Primary endpoint:** Quality of Life (EORTC QLQ-C30)
Secondary Endpoints	Progression free survival 1 (time of randomization to cancer progression under maintenance therapy or observation arm), Progression free survival 2 (time of randomization to cancer progression under second line physician´s choice chemotherapy), Toxicity (NCI-CTCAE V. 5.0), Overall treatment utility (OTU), ctDNA levels for detection of early disease progression, tumor microbiome diversification under chemotherapy, chemosensitivity testing in ex vivo tumor organoids, Quality of life.
Inclusion criteria	1. Written informed consent and any locally-required authorization obtained from the subject 2. Age ≥ 18 years at time of study entry 3. Metastatic pancreatic adenocarcinoma.

	4. ECOG <= 2. Patients must be fit to receive further chemotherapy with FOLFIRI, therefore no adverse reactions to either 5-FU, folinic acid or irinotecan have to be reported, except of controlled irinotecan-related diarrhea 5. 8 – 12 cycles (16 – 24 weeks) of treatment with FOLFIRINOX 6. At least stable disease based on radiographic RECIST 1.1 and clinical (stable or decreasing CA 19-9 levels and no development of signs of disease progression like ascites or thrombosis) assessments. 7. Adequate bone marrow, renal and hepatic function 8. Female subjects must either be of non-reproductive potential 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. 9. Male and female subjects of childbearing potential must agree to use highly effective methods of contraception from screening, and must agree to continue using such precautions for 6 months after the final dose of investigational product. 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. 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
Main Exclusion criteria	1. Active infection > Grade 2 NCI-CTCAE V5.0 2. Serious concomitant 3. Secondary malignancies except for basal cell carcinoma of the skin during the last 3 years 4. Need of immuno-suppressive therapy (e.g. pts after transplantations) 5. Severe non-healing wounds, ulcers or bone fractures 6. Female subjects who are pregnant, breast-feeding or intent to become pregnant; as well as sexually active male or female patients who are unwilling to employ highly effective methods of contraception 7. Any condition, that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results 8. Any psychological, familial, or sociological conditions that do not permit compliance with the protocol. 9. Participation in another clinical study with an investigational product during the last 15 days before inclusion
Statistical considerations	The first primary endpoint overall survival will be analyzed by a Cox proportional hazards regression model with treatment group and stratification factors (disease status: stable disease vs remission, ECOG 0-1 vs. 2 and CA19-9 <1000kU/l or ≥1000kU/l) as fixed effects. The 95% confidence interval of the treatment contrast will then be compared to the non-inferiority margin of 1.5. **Non-inferiority for overall survival** is shown if the upper bound of the 95% confidence interval of the treatment contrast is smaller than the non-inferiority margin. If the null hypothesis concerning the first endpoint can be rejected, the secondary endpoint can be evaluated in a confirmatory way. To determine the second primary hypothesis (**superiority in quality of life**) a baseline-adjusted regression using QoL at 12 weeks after randomization as dependent variable and treatment group as well as stratification factors as fixed effects will be fitted. Subgroup and toxicity/safety analysis will be performed by descriptive analyses

Flow Chart	

Pankreaskarzinom – Operable Patienten

AIO-YMO/PAK-0218/ass: Prognostic role of circulating tumor DNA in resectable pancreatic cancer (PROJECTION)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-YMO/PAK-0218/ass	
Status:	Rekrutiert	
Rekrutierungszeitraum:	Q4/2020 – Q4/2022	
Zentren:	geplant: 6	initiiert: 5
Patienten:	geplant: 132 (Max 200)	aktuell eingeschlossen: 20
Weitere Zentren:	Nicht geplant.	
Letzte Aktualisierung	15.10.21	

STUDY TYPE	Non-interventional, exploratory
PRINCIPAL INVESTIGATOR	Dr. Benedikt Westphalen Medizinische Klinik und Poliklinik III, Klinikum der Universität München Marchioninistr. 15, 81377 München
TRIAL OFFICE	ClinAssess
SPONSOR	Klinikum der Universität München
CONDITION	Resectable pancreatic adenocarcinoma
DESIGN	Non interventional, exploratory.
INDICATION	Resectable pancreatic adenocarcinoma
Primary Objective	Comparison of disease-free survival (DFS) of patients with preoperative presence of ctDNA (Group A) and absence of ctDNA (Group B)
INTERVENTION(S)	None
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Comparison between preoperative and postoperative ctDNA levels (only in patients in Group A) Comparison between mutational status in tissue and blood (only in patients in Group A)

	Comparison of DFS based on tumor tissue mutational status (patients in Group A and Group B) Stratified by ctDNA status, molecular subtypes of FoundationOne CDx (F1CDx) and clinical parameters
BACKROUND/RATIONALE	Pancreatic ductal adenocarcinoma (PDAC) remains an almost uniformly lethal disease. Although significant progress has been made in the understanding of the molecular biology of pancreatic cancer, this knowledge has not translated into an improved prognosis for patients suffering from this devastating disease. Especially, mechanisms underlying early relapse after potentially curative surgery, resistance to therapeutic interventions as well as response to chemotherapy are incompletely understood. Alarmingly, pancreatic cancer is on the rise and will become the second leading cause of cancer-related death in Germany and the US by 2020 In order to treat a patient with potentially harmful systemic chemotherapy, a diagnosis has to be made. Many countries such as Germany demand a histological confirmation of malignancy in order to allow for treatment with chemotherapy. Due to its delicate location, biopsies of the pancreas are technically challenging and pose the risk of complications. Furthermore, cytological and histological diagnosis of pancreatic malignancy is highly depended on the expertise of the gastroenterologist, the underlying pancreatic disease and the on-site pathologists. Accordingly, novel means to diagnose and monitor patients with pancreatic cancer are of major clinical significance. Liquid biopsies have the potential to close this diagnostic gap as they rely on tumor-specific signatures in the circulation and are thus more specific than traditional tumor markers. Generally, analysis of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) holds the biggest promise to adequately diagnose and monitor malignant disease based on liquid biopsies. While capturing and analyzing CTCs is complex, isolation and processing of ctDNA is relatively simple. Genetically, pancreatic cancer is defined by near ubiquitous activating mutations in the KRAS oncogene. Furthermore, mutations in p53, SMAD4/DPC4 and CDKN2A are observed with a high frequency. This overrepresentation of a relatively small group of highly conserved mutations renders pancreatic cancer especially suitable for ctDNA-based approach. While limited data based on small single center studies on liquid biopsies in pancreatic cancer exist a comprehensive and methodically standardized analysis of the value of ctDNA in the diagnosis, management and prognosis of pancreatic cancer is missing. Preliminary data from small clinical trials suggest, that the presence of preoperative ctDNA has a major prognostic impact on the disease-free and overall survival in patients undergoing curative surgery for resectable pancreatic cancer
KEY EXCLUSION CRITERIA	1. Non-resectable disease as determined by a local tumor board 2. Metastatic pancreatic disease 3. Previous neoadjuvant chemotherapy 4. Previous neoadjuvant radiotherapy 5. Histology other than PDAC such as acinar, neuroendocrine, mixed histology etc. in the resection specimen 6. Malignant disease other than PDAC within previous year (***exception***: patients with adequately treated and completely resected basal cell or squamous cell skin cancer; in situ cervical, breast or prostate cancer within previous year may be included)
KEY INCLUSION CRITERIA	1. Adult patients ≥ 18 years of age 2. Pancreatic mass, suspicious of pancreatic cancer, deemed resectable and resection planned. 3. Patient deemed medically fit for adjuvant chemotherapy by the investigator 4. Patient's legal capacity to consent to study participation 5. Signed and dated informed consent to participate in the study
STATISTICAL ANALYSIS	The analysis of the study will be exploratory and primarily use descriptive statistical methods. The primary analysis of the study will compare the disease-free survival time of patients with preoperative ctDNA positivity (Group A) to patients with preoperative ctDNA negativity (Group B) based on a Cox Proportional Hazards model with adjustments for relevant covariates.

SAMPLE SIZE	Under the assumptions of proportional hazards and exponential distribution, the study is planned to detect a difference (ratio of 1.8) in disease-free survival between ctDNA positive (Group A) and ctDNA negative patients (Group B) with a power of 80%, which requires a total number of 119 events (tumor disease recurrence or death) to be observed. To take deviations from assumptions into account, inclusion of 132 patients overall (about 44 patients with preoperative ctDNA positivity) in total is planned. An interim analysis will be conducted after 60 events have occurred to detect deviations from the statistical assumptions.
TRIAL DURATION	***Accrual period:*** The accrual period is estimated to last 24 months. ***Duration of individual observation*** Until occurrence of relapse (or death if death occurs earlier than relapse) for a maximum of 36 months after the date of surgery ***Estimated study duration:*** 5 years from the first patient enrolled until the end of study ***Start of the study:*** First patient First visit (FPFV): Date of the informed consent by the first patient enrolled *Planned* QII/2019 ***End of the study:*** Last patient's last Follow up visit *Planned* QII/2024

AIO-PAK-0121/ass -An open labelled phase III adjuvant trial of disease-free survival in patients with resected pancreatic ductal adenocarcinoma randomized to allocation of oxaliplatin- or gemcitabine-based chemotherapy by standard clinical criteria or by a transcriptomic treatment specific stratification signature – ESPAC-6

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-PAK-0121/ass -**		
Status:	in Vorbereitung		
Rekrutierungszeit:	von: Q1/2022	bis: Q2/2025	
Anzahl Zentren:	geplant: 30	aktuell initiiert: 0	aktiv rekrutierend: 0
Weitere Zentren:	auf Anfrage		
Anzahl Patienten:	geplant: 394	aktuell eingeschlossen: 0	
Letzte Aktualisierung	13.10.2021		

STUDY TYPE	Open labelled phase III multicentre randomized trial
PRINCIPAL INVESTIGATOR	Lead Coordinating Investigator: Prof. Dr. Dr. med. Markus W Büchler University Hospital Heidelberg Abteilung für Allgemeine, Viszerale und Transplantationschirurgie Im Neuenheimer Feld 420 69120 Heidelberg

TRIAL OFFICE	Institute of Clinical Cancer Research IKF GmbH at Northwest Hospital Steinbacher Hohl 2-26 60488 Frankfurt am Main
SPONSOR	Ruprecht-Karls-University Heidelberg, Medical Faculty represented by Universitätsklinikum Heidelberg and Commercial Director Im Neuenheimer Feld 672 69120 Heidelberg
CONDITION	Pancreas
DESIGN	Open labelled phase III multicentre randomized trial.
INDICATION	Pancreatic ductal adenocarcinoma (PDAC) MedDRA code: 10033575 Concept ID: C0346647 ICD-O-3 site C25
OBJECTIVE(S)	**Primary Objective** The main purpose of the study is to determine whether disease free survival in patients with resected pancreatic ductal adenocarcinoma (PDAC) treated with standard adjuvant chemotherapy regimens (oxaliplatin- or gemcitabine-based), is superior using allocation based on a treatment specific signature (TSS), compared to the same chemotherapy regimens allocated according to standard clinical criteria. The primary estimand for the primary objective is defined as follows: Population: all patients fulfilling the in- and exclusion criteria. Variable/Endpoint: disease-free survival, defined as time from randomisation to disease recurrence (growth or metastasis) or death from any cause. Post-randomisation events: death from any cause is incorporated into the variable definition (composite strategy); changes in treatment and termination of treatment before the end of the 24 weeks treatment will be ignored (treatment policy strategy); event-free patients at the end of the follow-up period will be censored and drop-outs will be censored at the last observation (hypothetical strategy). Summary measure: hazard ratio for the endpoint disease-free survival between the two treatment arms. **Secondary Objectives** Secondary objectives of the study are to assess overall survival (median, 3 year survival rate), metastasis free survival; survival based on targeted signatures (TSS) in test versus control arms, and survival using targeted therapies initially on relapse compared to standard first-line therapies on relapse.
INTERVENTION(S)	All medication within the study is used within clinical routine. Therapeutic intervention of standard adjuvant chemotherapy comprising oxaliplatin- or gemcitabine-based regimens based on standard clinical criteria, compared to selection using a treatment specific signature and prediction model.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	The ESPAC-6 translational research programme will generate a rich resource of archival patient material, Patient-Derived Organoids (PDOs) and prospective data (randomised and controlled). The translational research protocol will utilise patient tissues including blood and primary resectable and recurrent locally advanced or metastatic tissue to exhaustively characterise the molecular mechanisms underpinning response to adjuvant therapy.

	ESPAC-6 will co-ordinate the sequencing and analysis of all patient material, included in the trial, and harmonise efforts to generate PDOs. ESPAC-6 is funded to sequence all patient material (RNA and DNA) with additional supplementary funding for PDO generation. ESPAC-6 will, where possible, complement existing translational research programmes currently being undertaken by partner organisations and does not wish to act as a competing interest. Partner organisations may contribute material to the ESPAC-6 translational research programme at their discretion, however, all data generated/funded by ESPAC-6 must be made available to all contributing partner organisations.
BACKROUND/RATIONALE	At present selection of therapy is based entirely on clinical criteria. It is becoming increasingly apparent that different tumour types respond differently to gemcitabine based versus non- gemcitabine-based regimens. For example, tumours expressing high levels of hENT1 are more likely to be associated with longer survival from gemcitabine whilst tumours expressing high levels of GATA6 are more likely to be associated with longer survival from 5FU. The use of a Treatment Specific Signature based on RNAseq may also select patients with pancreatic cancer more likely to respond to either oxaliplatin-based or gemcitabine-based therapy. At the present time the best that can be expected for resectable PDAC with resection and adjuvant therapy using standard clinical criteria is say 20-50%. By selecting patients with specific transcriptomic signatures the upper level could be increased to say 70%. This would have major impact in the treatment in the disease. It would also facilitate the introduction RNAseq into routine clinical practice. Potentially this principle could be extended to other difficult-to-treat cancer types.
KEY EXCLUSION CRITERIA	1. Solid pseudopapillary neoplasm, neuroendocrine neoplasm, pancreatoblastoma, bile duct cancer, and ampullary cancer. 2. Distant metastases, including ascites or malignant pleural effusion. 3. Macroscopic incomplete tumour removal (R2 resection). 4. CA 19-9> 180 U / ml within 21 days of registration on study. 5. Cardiomyopathy or congestive heart failure, NYHA III-IV or coronary heart disease symptoms. 6. Major comorbidity that may preclude the delivery of treatment or known active infection (HIV or untreated chronic hepatitis B or active hepatitis C) or uncontrolled diabetes 7. Pre-existing neuropathy, Gilbert's disease or known genotype UGT1A1*28 /*28. 8. Inflammatory disease of the colon or rectum, or intestinal obstruction, or severe postoperative uncontrolled diarrhoea. 9. Known Dihydropyrimidine dehydrogenase (DPD) deficiency 10. Pregnancy and lactation. 11. Participation in other clinical trials or observation period of competing trials, respectively. 12. History of hypersensitivity or other known contraindication 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. 13. 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 or bladder, or low/intermediate risk prostate cancer (Gleason score ≤7) with normal PSA levels. 14. Any other concurrent antineoplastic treatment including irradiation
KEY INCLUSION CRITERIA	1. Histologically proven pancreatic ductal adenocarcinoma including variants, and acinar cell carcinoma. 2. Patient had provided tumour tissue at resection for RNAseq

	3. Macroscopically complete resection (R0 or R1 resection). 4. Female and male Patients aged from 18 to 79 years. 5. WHO performance status 0-1. 6. No prior radiotherapy and no previous chemotherapy. 7. Full recovery from surgery and patient able to receive chemotherapy: adequate oral nutrition of ≥ 1500 calories per day and free of significant nausea and vomiting 8. Adequate hematologic function: Absolute neutrophil count ≥ 1,500 cells/mm^3, platelets ≥ 100,000 cells/mm^3 and haemoglobin ≥ 8 g/L (transfusion permitted). 9. Serum total bilirubin ≤ 1.5 times the institutional upper limit of normal. 10. Creatinine clearance ≥ 50 mL/min. 11. Patient of child-bearing potential (for female patient: study entry after a menstrual period and a negative pregnancy test) must agree to use highly effective methods of contraception during the study and for 4 months after the last study treatment for women and 6 months for men. 12. Intended interval since surgery between 21 and 84 days at date of randomization. 13. Public or private health insurance cover. 14. Ability of subject to understand character and individual consequences of the clinical trial. 15. Not legally incapacitated. 16. Written informed consent.
OUTCOME(S)	Primary Disease free survival, time from randomization to disease recurrence or death from any cause Secondary • Overall survival • Metastasis free survival • Overall survival from recurrence • Quality of Life (EORTC QLQ C-30) • Survival based on targeted signatures (TSS) in arm A (test) versus arm B (control). • Response to targeted therapies • Assessment of safety: toxicity according to NCI-CTC v.5.0; adverse and serious adverse events
STATISTICAL ANALYSIS	Primary endpoint analysis and population: Analysis of the primary endpoint disease free survival will be carried out using a Cox regression model. The Cox model allows evaluation of differences in the hazards between the test and control arm while accounting for the strata resection status (R0 vs. R1) and “post-operative serum Carbohydrate Antigen (CA) 19-9 levels <37KU/L (yes/no)”. Hereby, the robust sandwich estimate of the covariance matrix proposed by Lin and Wei (1989) 11 is used for the test for treatment effect. This test allows valid statistical inference also in situations where the proportional hazards assumption is violated, which may be the case in the current situation. The two-sided significance level is set to α= 0.05. The hazard ratio for the treatment effect will be estimated alongside a 95% confidence interval. Kaplan-Meier curves will be created, median, and 3-year disease free survival rates will be calculated with 95% confidence intervals. The analysis of the primary endpoint will be conducted on the full analysis set (including all randomized patients following the intention-to-treat principle). Death, as intercurrent event occurring after randomization, is handled by inclusion into the definition of the primary endpoint which reflects a composite strategy (according to the ICH E9 (R1) addendum). Patients with incomplete observation time due to lost to follow-up or early drop-out will be censored at last observation (hypothetical strategy). Further post-

	randomization events (e.g. treatment discontinuation due to toxicities) will be ignored. This reflects a treatment policy approach. Safety: The proportion of grade 3 and 4 toxicity will be compared across treatments using time to event methods and frequency counts. Adverse and serious adverse events are collected throughout the study and will be tabulated and compared between study arms. Secondary endpoint analysis: Overall-survival (OS) will be tested in a hierarchical manner if the null hypothesis regarding the primary endpoint was rejected. If not, OS will be analysed as the other secondary outcomes in a descriptive manner which means that p-values will not be interpreted in a confirmatory sense. Time to event endpoints will be analysed analogously to the primary endpoint. Quality of life will be assessed over time and treatment groups compared using longitudinal analysis. Joint modelling of quality-adjusted survival analysis will be undertaken to allow a simultaneous assessment of quality of life and survival.
SAMPLE SIZE	To be assessed for eligibility: n= approximately 600 To be allocated to study: n=394 To be analysed: n=394 The sample size was calculated for the primary endpoint disease free survival (DFS) based on a two-sided significance level of α = 5 % and a power 1-β of 80 %, assuming an accrual time of 36 months and a follow-up time of 36 months (including the 6 months of treatment). Based on previous studies (ESPAC-4, PRODIGE) we assume a 35 % 3 year-disease free survival rate for the control arm. We expect a hazard ratio (HR) of 0.710 which corresponds to a 3 year- disease free survival rate of 47.45 % in the test arm. Furthermore, we expect an exponentially distributed drop-out rate of 10 %. This results in 394 patients to be included in the study to observe the necessary 268 events. The use of a Cox regression model adjusting for covariates is expected to yield an additional increase in power due to less unexplained variance. ADDPLAN v6.1.1 and the formula by Schoenfeld (1981) 12 were used to calculate the sample size.
TRIAL DURATION	Recruitment period (months): 40 Follow-up for each patient from date of randomization, at least (months): 36 First patient in, to last patient out (months):76 Time for data clearance and analysis (months): 6 Duration of the entire study (months): 82
PARTICIPATING CENTERS	Approx. 30 sites in Germany
NUMBER of PATIENTS	394 (planned)
CURRENT NUMBER of PATIENTS	Not applicable, recruitment not yet started

Pankreaskarzinom, neoadjuvant, perioperativ

AIO-PAK-0220/xx: Neoadjuvant treatment in frail patients with pancreatic adenocarcinoma - A prospective, parallel-group, randomized multi-center Phase II AIO/CHIR-Net Trial (FrailPanc)

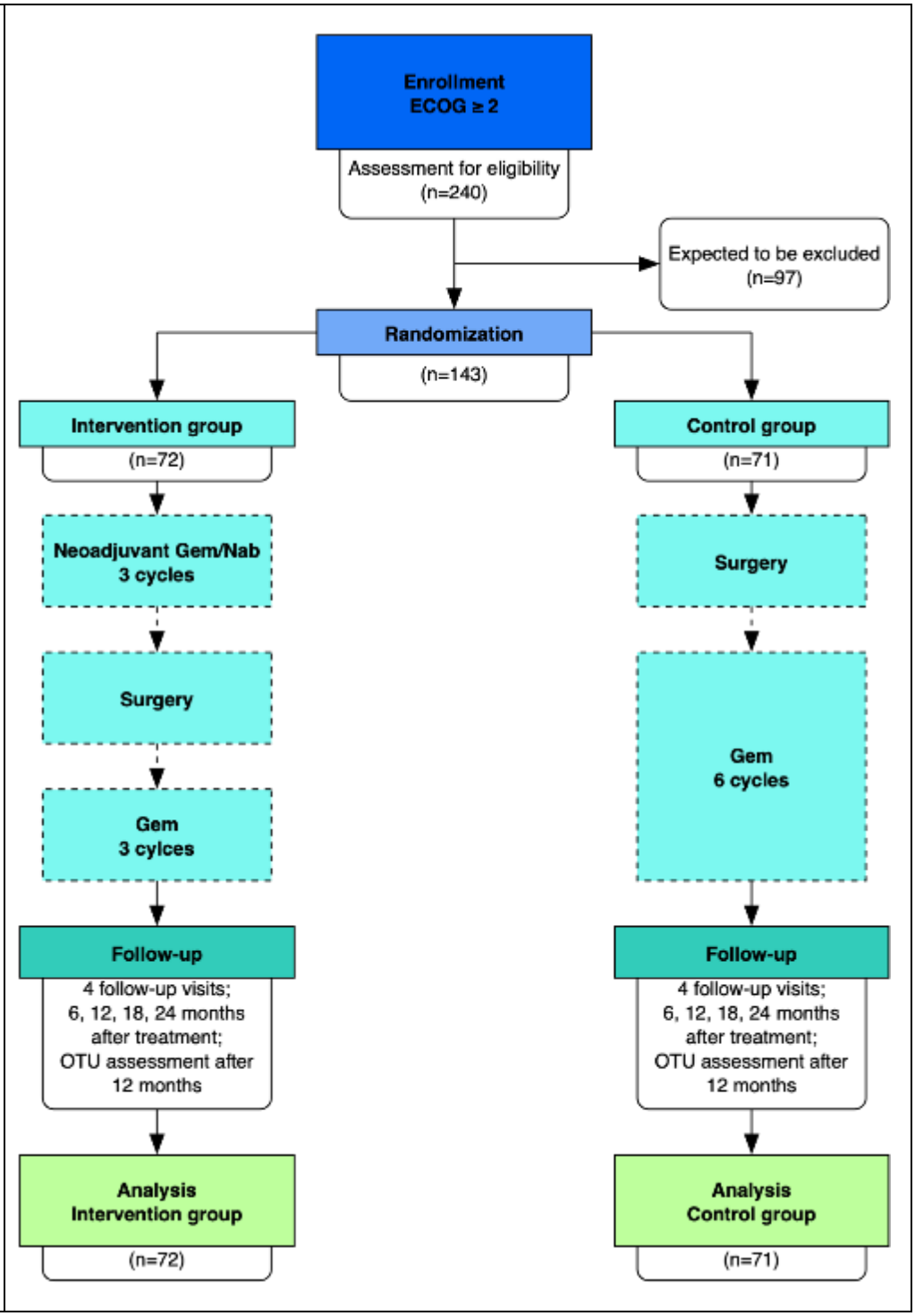
AIO-Studie

Studiennummer/-Code:	**AIO-PAK-0220/ass/xx - FrailPanc**		
Status:	in Vorbereitung		
Rekrutierungszeit:	von:	bis:	
Anzahl Zentren:	geplant:	aktuell initiiert:	aktiv rekrutierend:
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant:	aktuell eingeschlossen:	
Letzte Aktualisierung	04.05.2020		

Study phase	Phase II
Study design	Prospective, randomized multi-center Phase II study to evaluate in frail patients with anatomically resectable or borderline resectable pancreatic cancer two primary hypotheses: 1) Improvement of the 2-year overall survival 2) Improvement of the Overall Treatment Utility (OTU) Score by neoadjuvant treatment.
Sponsor details	University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg, Germany
Coordinating Investigators	Coordinating Investigator Surgery PD Dr. med. Faik G. Uzunoglu, Dept. of General-, Visceral- and Thoracic Surgery University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg email: f.uzunoglu@uke.de Coordinating Investigator Medical Oncology PD Dr. med. Marianne Sinn II. Department of Medicine University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg email: ma.sinn@uke.de
Study Coordinator	PD Dr. Marianne Sinn; PD Dr. med. Faik G. Uzunoglu
Countries	Germany
Centre(s)	n= 20-25
Planned sample size (N)	n= 240
Planned study start/end dates	FPI: Q1/2021 LPI: after approx. 36 months LPLT: after approx. 44 months End of Follow up period after LPLT: after approx. 68 months Data base lock: after approx. 72 months Study report: after approx. 74 months Publication after approx. 79 months

Recruitment period	Treatment phase: From start of study treatment (Gemcitabine + *nab-Paclitaxel* or surgery) to end of treatment (last chemotherapy cycle). Follow-up phase**:** After completion of study treatment, all patients will be followed-up for overall survival and Overall treatment utility (OTU), Progression Free Survival, Toxicity, Quality of Life, Geriatric Assessments, pathological resection status and response, in-hospital mortality, perioperative severe morbidity, delayed gastric emptying, fistula rates, as well as completion of in total 6 cycles of chemotherapy.
Rational and Objectives	Pancreatic adenocarcinoma (PDAC) is one of the few cancer types with a still raising mortality and predicted to become the second common cause of cancer related death by 2030. Overall survival remains poor with a 5-year survival for all stages about 8%. For primarily resectable PDAC, substantial progress was made in the last decade by the combination of surgery and (intensified) adjuvant chemotherapy leading to 5-year survival rates of 30-50%. Actually, the effect of neoadjuvant/ perioperative chemotherapy and surgery is investigated in several ongoing clinical trials. However, a relevant subgroup of PDAC patients present themselves with a reduced performance status (ECOG ≥2). These patients are most likely not eligible for an intensive perioperative chemotherapy regime and are routinely excluded from most clinical trials. At the same time a reduced ECOG status is often times associated with elderly patients (age ≥70). By taking in consideration that PDAC patients present themselves at a median age of 70 years, data related to the perioperative chemotherapy for a substantial subgroup of PDAC patients is currently not available. The aim of our trial concept is to focus on the role of neoadjuvant chemotherapy in frail patients. Frail patients (defined in this trial as ECOG ≥2 or inability to receive mFOLFIRINOX) with medical as well as technical operability (based on interdisciplinary tumor board assessments) will be randomized in two groups: gemcitabine based combination therapy preoperatively, followed by surgery and adjuvant therapy (group A) versus surgery followed by adjuvant gemcitabine. While the primary endpoint will be the overall survival, this endpoint does not accommodate the complexity of frail cancer patients entirely. We therefore decided to use the Overall treatment utility (OTU) as a co-primary endpoint in a hierarchical order. The OTU intends to individually capture the balance of benefits and harms from cancer treatments and was developed within the FOCUS2 trail in elderly colorectal cancer patients. The OTU combines clinical and radiological response, toxicity, adverse events and patient-reported acceptability of treatment and therefore might allow conclusions regarding the optimal treatment strategy for frail patients by taking into account the physicians and patients appreciation of the optimal therapy (“Are you glad you gave it?”; “Are you glad you received it?”). The impact on clinical practice of the trial will be the establishment of a more individual approach in this complex patient collective.
Primary Endpoint	Overall survival (OS) Co-primary endpoint: overall treatment utility (OTU)
Secondary Endpoints	Progression Free Survival, Toxicity, Quality of Life, Geriatric Assessments (Mini-Mental State Exam (MMSE), instrumental activities of daily living (IADL), Geriatric Depression Scale (GDS)), pathological resection status and response, in-hospital mortality, perioperative severe morbidity, delayed gastric emptying, fistula rates, completion of in total 6 cycles of chemotherapy.
Inclusion criteria	11. Written informed consent and any locally-required authorization obtained from the subject 12. Age ≥ 18 years at time of study entry 13. Histologically or cytologically proven Pancreatic adenocarcinoma of the head or body (PDAC) • proven by biopsy/cytology or • high-grade suspicion based on o computed tomography (CT) o Ca 19-9 >100 U/ml o Hyperbilirubinemia o B-symptoms o interdisciplinary tumor board recommendation 14. Eastern Cooperative Oncology Group (ECOG) score ≥ 2 or inability to receive mFOLFIRINOX 15. Medical and technical operability defined by tumor board assessment 16. No previous chemo- or radiotherapy

	17. Patient compliance and geographical situation allowing an adequate follow-up 18. 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
Main Exclusion criteria	10. Active infection > Grade 2 NCI-CTCAE V5.0 11. Secondary malignancies except for basal cell carcinoma of the skin during the last 5 years 12. Need of immuno-suppressive therapy (e.g. pts after transplantations) 13. Locally advanced or metastatic PDAC 14. Concomitant serious systemic disease (with life expectancy < 6 months) 15. Known HIV infection 16. Known allergic reactions against the study drugs 17. Patients undergoing dialysis 18. Need of immunosuppressive therapy (e. g. transplantations) 19. Participation in another experimental clinical trial within four weeks prior to study entry 20. Other primary malignancy in the patient's history in the last five years (except for successfully treated basalioma or carcinoma in situ of the cervix uteri)
Statistical considerations	Power = 80%, two-fold significance level = 5% Events (n=93); patients included (n=143); control group (n=71); interventional group (n=72) The sample size is calculated with PASS 16 using the Log rank Tests Proportion Surviving function. In the CONKO-001 trial, the 2-year overall survival rate was about 50% for patients with resectable PDAC treated with adjuvant gemcitabine. Even if the overall rates have increased in more recent trials, a decrease of 10% for frail patients is expected. Hence, an improvement in 2-year overall survival in elderly and/or frail patients with resectable PDAC from 40% with adjuvant chemotherapy to 60% by the use of neoadjuvant chemotherapy is assumed. This corresponds to a hazard ratio (HR) of 0.56 of the intervention group compared to the control group. A dropout-rate of 20% during the period of the first patient in to last patient out of 68 months (=5.67 years) is considered which leads to a dropout-rate of 3.5% per year. The accrural time is set to 36 months (=3 years). To detect the improvement in 2-year overall survival with a power of 80% and a two-sided significance level of 5%, 93 events must be observed. This leads to 143 patients in total, 71 in the control group and 72 in the treatment group. Since there are no assumptions about the efficacy with respect to the OTU, the sample size is calculated only for the first primary endpoint. The primary analyses will be based on the data of the intention to treat (ITT) population. In secondary analyses also the data of the per protocol (PP) population will be used. The primary outcome ‘overall survival’ will be analyzed by a Cox proportional hazards regression model with treatment group and stratification factor (resectable vs. borderline resectable) as fixed effects. The treatment effect will be reported as hazard ratio with two-sided 95% confidence interval and p-value testing the null hypothesis of no treatment effect. If the primary hypothesis regarding the overall survival can be rejected, the second primary hypothesis regarding the OTU can be analyzed in a confirmatory manner (hierarchical ordered primary hypotheses). For this analysis a binary logistic regression model will be used on the post-treatment score (dichotomized in poor vs good/intermediate), with treatment group, resectable vs. borderline resectable as fixed effects.

Trial design	

Registerstudie

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

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)	
Studiennummer/-Code:	AIO-YMO/PAK-0215 - PDAC, PaCaReg	
Rekrutierungszeitraum:	Rekrutierung gestartet 10/2018 geplant von/bis: nicht festgelegt	
Anzahl Zentren:	geplant: nicht festgelegt	initiiert: 6
Anzahl Patienten:	geplant: nicht festgelegt	aktuell eingeschlossen: 54
Weitere Zentren:	Offen für weitere Zentren	
Letzte Aktualisierung	Oktober 2020	

Studienleitung	Dr. med. Thomas Ettrich Universitätsklinikum Ulm, Klinik für Innere Med. I 89081 Ulm, Tel. 0731-500 44774, thomas.ettrich@uniklinik-ulm.de Mentoring Investigator: Univ.-Prof. Dr. Thomas Seufferlein Universitätsklinikum Ulm, Klinik für Innere Medizin I
Die Synopse finden ist zu finden unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologists	

Arbeitsgruppe Supportive Therapie

Registerstudie: Diagnostik und Therapie der Tumortherapie-induzierten Anämie

Qualitätssicherung zum Anämiemanagement bei Patientinnen und Patienten mit soliden Tumoren und hämatologischen Neoplasien

AIO-Studie

Studiennummer/-Code:	**AIO-SUP-0121**		
Status:	in Rekrutierung		
Rekrutierungszeit:	von: Oktober 2021	bis: Februar 2022	
Anzahl Zentren:	geplant: ca. 200	aktuell initiiert: 72	aktiv rekrutierend:57
Weitere Zentren:	keine weiteren Zentren geplant.		
Anzahl Patienten:	geplant: 1000	aktuell eingeschlossen: 241	
Letzte Aktualisierung	November 2021		

STUDY TYPE	Repräsentative, retrospektive, epidemiologische Registerstudie in Kooperation mit der AGSMO
PRINCIPAL INVESTIGATOR	Prof. Dr. Hartmut Link Innere Medizin, Hämatologie Internistische Onkologie Finkenhain 8 67661 Kaiserslautern Tel.: +49 631 - 350 5558 Fax: +49 631 - 372 8146 E-Mail: link@aio-portal.de
TRIAL OFFICE	Ansprechpartner: Markus Kerkmann, Laura Holtmann MMF GmbH Heideblick 59 44229 Dortmund E-Mail: anemia@mmf-do.de
SPONSOR	AIO-Studien-gGmbH Ansprechpartner: Markus Detzner Kuno-Fischer-Straße 8 14057 Berlin E-Mail: detzner@aio-studien-ggmbh.de
CONDITION	Patienten mit Tumortherapie-induzierter Anämie mit Hb ≤ 10g/dl (6,2 mmol/l) bei folgenden Krebserkrankungen: ▪ Gastrointestinale Tumoren (Kolon, Rektum, Magen, Ösophagus und Pankreas) ▪ Mammakarzinome ▪ Lungenkarzinome ▪ Maligne Lymphome (NHL und Hodgkin Lymphome)
DESIGN	Analyse der Versorgungsstruktur und Rekrutierung (Phase 1): In einem ersten Schritt werden Daten zu Versorgungseinrichtungen, die Patienten in den genannten Indikationen in Deutschland behandeln, erhoben (gastroenterologische, gynäkologische, hämato-/onkologische und pneumologische Klinikabteilungen, sowie niedergelassene Hämato-/ Onkologen und Gynäkologische Onkologen). In Phase 1 werden alle Zentren in Deutschland, die potenziell Patienten in den genannten Entitäten behandeln, kontaktiert und Daten über den Versorgungsgrad der Einrichtung und die Anzahl der behandelten Patienten mit einem einseitigen Pen-to-Paper-Formular erfasst. Darüber hinaus wird die Bereitschaft der Versorgungseinrichtungen, sich an der Dokumentation der Patienten zu beteiligen, erhoben (Phase 2).

	Patientendokumentation (Phase 2) In Phase 2 wird ein mehrseitiges elektronisches Fallaktenformular (eCRF) ausgefüllt, um die Patienten- und Behandlungsdaten, die für den Zweck der Studie relevant sind, zu erfassen. Alle Daten werden retrospektiv und anonym anhand der Patientenakten gesammelt. ▪ Patienten- und krankheitsbezogene Variablen (Alter, ECOG-Performance-Status, Staging, relevante Komorbidität) ▪ Medikamentöse Tumortherapie (Chemotherapie, Antikörper, Immuntherapie, Kinase-Inhibitoren: Beginn/Ende, Subtanzen bzw. Regime) ▪ Strahlentherapie (Beginn/Ende, bestrahlte Region) ▪ Labordiagnostik (soweit verfügbar) mit Hb, Hk, MCV, MCH, Retikulozyten und/oder Ret-Hb, Ferritin, Transferrin und/oder Transferrin-Sättigung (TSAT), Holo-Trans-Cobalamin (Vitamin B12), Folsäure, Zinkprotoporphyrin, Kreatinin-Clearence (GFR), EPO-Spiegel, Hepcidin-Spiegel ▪ Daten zur Anämietherapie (Transfusion von EK; Eisensubstitution p.o. oder i.v.; ESA) Um die Datenqualität zu sichern, wird der wissenschaftliche Projektleiter zwei Mitarbeiter des beauftragten Instituts in inhaltlichen Fragen der Studie schulen. Dieses Wissen wird in die Programmierung der Benutzeroberfläche und der Patientendatenbanken einfließen, so dass das Programm anhand von definierten Anforderungen und Rahmenbedingungen auf Vollständigkeit und, soweit möglich, auf Plausibilität überprüft wird. Diese Prüfungen begleiten den Prozess der Dateneingabe in das eCRF und ermöglichen die sofortige Validierung der Daten.
INDICATION	Anämie und Eisenmangel bei Patientinnen und Patienten, die wegen einer Krebserkrankung medikamentös oder radiotherapeutisch behandelt werden
OBJECTIVE(S)	Primäres Studienziel: Überprüfung der Leitlinienadhärenz bei Krebspatienten mit Tumortherapie-induzierter Anämie und hohem Risiko für Anämie-bedingte Komplikationen Sekundäre Studienziele: Explorative Analyse von patientenspezifischen, versorgungsspezifischen Parametern, die mit einer (nicht-)leitliniengerechten Diagnose und Therapie korrelieren, um spezifische Erkenntnisse (patienten- oder einrichtungsspezifisch) für zielgerichtete Fortbildungen zu gewonnen
INTERVENTION(S)	Keine. Erfassung der klinischen Routine
BACKROUND/RATIONALE	Anämie und Eisenmangel sind häufige Komplikationen bei Patientinnen und Patienten mit Krebserkrankungen, insbesondere wenn diese chemotherapeutisch behandelt werden. Die Therapie- induzierte Anämie (TIA) ist dabei sowohl mit einer reduzierten Lebensqualität (QoL) assoziiert als auch mit Konsequenzen für ein geringeres Therapieansprechen (ORR) und ein reduziertes Gesamtüberleben (OS), wobei der kausale Zusammenhang noch nicht vollständig geklärt ist. Die 2018 aktualisierte ESMO Guideline „Management of Anaemia and Iron Deficiency in Patients With Cancer“ gibt einen dezidierten Algorithmus als Entscheidungshilfe bei der Diagnose und Therapie der Anämie bei Tumorpatienten an, um Anämie-bedingte Komplikationen zu reduzieren. Dieser umfasst Empfehlungen zu Eisen-Substitution, Erythrozyten Stimulierenden Agenzien (ESA) und Transfusion mit Erythrozyten-Konzentraten (EK) in Abhängigkeit von verschiedenen Diagnoseparametern und der jeweiligen antitumorösen Therapie. Die dargestellten Therapieempfehlungen entsprechen dabei in ihren Kernpunkten den Empfehlungen der Onkopedia-Leitlinie zur Eisenmangelanämie und der S3-Leitlinie zur Supportiven Therapie.

<table>
<tr><td>KEY EXCLUSION CRITERIA</td><td>Beobachtungszeit weniger als 4 Wochen, fehlender Patientenkontakt nach Anämiediagnose</td></tr>
<tr><td>KEY INCLUSION CRITERIA</td><td>Eingeschlossen werden Patientinnen und Patienten in den u.g. genannten Indikationen, die in der Zeit von 01.01.2021 – 30.06.2021 (Q1-Q2/2021) eine medikamentöse Tumortherapie und/oder Radiotherapie erhalten haben und bei denen der Hämoglobinwert mindestens einmal unter 10g/dl (6,2 mmol/l) gesunken ist. Die Beobachtungszeit der Patienten nach der Anämiediagnose soll mindestens 4 Wochen betragen.
Gastrointestinale Tumoren
(Kolon, Rektum, Magen, Ösophagus und Pankreas)
Mammakarzinome
Lungenkarzinome
Maligne Lymphome (NHL und Hodgkin Lymphome)</td></tr>
<tr><td>OUTCOME(S)</td><td>Umsetzung der Leitlinienempfehlungen bei der Diagnostik und Therapie der Tumortherapie-induzierten Anämie</td></tr>
<tr><td>STATISTICAL ANALYSIS</td><td>Die Datenerhebung aus den Patientenakten erfolgt anonymisiert durch die beauftragte Institution nach der Methodik einer repräsentativen Umfrage. Die wissenschaftliche Leitung definiert auf Grundlage der aktuellen ESMO-Leitlinie (2018) sowie der S3-Leitlinie Supportive Therapie und der DGHO Onkopedia Leitlinie Standards für eine leitliniengerechte Therapie. Es werden die Erfüllung oder die Grade der Abweichung von diesen Standards ermittelt.</td></tr>
<tr><td>SAMPLE SIZE</td><td>Um eine zuverlässige, repräsentative Stichprobe der in Deutschland behandelten Patienten zu erhalten, wird die Verteilung der zu dokumentierenden Fälle in den einzelnen Indikationen auf die beteiligten Einrichtungen festgelegt. Dazu werden die in Phase I erhobenen Daten der Einrichtungen zu Patientenzahlen und Behandlungsstruktur verwendet:
Die teilnehmenden Zentren werden aufgrund wesentlicher Unterscheidungsmerkmale (Einrichtungstyp, Versorgungsgrad und Anzahl der behandelten Patienten) in Cluster eingeteilt. Diese Stichprobe wird entsprechend der vorherigen Versorgungsstrukturanalyse moduliert. Durch diesen Ansatz können die tatsächlichen Prozentsätze der verschiedenen Versorgungseinrichtungen in einem Indikationsgebiet anteilig in der Patientendokumentationsstichprobe berücksichtigt werden.
Der Stichprobenumfang wird auf Basis der jährlichen Inzidenz der Grunderkrankung und der relativen Häufigkeit von Anämie bei Patienten unter systemischer Therapie bei diesen Indikationen berechnet. Die Stichprobe sollte 0,5 % der jährlichen Inzidenz der therapieinduzierten Anämie repräsentieren, um ausreichende Daten zu generieren.
<table>
<tr><th>Erkrankung</th><th>Jahresinzidenz in Deutschland</th><th>Häufigkeit von Anämie</th><th>geplante Stichprobe</th></tr>
<tr><td>Gastrointestinale Tumoren</td><td>~ 98.0000</td><td>61-63%</td><td>~ 350</td></tr>
<tr><td>Mammakarzinom</td><td>~ 70.000</td><td>62-71%</td><td>~ 300</td></tr>
<tr><td>Lungenkarzinom</td><td>~ 57.500</td><td>77-83%</td><td>~ 250</td></tr>
<tr><td>Maligne Lymphome</td><td>~ 21.000</td><td>73-79%</td><td>~ 100</td></tr>
<tr><td>Total</td><td>~246.500</td><td>68-75%</td><td>~ 1.000</td></tr>
</table></td></tr>
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Arbeitsgruppe Thorakale Onkologie

SCLC, limitiert

AIO-TRK-0320: Thoracic radiotherapy with atezolizumab in small cell lung cancer extensive disease: a randomized, open-label, multicenter phase II study (TREASURE)

AIO-Studie

Studiennummer/-Code:	AIO-TRK-0320 - TREASURE		
Status:	in Rekrutierung		
Rekrutierungszeit:	von: 30.09.2020	bis: 30.09.2022	
Anzahl Zentren:	geplant: 17	aktuell initiiert: 17	aktiv rekrutierend: 4
Weitere Zentren:	sind leider nicht möglich		
Anzahl Patienten:	geplant: 104	aktuell eingeschlossen: 32	
Letzte Aktualisierung	30.09.2021		

STUDY TYPE	Investigator-initiated trial (IIT)
PRINCIPAL INVESTIGATOR	Dr. Farastuk Bozorgmehr Prof. Dr. Stefan Rieken Univ.-Prof. Dr. Michael Thomas
TRIAL OFFICE	Department of Thoracic Oncology/ Internal Medicine Thoraxklinik at Heidelberg University Hospital Röntgenstr.1 69126 Heidelberg
SPONSOR	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
DESIGN	Prospective, randomized, open-label, multicenter, phase II trial.
INDICATION	SCLC extensive disease
OBJECTIVE(S)	Primary objective: The objective of this study is to investigate the treatment efficacy of combining thoracic radiotherapy (TRT) with the IMpower133 regimen in the upfront treatment of ED SCLC patients. Secondary objectives: Additionally, with this study, we aim to determine the safety and tolerability of the combination of immunological and radiological treatment in the first-line setting of advanced SCLC. Furthermore, blood, stool and tissue samples are collected prospectively for the separate translational program.
INTERVENTION(S)	At time of inclusion into the study, all patients must have received four cycles of induction therapy with carboplatin/etoposide and atezolizumab independently of the study as part of standard of care therapy. After 1:1 randomization, eligible patients will receive either atezolizumab (1,200 mg fixed dose, Q3W) and TRT (30 Gy in 10 fractions) in arm A or atezolizumab only (1,200 mg fixed dose, Q3W) in arm B.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	An accompanying translational research project will investigate the mechanisms behind potential tumor-specific immune effects that might be induced by the combination of PD-L1 inhibition and radiotherapy and will explore potential biomarkers for such a treatment. To this end, blood and stool samples will be obtained at baseline, on day 1 of the second and the fourth cycle, and at the time of disease progression. Collection of tumor tissue samples will take place at baseline and his highly recommended in case of a re-biopsy after disease progression under study treatment. While the baseline tissue collection is mandatory, collection of all other biomarker samples is optional, i.e. patients can participate in the clinical trials if they do not consent to the collection of biomarker samples.

BACKROUND/RATIONALE	In the past years, immune checkpoint inhibitors have revolutionized the therapeutic landscape for lung cancer. Along this line, the IMpower133 trial showed that the addition of the PD-L1 inhibitor atezolizumab to first-line platinum/ etoposide chemotherapy resulted in improved outcome for patients with advanced small cell lung cancer (SCLC) leading to approval of this regimen. At the same time, accumulating preclinical and clinical data suggest beneficial synergisms of radiotherapy and immunotherapy in cancer patients via the radiation-mediated induction of anti-tumor immunogenicity and establishment of an immunostimulatory environment. Combining the recent findings, the TREASURE clinical trial aims to i.) increase the efficacy of combined atezolizumab- and chemotherapy by adding radiotherapy, ii.) determine the safety and tolerability of the combination of chemotherapeutic, immunological and radiological treatment in the first-line setting of advanced SCLC, and iii.) to collect tumor tissue as well as blood and stool samples for separate biomarker research projects.
KEY EXCLUSION CRITERIA	History of autoimmune disease Prior treatment with immunotherapeutic drugs Prior therapy for limited-stage SCLC with curative intent Prior radiotherapy to lung and mediastinal lymph nodes within the past 5 years before the first dose of study drug History of interstitial lung disease (ILD) (including but not limited to idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP)/cryptogenic fibrosing alveolitis (CFA)), non-infectious pneumonitis, drug-induced pneumonitis, idiopathic pneumonitis. History of active primary immunodeficiency Clinical diagnosis of active tuberculosis Positive testing for hepatitis B virus surface antigen (HBV sAg), hepatitis C virus ribonucleic acid (HCV RNA), or human immunodeficiency virus (HIV) Current use of immunosuppressive medication 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.
KEY INCLUSION CRITERIA	Fully-informed written consent ED SCLC ECOG performance-status score ≤1 Any response after four cycles of induction chemo-immunotherapy defined as CR/PR or thoracic SD with CR/PR of extrathoracic lesions Thoracic treatment volume considered treatable using acceptable radiation fields as judged by a radiation oncologist 28 ± 7 days between last administration of chemo-immunotherapy and randomization. Patients with a history of treated CNS metastases are eligible, if there is no ongoing requirement for corticosteroids as therapy for CNS disease. Patients with asymptomatic brain metastases that do not require local therapy with irradiation (whole brain irradiation) can be included. No previous radiotherapy to lung and mediastinal lymph nodes within the past 5 years before the first dose of study drug Availability of pre-treatment tumor tissue specimen FEV1 ≥ 40% (%Soll) Adequate bone marrow, renal function, and hepatic functions
OUTCOME(S)	Primary endpoint: Overall survival (time to event) Secondary endpoints: 1- and 2-year OS rate PFS according to RECIST 1.1 Response rate according to RECIST 1.1 Intrathoracic tumor control (defined as rate of intrathoracic progression and time to intrathoracic progression) Safety evaluation: Incidence, nature, causal relationship and severity of Adverse Events according to CTC v5.0 Frequency of abnormal laboratory parameters Feasibility in terms of:

	Frequency of treatment withdrawal (either due to adverse events or other reasons) Cmpletion of radiotherapy Cancer related quality of life (FACT-L) Collection of biomarker samples for separate biomarker research project
STATISTICAL ANALYSIS	The primary endpoint will be analyzed by performing multivariate cox-regression adjusting for the variable therapy group and the stratification variables. Secondary endpoint analyses will be performed descriptively. Safety analysis will comprise a description of relative and absolute frequencies of treatment-related adverse and serious adverse events. Feasibility will be analyzed by a description of relative and absolute frequencies of treatment withdrawal. Furthermore, a safety interim analysis with the possibility to terminate the trial will be performed in arm A after half of the patients in this arm (n=23) have been followed for three months after the end of TRT.
SAMPLE SIZE	n=92, incl. Drop Out n=104 (52 per arm)
TRIAL DURATION	Duration of recruitment: 24 months starting from FPI Follow-up: 24 months total trial duration: 48 months

SCLC, metastasiert

AIO-TRK-0119: Single-Arm Phase II-Study in Patients with extensive stage small-cell lung cancer (ES-SCLC) with Poor Performance Status receiving Atezolizumab-Carboplatin-Etoposide (SPACE)

AIO-Studie

Studiennummer/-Code	AIO-TRK-0119 - SPACE	
Status	Rekrutierung	
Rekrutierungszeitraum	2020 - 2022	
Zentren:	geplant: 20	initiiert: 20
Patienten:	geplant: 70	aktuell eingeschlossen: 36
Weitere Zentren	sind leider nicht mehr möglich!	
Letzte Aktualisierung	Oktober 2021	

National Coordinating Investigator	Prof. Dr. Martin Reck LungenClinic Grosshansdorf GmbH Wöhrendamm 80 22927 Großhansdorf E-Mail: m.reck@lungenclinic.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin Phone: +49 30 814534431 Fax: +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Study design	Single-arm, open-label, exploratory phase II study
Duration of study	Enrollment: 24 month total study duration 36 months (incl. follow-up)
Indication	Stage IV SCLC, treatment-naïve [i.e. ED-SCLC or ES-SCLC according to VALSG, respectively]

Target population	Treatment-naïve patients with stage IV SCLC and ECOG performance status 2 (eligible for carboplatin-based chemotherapy) with or without asymptomatic brain metastases
Total number of sites	20 sites in Germany and Austria
Further sites desired	no
Primary objective	To explore the efficacy of carboplatin+etoposide in combination with atezolizumab in treatment-naïve, stage IV SCLC patients with ECOG PS=2 with or without asymptomatic brain metastases
Secondary objectives	• To assess additional efficacy parameters, e.g. PFS, ORR; • to assess the safety and feasibility of adding atezolizumab to carboplatin+etoposide in this patient population; • to assess quality of life and symptom burden in study subjects; • to assess PRO-CTCAE™
Exploratory objectives	To assess tissue and bloodbiomarkers and their correlation with patient baseline characteristics and outcomes
Planned number of patients	N=70
Current number of patients	N=36
Inclusion criteria	13. Written informed consent including participation in translational research obtained from the subject prior to performing any protocol-related procedures, including screening evaluations that are not SOC. 14. Age ≥ 18 years 15. ECOG 2 16. At least one measurable tumor lesion (according to RECIST1.1) 17. Histologically confirmed small-cell lung cancer (SCLC) 18. Stage IV disease (according to UICC8) 19. No active autoimmune disease 20. Adequate organ function defined as: • neutrophil count > 1.5 x 10^9/L • thrombocytes ≥ 100 x 10^9/L • hemoglobin ≥ 9 g/dL • INR ≤ 1.4 or aPTT ≤ 40 sec during the last 7 days before therapy [Subjects under therapeutic anticoagulation are permitted. See protocol for guidance] • bilirubin < 1.5 x ULN • AST (SGOT)/ALT (SGPT) < 3 x institutional ULN (< 5 x ULN in case of liver metastases) • creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 45 mL/min (if using the Cockcroft-Gault formula below): $$Female\ CrCl = \frac{(140 - age\ in\ years)\ x\ weight\ in\ kg\ x\ 0.85}{72\ x\ serum\ creatinine\ in\ mg/dL}$$ $$Male\ CrCl = \frac{(140 - age\ in\ years)\ x\ weight\ in\ kg\ x\ 1.00}{72\ x\ serum\ creatinine\ in\ mg/dL}$$ 21. Availability of tumor tissue/block 22. 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 72 hours prior to the first dose of IMP. 23. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. [WOCBP should use an adequate method to avoid pregnancy for 6 months after the last dose of IMP.] 24. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving IMP and who are sexually active with WOCBP will be instructed to adhere to

	contraception for a period of 6 months after the last dose of IMP. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) and men who are azoospermic do not require contraception. 25. 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.
Global Exclusion criteria. Assessments at screening and re-assessment before randomization	**Methodological criteria:** 1. Any preceding systemic anticancer therapy for stage IV SCLC. [Up to one full-cycle-dosing of carboplatin+etoposide chemotherapy within the context of SOC is permitted prior to study treatment.] (Note: Prior treatment for limited stage disease allowed). 2. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lives of previously used trial medication, whichever is longer 3. Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-Programmed cell death-ligand 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). 4. Previous treatment in the present study (does not include screening failure). **Medical criteria:** 5. Symptomatic CNS metastases. [Patients with asymptomatic brain metastases may be included.] 6. Major surgery ≤ 28 days before first dose of study treatment 7. Any uncontrolled systemic disease, condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to: a. known active HBV, HCV or HIV infection [Patients who are HIV-positive are allowed in the trial, so long as they are stable on anti-retroviral therapy, have a CD4 count ≥ 200 cells/µL, and have an undetectable viral load at the time of screening.] b. active tuberculosis c. any other active infection requiring systemic therapy d. history of allogeneic tissue/solid organ transplant e. 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 IMP f. other active malignancy requiring treatment g. clinically significant or symptomatic cardiovascular/cerebrovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrolment **Safety criteria:** 8. 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). 9. Known hypersensitivity to carboplatin, etoposide or atezolizumab or any of the constituents of the products. 10. Medication that is known to interfere with any of the agents applied in the trial. 11. Any condition or disease, which might interfere with the subject's ability to comply with the study procedures (e.g. dementia). **Regulatory and ethical criteria:** 12. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities [§ 40 Abs. 1 S. 3 Nr. 4 AMG].

	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].
Investigational agents	• atezolizumab
Treatment schedule	In the induction phase, patients receive four 21-day cycles of carboplatin (AUC of 5 mg/mL/min, administered intravenously on d1 of each cycle) and etoposide (cumulative total dose of ≥300 mg/m², administered intravenously on three consecutive days) with atezolizumab (1200 mg i.v. on day 1 of each cycle). The induction phase is followed by a maintenance phase during which patients receive atezolizumab (1200 mg i.v.) once every 3 weeks until the occurrence of unacceptable toxicity, disease progression or withdrawal of consent or death. On Day 1 (d1) of each cycle, all eligible patients will be administered study drug infusions in the order atezolizumab → carboplatin → etoposide. Note: If rapid initiation of chemotherapy is imperative for symptom and disease control, carboplatin and etoposide may be initiated before the first dose of atezolizumab. In this case, the first dose of atezolizumab may be administered up to 3 days after first dosing of carboplatin and etoposide, or it may be delayed until the start of the second cycle (c2d1).
Primary endpoint	• Overall survival (OS) incl. milestone 1-year OS rate

Secondary endpoints	• Objective response rate (ORR) (RECIST 1.1)
	• Progression-free survival (PFS)
	• Safety and tolerability
	• Quality of life:
	  ○ EORTC-QLQ-C30
	  ○ PRO-CTCAE

Translational research: Exploratory objectives and endpoints	• tumor tissue analysis (FFPE sample from primary diagnosis + blood sample at baseline) • optionally tumor tissue analysis at PD
Rationale Hypothesis	Small cell lung cancer (SCLC) is a rapidly proliferating, neuroendocrine tumor that accounts for about 15% of all lung cancers. Most patients have metastases at primary diagnosis involving sites like bone, adrenal glands, liver and brain. Compared with non-small-cell lung cancer (NSCLC) SCLC has a unique natural history with a shorter doubling time, higher growth fraction, earlier development of widespread metastases, and uniform initial response to chemo- or radiotherapy. The combination of cis- or carboplatin and etoposide is the standard of care in the first-line treatment of stage IV (extensive-disease) SCLC (ED-SCLC). Despite response rates of 50–80%, most patients relapse within six months and the median survival time is less than 10 months. Between 14 and 23% of SCLC patients develop brain metastases. New cytotoxic agents as well as targeted therapies have not been able to show any improvement of survival in this group of patients. Early phase trials of PD 1/PD L1-blocking immunotherapeutic agents in patients with recurrent or ED SCLC have shown promising response rates and good tolerability. Immunotherapy may also contribute to the efficacy of systemic treatment by maintaining initial responses to chemotherapy. A double-blind, placebo-controlled phase 3 trial indicates that the addition of atezolizumab to standard chemotherapy significantly improves overall survival and progression-free survival compared with chemotherapy alone in treatment-naïve patients with ED-SCLC who are in good general condition (ECOG 0 or 1). However, about one in three SCLC patients has a poor performance status (ECOG≥2), which is associated with even shorter survival times of under eight months. At present, there is little information regarding the feasibility, safety and efficacy of adding atezolizumab to standard chemotherapy for this considerable fraction of patients.

<table>
<tr><td></td><td>We expect, that atezolizumab in addition to chemotherapy is feasible in patients with stage IV SCLC and reduced performance status and therefore crucial efficacy data can be acquired in this trial to assess the clinical relevance of the combination in this particular patient population.</td></tr>
<tr><td>Safety data</td><td>• AEs, SAEs and treatment emergent adverse events</td></tr>
<tr><td>Sample size estimation and
statistical analysis considerations</td><td>Median overall survival of carboplatin/etoposide treated ED-SCLC patients is between 6 and 10 months. The addition of atezolizumab has recently been shown to extend OS by approximately two months in patients with an ECOG PS of 0 or 1. As yet, there is no pivotal trial which sufficiently represents patients with ECOG PS=2 which could be used as a proper historical control for this single-arm trial. Therefore, the sample size justification will not be based on a formal hypothesis test but rather on the exploratory objective of this trial to generate meaningful data on the feasibility and efficacy of the experimental treatment to determine if further investigation of this therapeutic modality is warranted in a future randomized setting.
Clinical scientists frequently operate with milestone rates to present survival statistics for the purpose of clarity and to emphasize clinical benefits. For example, the above-mentioned median survival times (8-12 months) translate (under the assumption of exponential survival curves) into the following 1-year OS rates: 35.3% and 50%, respectively. The pivotal IMpower133 trial, which investigated atezolizumab in combination with carboplatin/etoposide in patients with PS=0-1 achieved a 1-year OS rate of approx. 52%.

Table 1 summarizes the exact 95% CIs for a sample size of 70 subjects for a possible range of 1-year OS rates.

The sample size of **N=70** is considered to provide a reasonably reliable estimate of the 1-year OS rates for the experimental combination treatment as it will allow the assessment of clinical relevance of the combination.

Table 1: Example 1-year OS rates and exact CI under sample size of N=70 [Clopper Pearson method]

<table>
<tr><td>1-yr-OS rates</td><td>Exact 95% CI
Lower Limit</td><td>Exact 95% CI
Upper Limit</td></tr>
<tr><td>20%</td><td>11.4</td><td>31.3</td></tr>
<tr><td>30%</td><td>19.6</td><td>42.1</td></tr>
<tr><td>40%</td><td>28.5</td><td>52.4</td></tr>
<tr><td>50%</td><td>37.8</td><td>62.2</td></tr>
</table>

Furthermore, with a sample size of N=70 and assuming that the number of events follows a binomial distribution [B(50,p)], events with an incidence rate p > 4,18% will be observed at least once with a 95% probability.</td></tr>
<tr><td>Study plan / time lines</td><td>First Patient In (FPI): Q4/2019
Last Patient In (LPI): after approx. 24 months
Last Patient Last treatment (LPLT): after approx. 30 months
End of follow-up period after LPI: after approx. 36 months
Study report: after approx. 48 months
Publication: after approx. 50 months</td></tr>
</table>

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)

AIO-Studie	
Studiennummer/-Code:	AIO-TRK-0116 - BIOLUMA
Status:	in Rekrutierung
Rekrutierungszeitraum:	2017 - 2022
Weitere Zentren:	Anfragen an das PM Inken Terjung inken.terjung@uk-koeln.de
Anzahl Patienten:	geplant: 90 aktuell eingeschlossen: 82
Anzahl Zentren:	geplant: 20 aktuell initiiert: 18
Letzte Aktualisierung	Okt 2021

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 Vertreten durch: 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) 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. Die Rekrutierung für Kohorte 1 ist geschlossen. Patienten, die vor dem 25. April 2019 gescreent wurden, bekommen weiterhin die Prüfmedikation, wie im Protokoll beschrieben. Kohorte 2a: Kleinzelliges Lungenkarzinom (SCLC) Patienten mit kleinzelligem Lungenkarzinom in frühen oder fortgeschrittenen Stadien erhalten nach Versagen einer Platin-haltigen Erstlinientherapie eine Zweitlinientherapie mit der Kombination aus Nivolumab und Ipilimumab über vier Zyklen und anschließend eine Nivolumab-Monotherapie bis zum Tumorprogress. Die Rekrutierung für Kohorte 2a ist geschlossen Kohorte 2b: Kleinzelliges Lungenkarzinom (SCLC) mit hoher Tumor-Mutationslast Patienten mit kleinzelligem Lungenkarzinom und hoher Tumor-Mutationslast in frühen oder fortgeschrittenen Stadien erhalten nach Versagen einer Platin-haltigen Erstlinientherapie mit der Kombination aus Nivolumab und Ipilimumab über vier Zyklen und anschließend eine Nivolumab-Monotherapie bis zum Tumorprogress
Studienmedikation	(I) Nivolumab (II) Ipilimumab
Konzept der Studie	Der monoklonale IgG4-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. Zwei Phase III-Studien konnten bei Patienten mit rezidiviertem Adeno- und Plattenepithelkarzinom der Lunge ein verbessertes Gesamtüberleben um etwas drei Monate mit Nivolumab im Vergleich zur Standard-Chemotherapie zeigen. Basierend auf diesen Ergebnissen ist Nivolumab in den USA und in Europa bei rezidiviertem NSCLC zugelassen.

	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 Strategien zur Verbesserung der therapeutischen Aktivität von Nivolumab entwickelt werden. Kombinationstherapien könnten eine attraktive Strategie sein, um die Rate und Dauer der antitumoralen Immunantwort auf Checkpointblockade zu erhöhen. Die PD-L1 Immunhistochemie (PD-L1 IHC) wurde als 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 einer 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. BIOLUMA ist eine multizentrische, nicht-randomisierte Phase II-Studie bei Patienten mit AD-NSCLC und SCLC nach Versagen einer Platin-haltigen Erstlinien-oder Zweitlinientherapie. 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 Daten beim SCLC darauf hindeuten, dass das Ansprechen unter der Kombinationstherapie vor allem von der Tumor-Mutationslast abhängig ist, werden nur noch Patienten mit hoher Tumor-Mutationslast (TMB) in diese Kohorte eingeschlossen[6]. Die ursprüngliche Kohorte ohne TMB-Prescreening (Kohorte 2a) wurde geschlossen und eine neue Kohorte für SCLC-Patienten mit hoher TMB eröffnet (Kohorte 2b). Der primäre Endpunkt der Studie ist für beide Kohorten die Ansprechrate der Kombinationstherapie. 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 und von peripherem Blut. Die Gewinnung der Proben erfolgt vor Beginn der Studientherapie (optional in Kohorte 2b), sowie zum Zeitpunkt des Tumorprogresses unter der Nivolumab-Monotherapie vor Einleitung der Kombinationstherapie aus Nivolumab und Ipilimumab in Kohorte 1, bzw. optional nach Komplettierung der vier Zyklen der Kombinationstherapie vor Fortführung mit Nivolumab als Monotherapie in Kohorte 2a/b. Die Charakterisierung der Tumorzellen und des Tumormikromilieus erfolgt histologisch und immunhistochemisch. Die Rolle von spezifischen somatischen Mutationen und der Mutationslast wird mittels DNA-Sequenzierung (whole genome oder whole exome sequencing), Transkriptom-Sequenzierung (RNAseq), der Prädiktion von Neoepitopen und der Erstellung eines Modells zur HLA-Prozessierung erfolgen. Zelluläre und lösliche Bestandteile des Blutes werden mittels FACS und ELISA untersucht. 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 und Tumorgewebe.
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) in frühen oder fortgeschrittenen Tumorstadien (Kohorte 2a und b). Hinweis: Die Rekrutierung für die Kohorten 1 und 2a ist geschlossen. Patienten, die vor dem Rekrutierungsstopp am 25. April 2019 mit dem Screening für Kohorte 1 begonnen haben, werden weiterhin gemäß Prüfplan behandelt. SCLC-Patienten mit hoher TMB werden ab dem 29. Oktober 2018 in die Kohorte 2b eingeschlossen. 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 2a und 2b optional 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 und am Ende der Studientherapie bei Tumorprogress in Therapiephase A oder B für Kohorte 2a und 2b. 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 Komplettierung der Daten ebenfalls untersucht. Weiterhin werden die Expression von PD-L1/ PD-L2, die Immunzellinfilatration, 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 gewonnen.
Primäre Zielsetzung	<u>Kohorte 1:</u> Erhebung der Ansprechrate der Kombinationstherapie aus Nivolumab und Ipilimumab nach Tumorprogress unter Nivolumab-Monotherapie bei Patienten mit rezidiviertem AD-NSCLC in der Zweitlinientherapie. Hinweis: Die Rekrutierung für die Kohorten 1 und 2a ist geschlossen. Patienten, die vor dem Rekrutierungsstopp am 25. April 2019 mit dem Screening für Kohorte 1 begonnen haben, werden gemäß Prüfplan behandelt. <u>Kohorte 2a:</u> Erhebung der Ansprechrate der Kombinationstherapie aus Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC in der Zweitlinientherapie Hinweis: Die Kohorte 2a ist für neue Patienten geschlossen. Patienten mit SCLC, die nach dem TMB- Prescreening in die Bioluma Studie eingeschlossen werden können, kommen in die Kohorte 2b. <u>Kohorte 2b:</u> Erhebung der Ansprechrate der Kombinationstherapie aus Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC und hoher Tumor-Mutationslast in der Zweitlinientherapie..
Primärer Endpunkt	<u>Kohorte 1:</u> Die nach RECIST 1.1 durch den Prüfer erhobene Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab nach Tumorprogress unter Nivolumab-Monotherapie bei Patienten mit rezidiviertem AD-NSCLC. Hinweis: Die Kohorte 1 ist für neue Patienten geschlossen. Patienten, die vor dem, vom Leiter der Studie am 25. April 2019 eingeleiteten, Rekrutierungsstopp mit dem Screening auf Kohorte 1 begonnen haben, werden weiterhin behandelt <u>Kohorte 2a:</u>

	Die nach RECIST 1.1 durch den Prüfer erhobene Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC. Hinweis: Die Kohorte 2a ist für neue Patienten geschlossen. Patienten mit SCLC, die nach dem TMB- Prescreening in die Bioluma Studie eingeschlossen werden können, kommen in die Kohorte 2b. <u>Kohorte 2b:</u> Die nach RECIST 1.1 durch den Prüfer erhobene Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab bei Patienten mit rezidiviertem SCLC und hoher Mutationslast .
Sekundäre Zielsetzungen	• Erhebung der Wirksamkeit der Nivolumab-Monotherapie und der Kombinationstherapie mit Nivolumab und Ipilimumab • Charakterisierung der Sicherheit und Tolerabilität der Nivolumab-Monotherapie und der Kombinationstherapie mit Nivolumab und Ipilimumab • 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 • Korrelation von Neoepitop-Signaturen mit dem klinischen Therapieansprechen in der SCLC-Kohorte mit hoher Tumor-Mutationslast
Sekundäre Endpunkte	• OS, PFS, DCR und DOR unter der Nivolumab-Monotherapie und unter der Kombinationstherapie mit Nivolumab und Ipilimumab • Inzidenz und Schweregrad von unerwünschten Ereignissen (UEs) und schwerwiegenden unerwünschten Ereignissen (SUEs) unter der Nivolumab-Monotherapie und unter der Kombinationstherapie mit Nivolumab und Ipilimumab Alle Biomarker-bezogenen sekundären Endpunkte werden sowohl für die Nivolumab-Monotherapie, als auch für die Kombinationstherapie mit Nivolumab und Ipilimumab erhoben: • 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%) • Korrelation der PD-L1/PD-L2/PD-1-Positivität der Tumor-assoziierten Immunzellen vor der Studientherapie mit ORR, DCR, PFS, OS, TTR und DOR • Prädiktiver Wert der Zusammensetzung des Immunzellinfiltrates vor der Studientherapie für ORR, DCR, PFS, OS, TTR und DOR • Prädiktiver Wert von zusätzlichen ko-inhibitorischen Molekülen für ORR, DCR, PFS, OS, TTR und DOR • Prädiktiver Wert der RNA-Expression von PD-L1 und PD-L2 für ORR, DCR, PFS, OS, TTR und DOR • 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 • Prädiktiver Wert von Neoepitop-Signaturen mit ORR, PFS und OS in der SCLC-Kohorte mit hoher Tumor-Mutationslast
Explorative Zielsetzungen	• Beschreibung von Immunsystem-assoziierten Expressionsprofilen in Tumorbiopsaten und Korrelation mit dem klinischen Verlauf • Beschreibung der Zusammensetzung des Immunzellinfiltrates in Tumorbiopsaten und Korrelation mit dem klinischen Verlauf • Beschreibung der Zusammensetzung der Immunzellpopulationen im peripheren Blut vor, während und nach der Studientherapie und Korrelation mit dem klinischen Verlauf • Korrelation von Veränderungen des C-reaktiven Proteinwertes und der Leukozytenzahl mit dem klinischen Verlauf

	• Charakterisierung der molekularen Heterogenität der Tumorzellen in den Biopsaten • Korrelation des genetischen Subtyps (definiert nach gezielt behandelbaren Mutationen) mit dem klinischen Verlauf • Korrelation von bekannten Treibermutationen mit dem klinischen Verlauf 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: • Analyse der Mutationslast mittels DNA-Sequenzierung (Whole Genome Sequencing oder, je nach DNA-Gehalt der Biopsate, Whole Exome Sequencing) • Charakterisierung der Transkriptom-Expression mittels Whole Transcriptome Sequencing (RNAseq) • Muster der Infiltrate von Immunzellsubpopulationen mittels IHC • Proteinexpression von PD-L1 und PD-L2, mRNA-Expression und Muster der Immunzellsubpopulationen • Immunzellinfiltrat im Tumormikromilieu und Verhältnisse der Immunzellpopulationen im peripheren Blut • Evaluierung der Funktionsveränderung von T-Zellen des peripheren Blutes mittels Analyse von Aktivierungsmarkern und Änderungen der Zytokinlevel • 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	<u>Kohorte 1:</u> Die Rekrutierung der Kohorte 1 ist geschlossen. Bei einer Ausfallrate von ca. 50% (von Arm A nach B) ist diese Studie nicht ausreichend, um den primären Endpunkt zu bestimmen. Aus diesem Grund wurde Kohorte 1 geschlossen. Die Anzahl von 27 eingeschlossenen Patienten ist aber noch ausreichend, um die sekundären und explorativen Endpunkte zu analysieren. Der initiale statistische Plan war folgender: Die Studie folgt einem “one-stage A’Hern design” mit Ansprechverhältnissen (das heißt ORR der Kombinationstherapie) $\pi_0 = 0.075$ and $\pi_1 = 0.2$, $\alpha = 0.1$ and $\beta = 0.2$. Somit sind 33 auswertbare Patienten erforderlich. Die Nullhypothese H_0: $\pi \leq 0{,}1$ wird verworfen, wenn mindestens 5 Ansprechen aus 33 Patienten beobachtet werden[7]. Unter der Annahme einer Rate von 5% Behandlungsabbruch in Behandlungsteil A[2] und weitere 35% in Behandlungsteil B[8], müssen ungefähr 53 Patienten (d. h. ~ 33 / 0,95 / 0,65) eingeschlossen werden. 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. 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. Die Subgruppenanalysen erfolgen nach PD-L1-Positivität (ja/nein), Geschlecht und Therapieansprechen unter Nivolumab (primäre/sekundäre Resistenz). <u>Kohorte 2a:</u>

	Die Rekrutierung der Kohorte 2a ist geschlossen. Die Berechnung des Stichprobenumfangs für Kohorte 2a entspricht der ursprünglichen Berechnung für Kohorte 1 und erfordert 5 Ansprechen bei 33 auswertbaren Patienten, um die Nullhypothese zu verwerfen. Die Rekrutierung der Kohorte 2a ist geschlossen. Dies beruht auf Sicherheitsbedenken und der Tatsache, dass die Anzahl der zur Verwerfung der Nullhypothese erforderlichen Rate an Tumoransprechen bereits erreicht wurde (nicht stochastische Kürzung). Die Anzahl der eingeschlossenen nicht-TMB selektierten SCLC-Patienten (n = 18) ist ausreichend, um die sekundären und explorativen Endpunkte zu analysieren. <u>Kohorte 2b:</u> 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 $\beta = 0.15$. Demnach werden 41 evaluierbare Patienten benötigt. Die Nullhypothese $H_0: \pi \leq 0.075$ ist verworfen, wenn mindestens 6 von 41 Patienten ansprechen. Unter der Annahme einer Rate von etwa 10% nicht auswertbarer Patienten werden 45 ($\approx 41/0.9$) Patienten eingeschlossen. Unter der Annahme einer Prävalenz von 30% hoher Tumor-Mutationslast erwarten wir 150 Patienten zu screenen, um 45 Patienten mit hoher Tumor-Mutationslast zu identifizieren. Da im Rahmen der Erstlinientherapie von einer Dropout-Rate von 50%, sowie im Rahmen des Screenings von einer Dropout-Rate von 30% auszugehen ist, schätzen wir die Screening-Zahl auf 428, um 45 Patienten mit hoher Tumormutationslast einzuschließen. Im Falle eines Therapieendes wird kein auswertbarer Patient ersetzt. Die weiteren statistischen Methoden werden analog zur Kohorte 1 durchgeführt (siehe oben). Zeitpunkt der ersten Analyse: 1. Wenn der letzte Patient das erste Staging von Behandlungsteil B in Kohorte 1 und Behandlungsteil A in Kohorte 2a und 2b durch durchgeführt hat und 2. von mindestens 50% der Patienten ein Survival Follow Up vorliegt
Haupteinschlusskriterien	Hinweis: Die Kohorte 1 ist für neue Patienten geschlossen. Patienten, die vor dem Rekrutierungsstopp am 25. April 2019 mit dem Screening für Kohorte 1 begonnen haben, werden weiterhin gemäß Prüfplan behandelt • 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. • Kohorte 2a: Patienten mit histologisch oder zytologisch gesichertem SCLC im frühen oder fortgeschrittenem Stadium mit Tumorprogress nach Versagen einer platinhaltigen Erstlinientherapie mit oder ohne Anti-PD-1/PD-L1 Behandlung (nicht TMB-selektionierte SCLC-Patienten). Hinweis: Kohorte 2a ist für neue Patienten geschlossen. • Kohorte 2b: Zweitlinientherapie für Patienten mit histologisch oder zytologisch gesichertem SCLC und hoher Tumor-Mutationslast in frühem oder fortgeschrittenem Stadium mit Tumorprogress nach Platin-haltiger Erstlinientherapie mit oder ohne Anti-PD-1/PD-L1 Behandlung. Einschluss in Drittlinie ist erlaubt. Es werden nur SCLC Patienten eingeschlossen, deren Tumormutationslast aus der Routinebiopsie für die Erstdiagnose als TMB high bestimmt wurde (whole exome sequencing an FFPE Tumorgewebe). Die folgenden Einschlusskriterien gelten für die Kohorte 1 und 2a und 2b:

	• Unterschriebene und datierte Patienteneinwilligung, welche vor jeglicher Studien-spezifischen Maßnahme eingeholt werden muss und welche zuvor von einer unabhängigen Ethikkommission genehmigt wurde • Männliche oder weibliche Patienten ≥18 Jahre • Eastern Cooperative Oncology Group (ECOG) Performance Status von 0-1 • Studienpatienten müssen bereit sein, mindestens eine Tumorbiopsie durchführen zu lassen (Baseline) (Ausnahme: Kohorte 2b) • Der jeweilige Prüfarzt muss den Studienpatienten für fähig erachten, eine Tumorbiopsie durchführen zu lassen (Baseline) (Ausnahme: Kohorte 2b) • 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 • Kohorten 1 und 2a: 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 Prednisonäquivalent. • Kohorte 2b: Patienten mit ZNS- Metastasen dürfen eingeschlossen werden. Eine Bestrahlung zu Beginn der Studie ist erlaubt, wenn die Target Läsion außerhalb des Kopfes liegt.
Hauptausschlusskriterien	• Patienten mit Plattenpithelkarzinom der Lunge • Betrifft nur die Kohorte 1: aktivierende EGFR-Mutation oder ALK-Translokation • Kohorten 1 und 2a: Mehr als eine vorhergehende Chemotherapielinie beim fortgeschrittener Erkrankung • Kohorte 2b: Patienten nach Zweitlinientherapie dürfen eingeschlossen werden, wenn die Zweitlinientherapie keine Anti PD-L1, Anti-PD-L2 oder Anti-CTLA-4 Antikörper als Monotherapie oder in der Kombination mit einer anderen, als platinbasierten Chemotherapie gewesen ist. • 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 Hinweis: SCLC Patienten, die eine Kombinationstherapie aus platinbasierter Chemotherapie und Anti-PD-1/PD-L1-Behandlung erhalten haben, dürfen nicht eingeschlossen werden. Hinweis zu Kohorte 2b: SCLC Patienten, die mit einer Kombination aus platinbasierter Chemotherapie zusammen mit einem Anti-PD-1/PD-L1 behandelt wurden, dürfen eingeschlossen werden. • Vorliegen eines medizinischen Zustandes, der mit signifikant erhöhtem Risiko für Blutungskomplikationen im Rahmen der Tumorbiopsie einhergeht (z.B. bekannte Koagulopathie, therapeutische Antikoagulation) • Kohorten 1 und 2a: 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 • Kohorte 2b: höhere Dosen von Corticosteroiden sind im Rahmen einer Bestrahlung erlaubt • Aktuell vorliegende, oder innerhalb der letzten fünf Jahre vor Studieneinschluss zurückliegende, weitere Malignomerkrankung, mit Ausnahme von adäquat behandeltem Basalzellkarzinom oder

	Plattenepithelkarzinom der Haut, oder jedes anderen adäquat behandelten Carcinoma in situ • 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 • Aktive oder chronische Hepatitis B- oder Hepatitis C-Infektion • Bekannte Infektion mit dem humanen Immundefizienzvirus (HIV) oder positiver HIV-Test, oder bekannte AIDS-Erkankung (acquired immunodeficiency syndrome) • Kohorten 1 und 2a: 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 • Patienten mit interstitieller Lungenerkrankung, die symptomatisch ist, oder sich störend auf die Detektion oder das Management von Therapie-bezogenen pulmonalen Toxizitäten auswirken könnte • Jedwede/jedweder 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 • Bekannte Allergie oder schwere Hypersensitivitätsreaktion gegen einen Bestandteil der Studienmedikation, oder gegen jeglichen monoklonalen Antikörper
Studienuntersuchungen	Kohorte 1: 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). Kohorte 2: Der primäre Endpunkt der Kohorte 2a und 2b 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	Erster Patient erste Visite (FPFV): 04/2017 Letzter Patient erste Visite (LPFV): 02/2022 Letzter Patient letzte Visite (LPLV): 02/2023

NSCLC limitiert oder local fortgeschritten

AIO-TRK-0121: Prospektive Randomisierte Phase-II Studie mit einer Induktionschemotherapie und Radiochemotherapie mit oder ohne den PD-L1 Antikörper Durvalumab, gefolgt von einer Operation oder Radiochemotherapie-Boost und Konsolidierung mit Durvalumab bei Patienten mit resektablen Nicht-kleinzelligem Lungenkarzinom im Stadium III (ESPADURVA)

AIO-Studie

Studiennummer/-Code:	**AIO-TRK-0121 - ESPADURVA**
Status:	In beginnender Rekrutierung (CORONA PANDEMIE !!!)
Rekrutierungszeit:	von: 2020 bis: 2023
Anzahl Zentren:	geplant: 4 aktuell initiiert: 4 aktiv rekrutierend: 3
Weitere Zentren:	(z.B.) sind erwünscht und werden gerade verhandelt
Anzahl Patienten:	geplant: 90 aktuell eingeschlossen: 22
Letzte Aktualisierung	29.09.2021

STUDY TYPE	Prospektive Randomisierte Phase II – Studie
PRINCIPAL INVESTIGATOR	PD Dr. med W. Eberhardt
TRIAL OFFICE	WTZ- Essen, Ruhrlandklinik Essen, Strahlenklinik
SPONSOR	Universitätsklinikum Essen
Study Title	Prospective Phase-II Trial of induction chemotherapy and chemoradiotherapy plus/minus the PDL1 antibody durvalumab followed by surgery or definitive chemoradiation boost and consolidation durvalumab in resectable stage III NSCLC.
	Protocol Name: ESPADURVA EudraCT Number: 2019-000058-77 Clinical Phase: Randomized Phase-II Study Start: Planned Q4 2019
Investigational Product(s) and Reference Therapy:	Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration
Reference treatment: ESPATUE-protocol:	Induction chemotherapy with cisplatin (100 mg/m2) (either given in two days x 50 mg/m2 or three days x 33 mg/m2) and paclitaxel 175 mg/m2 per cycle given every 21 days for three cycles followed by concurrentchemoradiotherapy based on cisplatin (50 mg/m2 d 2 + d 9) and vinorelbine (20 mg/m2 d 2 + d 9) and radiotherapy (45 Gy HFA-RTx) followed by definitive local treatment (surgery or definitive chemoradiation boost (20 Gy, CF-RTx) plus consolidation durvalumab treatment every four weeks for eight months Research Hypothesis Multimodality strategies have been included into several of our phase-II and also randomized phase-III studies [Eberhardt et al 1998, Eberhardt et al 2013, Eberhardt et al 2015b; Goeckenjan et al 2010]. We

	have currently developed a surrogate endpoint pCR at the time of surgery after induction therapy in this predefined setting [Pöttgen et al 2013, Pöttgen et al 2015; Pöttgen et al 2016]. PD-1 antibody treatment with pembrolizumab has recently become a preferred treatment strategy in patients with high expression of PD-L1 immunomarker in tumor cells for the first line therapy of stage IV NSCLC patients [Reck et al 2016]. Platinum-based doublet chemotherapy containing paclitaxel combined with a PD-1 antibody has shown promising safety and effectiveness in a prospective phase I study [Rizvi et al 2016]. Concurrent PD-L1 immune checkpoint blockade and thoracic radiotherapy has been found save in a prospective trial [Levy et al 2016]. Concurrent PD-1 blockade and radiotherapy is more effective than sequential application of both modalities according preclinical data [Dovedi et al 2014; Gong et al 2017]. Durvalumab (PD-L1) is currently investigated alone or in combination with conventional platinumbased chemotherapy in stage IV NSCLC. Durvalumab has been investigated as a consolidation therapy after concurrent chemoradiotherapy for irresectable stage III NSCLC with a significant increase in PFS already openly reported [Pacific-trial: Antonia et al 2017]. The aim of this study is to investigate the introduction of durvalumab immunotherapy within our induction chemotherapy and concurrent chemoradiotherapy protocol in patients with resectable stage III NSCLC with positive and high PD-L1 expression in the tumor and evaluate feasibility and Progression-Free Survival of this approach and investigate the rate of pathological complete responses in resected specimen as an important surrogate endpoint of efficacy.
Objectives:	To compare a complex induction multimodality protocol (ESPATUE) + concurrent immunotherapy with PD-L1 antibody durvalumab given every three weeks to the same induction multimodality protocol without durvalumab immunotherapy induction followed by definitive local treatment (surgery for those considered resectable or chemoradiation boost for those not considered to be R0-resectable) followed by consolidation durvalumab treatment in both arms.
Primary Objective:	The primary objective is to assess the efficacy of a multimodality treatment in resectable stage III nonsmall-cell lung cancer patients including a complex induction chemoimmunotherapy followed by a radiochemoimmunotherapy and definitive surgical resection or radiochemotherapy-boost and immunotherapy consolidation for 32 weeks versus the same multimodality treatment protocol without immunotherapy in the induction and radiochemotherapy as measured by two-year progression-free survival. The primary objective will be measured by the primary endpoint which is the progression-free survival rate (PFS) at 2 years. Reason for this choice / advantage: To determine the PFS-rate at two years only one follow-up visit with exact imaging will be necessary. To exactly determine the median progression-free survival several follow-up visits within a short time-schedule and with several imaging investigations included would be

	necessary. Disadvantage: Two-year minimal follow-up will be necessary. Arm A: induction therapy with three cycles cisplatin and paclitaxel combined with concurrent durvalumab (1200 mg flat dose qd 21 x 3) and a concurrent chemoradiotherapy of cisplatin and vinorelbin and combined with durvalumab (1200 mg flat dose qd 21 x 2) together with 45 Gy hyperfractionated radiotherapy (2 x 1.5 Gy pro die) followed by surgery if possible and then sequential consolidation durvalumab (1500 mg flat dose qd 28 x 9). Arm B: ESPATUE induction therapy with three cycles cisplatin and paclitaxel and a concurrent chemoradiotherapy of cisplatin and vinorelbin together with 45 Gy hyperfractionated radiotherapy (2 x 1.5 Gy pro die) followed by surgery without concurrent durvalumab and then sequential durvalumab consolidation therapy (1500 mg flat dose qd 28 x 9) [see also: Eberhardt et al 2015b]. The PFS rate at 2 years from both arms combined will be compared with a predefined bench mark result and results from both arms will be compared with each other.
Secondary Objective:	The secondary objective is to analyze the toxicity and efficacy of a multimodality treatment in resectable stage III non-small-cell lung cancer patients including a complex induction chemoimmunotherapy followed by a radiochemoimmunotherapy and definitive surgical resection or radiochemotherapy-boost and immunotherapy consolidation for 32 weeks versus the same multimodality treatment protocol without immunotherapy in the induction and radiochemotherapy as measured by response, survival parameters, QoL, compliance and treatment toxicity effects. The secondary objective will be will be achieved by the following secondary endpoints: • To investigate the rate of pathological complete response with the addition of durvalumab to the bimodal induction protocol versus pCR following the same induction protocol without durvalumab (ESPATUE) • To investigate the toxicity of this induction protocol and the following surgical resection in both arms • To compare the results of this combined modality with our sequential phase-II and phase-III trials • To investigate 2-y-overall survival rate in the ITT population • To investigate functional response (PET-CT-scan) to induction therapy prior to thoracotomy • To investigate RECIST response to induction therapy in the whole population and in both arms • Progression free survival time (PFS) • Overall survival (OS) • Histopathologic complete response (pCR) (data from repeat bronchoscopy/EBUS/surgery) • Radiological response (RECIST criteria) • Analysis of the SUVmax response and MTV response on the planning PET-CT in comparison to the pretreatment PET-CT in dependence on immunotherapy • Pulmonary fibrosis or pneumonitis or dyspnoea or other pulmonary adverse events of CTCAE v5.0 grade ≥ 3 within 60 days from start of therapy • Other adverse events as measured by CTCAE v5.0 • Quality of life (EORTC QLQ-C30, QLQ-LC13 and FACT-L) • Estimation number of fully compliant patients

Exploratory Endpoints:	• To define the rate of PD-L1 > or = 50% patients in the group of stage III NSCLC patients (screened population) • To define the R0 (complete resection) rate of the ITT patients following induction therapy • To monitor brain-relapse-free survival in the ITT patients • Brain-relapse-free survival • R0-resection rate • Heart toxicity at the end of therapy and during follow-up using functional and non-invasive assessments • Therapy-associated changes in lung parenchyma on CT-scans during follow-up using a radiomic multiparameter analysis, in dependence on immunotherapy • Analysis of the relation between dose-distribution parameters on treatment related toxicity and effectiveness in dependence on concurrent immunotherapy • Analysis of the effect of the breathing control strategy on precision of radiotherapy • Positron emission tomography (PET) response of the primary tumor and lymph nodes using the tracer 18F-fluoro-deoxyglucose as a prognostic marker • Assessment of Tumor Progression Patterns The study contains optional sampling for the Biobank (tumor tissue, plasma, serum). Translational research is important to make advances in understanding tumor biology and immunology with the aim to identify the group of patients most likely to benefit from therapy. Exploratory endpoints of this translational research program with the samples from the Biobank may include, but are not limited to the following ones: • Analysis of the prognostic value of tumor biomarkers from the pretreatment tumor biopsy or the resection specimen on treatment outcome • Changes of Lymphocyte subsets in peripheral blood during induction therapy • To investigate soluble HLA-G and HLA-E and soluble PD-1 and PD-L1 in plasma prior start of treatment as a prognostic/predictive marker as well as at the time after chemoradiation • Presence, phenotype and clonality of tumor infiltrating lymphocytes in NSCLC lesions prior to and after therapy (FFPE tissue, fresh frozen tissue, native biopsy material) • Tumor infiltrating lymphocytes in the surgical specimen after induction therapy compared with the pre-treatment biopsy • Expression of immune modulatory molecules in the tumor prior to therapy and after therapy (FFPE tissue, fresh frozen tissue, native biopsy material) • Presence of inflammatory and immune responses in the draining lymph nodes before, under and after therapy (FFPE tissue, fresh frozen tissue, native biopsy material) • Analyses of the activation status of circulating lymphocytes before, during, and after therapy • To investigate lymph node response to the chemoimmuno-induction therapy • To investigate other translational markers in the treated ITT population (both in blood as well as in the tumor and LN) • T-cell repertoire in mediastinal lymph nodes and in the primary tumor at the time of diagnosis and at thoracotomy

	• Tumor mutational burden (TMB) measured by an adequate, validated and accepted laboratory assay (at the time of study start)
Study Design:	• All patients will undergo initial staging investigations (see Schedule of Study Assessments) as well as diagnostic work-up for functional and medical resectability (based on cardio pulmonary risk evaluation and interdisciplinary tumor board) • Resectable patients will then be offered randomization into induction protocol plus concurrent immunotherapy with durvalumab (1200 mg flat dose given every three weeks) (Arm A) versus induction protocol without immunotherapy (Arm B) • All patients will be offered three cycles of induction chemotherapy consisting of cisplatin and paclitaxel (standard ESPATUE-doses) • All patients without proven disease progression during induction will be taken to concurrent neoadjuvant radiochemotherapy (cc-HFA-RTx 45 Gy bid + cisplatin/vinorelbine) • Following induction CTx + CTx/RTx restaging between days 16 and 21 (after start of RTx) will include thorax CT-scan (including angiographic bolus-tracking) • Patients evaluated to be unresectable or who refuse to be operated on following induction treatment will receive a standard conformal radiotherapy boost; boost RTx should be started immediately after the last fraction of the first 45 Gy radiation series and is recommended to be given without any break • Patients evaluated to be resectable following the induction CTx + CTx/RTx will be taken to thoracotomy and will be completely resected the primary tumor combined with a standard mediastinal lymph node dissection • The decision of resectability/unresectability will be documented within a multidisciplinary conference (tumor board) and will be a written and rationally founded consented document; also patients decision different from this proposed strategy will be documented in detail • All patients in both treatment arms will be offered durvalumab consolidation therapy with 1500 mg durvalumab given as flat dose iv infusion over one hour every four weeks (9 times for a total of 32 weeks)
Number of Centers:	approximately 4 study sites in Germany
Number of Patients:	Inclusion of 90 patients with resectable NSCLC stages IIIA (N2) and selected resectable stages IIIB with the aim to have 84 patients with a complete follow-up in arms A and B (2:1 randomization)
Study Population:	Resectable NSCLC stages IIIA(N2) and selected IIIB non-small-cell lung cancer patients
Inclusion Criteria:	1. Body weight >30 kg 2. Age ≥ 18 years and < 75 years 3. Male or female patients. Female (as well as male) patients have to take care of effective measures of anticonception 4. Histologically proven non-small cell lung cancer 5. Selected patients with non-small cell lung cancer stages IIIA and IIIB:

	• IIIA: one or more lymph node levels involved at EBUS/mediastinoscopy • IIIA: bulky N2-disease histologically proven at EBUS/cervical mediastinoscopy/parasternal mediastinotomy, not diffuse mediastinal involvement • selected IIIB: N3-disease with contralateral mediastinal nodes involved at EBUS/mediastinoscopy • potentially resectable T4-disease: o involvement of the pulmonary artery (angiogr.-CT/MRI/TEE), o involvement of the carina (histologically proven), o involvement of the left atrium (angiogr.-CT/MRI/TEE), o involvement of the vena cava (angiogr.-CT/MRI/TEE), o involvement of ipsilateral intrapulmonary satellite nodules, o mediastinal involvement (not diffuse) 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 7. Resectable disease at the time of inclusion 8. Fulfillment of adequate criteria for functional and medical resectability as described in the ERS/ESTS guidelines [Brunelli et al 2009] and acceptable general clinical condition for multimodality treatment (interdisciplinary committee) 9. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g, 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 10. Must have a life expectancy of > 12 weeks 11. Adequate normal organ and marrow function as defined below: o Haemoglobin ≥ 9.0 g/dL o Absolute neutrophil count (ANC) > 1.5 x 109/L (> 1500 per mm3) o Platelet count ≥ 100 x 109/L (≥ 100.000 per mm3) o Serum bilirubin ≤ 1.5 x institutional 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. o AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal Clinical Study Protocol Drug Substance Durvalumab Study Name ESPADURVA Version 2.3, Date 09-June-2020 Page 8 of 157 o Measured creatinine clearance (CL) > 40 mL/min or Calculated 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: Males: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) 72 x serum creatinine (mg/dL) Females: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) x 0.85 72 x serum creatinine (mg/dL) 12. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal

	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: o 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) o 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-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) 13. 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 14. Stable cardiac function (no Myocardial infarction (MI) within 6 months, no heart failure NYHA III-IV)
Exclusion Criteria:	Patients should not enter the study if any of the following exclusion criteria are fulfilled: 1. resectable IIB or selected IIIA (T3N0; T3N1) 2. unresectable disease pre-treatment 3. mixed histology with areas of small cell carcinoma (neuroendocrine markers) 4. clinically symptomatic vena cava superior syndrome 5. diffuse mediastinal involvement 6. patients with T3N3 and T4N3 tumors (IIIC IASLC/UICC 8) 7. invasion of the thoracic aorta (T4 – aorta) 8. invasion of the heart (except left atrium – T4 – heart) 9. invasion of the esophagus (T4 – esophagus) 10. invasion of spine (T4 – spine) 11. (full blown) Pancoast-syndrome in tumors of the superior sulcus (T3-4 Nx) 12. malignant (positive) pericardial effusion (M1a – pericardial effusion) 13. malignant (positive) pleural effusion (M1a – pleural effusion) 14. involvement of the contralateral hilar nodes (if any data available) 15. endobronchial tumor extension to the contralateral main stem bronchus 16. ipsi- or contralateral supraclavicular nodes (N3 – supraclavicular nodes) 17. lung or heart function not allowing at the time of inclusion the intended surgical procedure 18. previous administration of chemotherapy and/or radiotherapy 19. previous immunotherapy 20. insufficient patients compliance (e.g. symptomatic psychiatric disorder) 21. loss of weight > 10 % in the last six months 22. missing written informed consent or definitive refusal for participation 23. Participation in another clinical study with an investigational product during the last 12 months 24. Concurrent enrolment in another clinical study, unless it is an observational (noninterventional)

	clinical study or during the follow-up period of an interventional study 25. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day 26. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan 27. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable 28. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable 29. History of allogenic organ transplantation 30. History of a stem cell transplantation 31. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], 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: – Patients with vitiligo or alopecia – Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement – Any chronic skin condition that does not require systemic therapy – Patients without active disease in the last 5 years may be included but only after consultation with the study physician – Patients with celiac disease controlled by diet alone 32. 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 33. History of another primary malignancy except for – 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 – Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease – Adequately treated carcinoma in situ without evidence of disease 34. History of active primary immunodeficiency 35. 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 or HIV-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 36. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: – Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) – Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent – Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) 37. Current or prior use of immunostimulatory agents within 14 days before the first dose of durvalumab 38. Receipt of live attenuated vaccine within 90 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 90 days after the last dose of IP 39. 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 durvalumab monotherapy 40. Known allergy or hypersensitivity to durvalumab or any excipient
Investigational Product(s), Dose and Mode of Administration:	Patients in the durvalumab induction treatment group will receive 1200 mg durvalumab via IV infusion Q3W given prior to induction chemotherapy application in cycles one, two and three on day 1 of these cycles as well as at the start of concurrent chemoradiotherapy (day 2 of Block 2). Patients not resected but instead given definitive chemoradiation boost may receive durvalumab as given above for one more cycle concurrently to the boost radiotherapy. In the consolidation durvalumab phase (Block 4) are all patients in both arms planned to be given a consolidation durvalumab treatment of 1500 mg given via IV infusion every four weeks for up to a maximum of 8 months (up to 9 doses/cycles). The last administration of durvalumab is planned 32 weeks after the end of Block 3 or until confirmed disease progression or unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If a patient's weight falls to ≤ 30 kg in the consolidation phase (Block 4), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between the Investigator and the country coordinating investigator, until the weight improves to ≥ 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W, see also Appendix 1.
Study Assessments and Criteria for Evaluation:	Initial staging investigations should include PET-CT, EBUS-TBNA, mediastinoscopy (if clinically indicated), MRI-brain (CT brain if MRI cannot be performed) before the start of treatment. Further

	investigations see the Schedule of Study Assessments. A further PET-CT has to be added as current standard pre-radiotherapy-planning investigation in the last week of the third cycle of induction chemotherapy (Block 1).
Safety Assessments:	See Schedule of Study Assessments for details regarding hematology, clinical chemistry, C-reactive protein (CRP), ECG and physical examinations as well as other scheduled investigations during induction chemotherapy and throughout the study.
Efficacy Assessments:	CT scans of thorax/upper abdomen every three months post definitive local treatment. Pharmacodynamic / Pharmacokinetic Assessments (if applicable): Not applicable.
Sample Size Determination, Statistical Methods and Data Analysis:	The primary endpoint is progression-free survival rate at 2 years. It is expected that progression-free survival rate (PFS) at two years is 35% according to historical controls comprising comparable resectable stage III patient cohorts treated with neoadjuvant radiochemotherapy followed by surgery (H0) [Eberhardt et al 2015b; Senan et al 2016; Bradley et al 2015]. H0 can be rejected at one sided alpha =0.025 using an exact binominal test, if 39 or more patients among 84 recruited patients in both randomization arms with durvalumab maintenance or durvalumab during induction and maintenance combined at two years are alive without progression at 2 years. In the case of rejection of H0, the gate is opened for a second comparison in fixed sequence as step 2. Here, PFS data from both treatment arms will be compared by a log rank test.
Toxicity run in Phase:	Neoadjuvant chemotherapy plus radiochemotherapy combined with durvalumab immunotherapy does not increase dose limiting toxicity. This hypothesis is rejected if > 3 patients among the first 7 patients in the durvalumab treatment Arm A have pulmonary fibrosis or pneumonitis or bleeding of CTCAE Version 5.0 grade 3 or at least one patient has a grade ≥ 4 and at least another patient a grade ≥ 3 pulmonary fibrosis or pneumonitis or bleeding within 60 days from start of therapy. After these seven patients are randomised in the durvalumab treatment Arm A the recruitment is halted for 60 days until toxicity evaluation for these patients is completed to observe delayed toxicities in all treated patients. Otherwise, the trial will be stopped. In addition the trial will be stopped at any time during recruitment, if the rate of treatment associated deaths is > 15 % or of grade ≥ 3 pulmonary events is > 40%.
Hypothesis H0:	35% progression-free survival rate (PFS) of a comparable stage III population at two years according to historical controls [Eberhardt et al 2015b; Senan et al 2016; Bradley et al 2015].
Hypothesis H1:	The progression-free survival rate at two years in both arms together exceeds 35%. If H0 was rejected the PFS in both arms will be compared by log rank statistics between both arms. The power of the comparison is 80% to detect a HR of < or = 0.5 between arm B and arm A at a significance level of alpha = 0.05.
Participating Centers:	1. Universitätmedizin Essen (Universitätsklinikum und Ruhrlandklinik), 2. Robert-Bosch Krankenhaus Stuttgart, 3. Universitätsmedizin Oldenburg, Pius-Hospital Oldenburg, 4. Universitätsmedizin Freiburg, Universitätsklinikum

Further Centers desired:	yes, two more are in current negotiations
Number of Patients:	90 Pts
Current number of Patients:	22 Pts (29.9.2021)

AIO-YMO/TRK-0319: Thoracic Radiotherapy plus Durvalumab in Elderly and/or frail NSCLC stage III patients unfit for chemotherapy- Employing optimized (hypofractionated) radiotherapy to foster durvalumab efficacy (TRADEhypo)

AIO-Studie

Studiennummer/-Code:	AIO-YMO/TRK-0319 - TRADEhypo	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2020 – 2021	
Weitere Zentren:	nicht mehr möglich	
Zentren:	geplant: 20	initiiert: 16
Patienten:	geplant: 88	aktuell eingeschlossen: 22
Letzte Aktualisierung	30.09.2021	

STUDY TYPE	Investigator- initiated trial (IIT)
PRINCIPAL INVESTIGATOR	Dr. Farastuk Bozorgmehr (Farastuk.Bozorgmehr@med.uni-heidelberg.de) (LKP) Prof. Dr. Stefan Rieken (Deputy LKP) Univ.-Prof. Dr. Michael Thomas (Mentoring LKP)
Die komplette Synpopse ist zu finden unter den Studien der Arbeitsgruppe Young Medical Oncologist	

NSCLC ohne onkogenen Treiber, metastasiert

AIO-TRK-0220/ass: Breaking the big Five Barriers of Brain Metastasis: A prospective phase II, open-label, multi-center trial of combined nivolumab, ipilimumab and bevacizumab together with 2 cycles of induction chemotherapy in patients with non-squamous non-small-cell lung cancer (NSCLC) metastatic to the brain (Break B5-BM NSCLC Trial)

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-TRK-0220/ass - CA209-7WF / Break B5-BM-NSCLC**
Status:	in Vorbereitung
Rekrutierungszeit:	von: 04.21 bis: 10.23
Anzahl Zentren:	geplant: 10 aktuell initiiert:7 aktiv rekrutierend:7
Weitere Zentren:	sind aktuell leider nicht möglich
Anzahl Patienten:	geplant: 39 aktuell eingeschlossen: 5
Letzte Aktualisierung	29.10.2021

STUDY TYPE	Phase II
PRINCIPAL INVESTIGATOR	Dr. Daniel Heudobler Department of Internal Medicine III University Hospital Regensburg Franz-Josef-Strauß-Allee 11 93053 Regensburg, Germany Tel: +49-941-944-4800 Fax: +49-941-944-5502 E-mail: daniel.heudobler@ukr.de
TRIAL OFFICE	Department of Internal Medicine III University Hospital Regensburg Franz-Josef-Strauß-Allee 11 93053 Regensburg, Germany
SPONSOR	University Hospital Regensburg, Germany represented by the Chairman of the Board
CONDITION	Non-squamous non-small-cell lung cancer (NSCLC) metastatic to the brain
DESIGN	Prospective, open-label, multi-center
INDICATION	Non-squamous non-small-cell lung cancer (NSCLC) metastatic to the brain, first-line
OBJECTIVE(S)	Combined treatment with nivolumab, ipilimumab and bevacizumab given concomitantly with 2 cycles of induction chemotherapy will provide clinical benefit to subjects with non-squamous NSCLC metastatic to the brain.
INTERVENTION(S)	Nivolumab administered IV over 30 minutes at 360 mg every 3 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Besides PD-L1 predicting response to immune-oncology (IO) therapy is still very challenging. In particular, predictive data of brain metastasized patients of NSCLC are missing. Thus this trial cohort poses a unique opportunity to address this question and shed some light on mechanisms of IO response and resistance. Therefore, we aim to gain a comprehensive insight into this complex clinical and biological situation with a special focus on the following topics.
BACKROUND/RATIONALE	Brain metastases (BM) are a common site of tumor manifestation in a wide range of cancers, but they are particularly prevalent among patients with lung cancer. 40 to 60 percent of patients will develop brain metastases during their course of disease. With improved control of extracranial disease

	by systemic therapy, enabling the emergence of otherwise not clinically manifested metastasis, the proportion of NSCLC patients experiencing BMs will even increase. There are five mechanical/immunological barriers protecting NSCLC brain metastases from a sufficient immune/treatment response: - The limited anatomical volume causing edema - The immunological barrier at the BBB - The immune-(privileged) suppressive status of the brain parenchyma - The glial pseudo-capsule - The epithelial barrier at the MMPI Now, to achieve a long-lasting treatment response all five barriers have to be taken into account in the treatment of NSCLC brain metastases. Thus, we suggest a regimen of continuous double checkpoint blockade to enhance the leukocyte trafficking and achieve a long-lasting immune attack against the NSCLC brain metastasis. Further, we would add two cycles of chemotherapy to break down the epithelial barrier of the NSCLC at the MMPI. Finally, we would use anti-VEGF-a treatment to omit steroids, reduce intracranial pressure and perform an angio-immunogenic switch of the resident microglia and immune-suppressive TAM.
KEY EXCLUSION CRITERIA	**Target Disease Exceptions** *1.* History of known leptomeningeal involvement (lumbar puncture not required). *2.* History of whole brain irradiation *3.* History of intracranial hemorrhage *4.* Spinal cord compression not definitively treated with surgery and/or radiation, or previously treated spinal cord compression that has been clinically stable for less than 2 weeks prior to first dose of study drug *5.* Subjects with oligometastatic disease according to IASLC eligible for a definitive local therapy in curative intent *6.* Subjects with oncogenic driver mutations which are sensitive to available targeted inhibitor therapy (i.e. EGFR mutation, ALK or ROS1 translocation, BRAF V600 mutation, NTRK fusion). Subjects with unknown or indeterminate EGFR or ALK status are excluded. *7.* Uncontrolled pleural effusion, pericardial effusion, or ascites (patients with pleural drainage system like PleurX catheter and controlled situation are eligible) *8.* Uncontrolled tumor-related pain: Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) may be treated by radiotherapy **General Medical Exclusions** *9.* Autoimmune disease: subjects with a documented history of inflammatory bowel disease, including ulcerative colitis and Crohn's disease are excluded from study treatment as are subjects with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus, autoimmune vasculitis [eg, Granulomatosis with polyangiitis, (Wegener's)], and sarcoidosis including interferon-induced sarcoidosis. Subjects with motor neuropathy considered of autoimmune origin (eg, Guillain-Barre Syndrome and Myasthenia Gravis) are excluded from study treatment.

	a. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. *b.* Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study. *10.* Subjects with major medical, neurologic or psychiatric condition who are judged as unable to fully comply with study therapy or assessments should not be enrolled. *11.* Any concurrent malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix. For any prior invasive malignancy, at least 5 years must have elapsed since curative therapy and patients must have no residual sequelae of prior therapy. *12.* Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to start of study treatment, unstable arrhythmias, or unstable angina. *a.* Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. *13.* Major surgical procedure other than for diagnosis or treatment of symptomatic brain metastasis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study *14.* Prior allogeneic bone marrow transplantation or solid organ transplant *15.* Active or latent tuberculosis *16.* Symptomatic interstitial lung disease *17.* Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. *18.* Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) even if fully immunocompetent on ART—due to the unknown effects of HIV on the immune response to combined nivolumab plus ipilimumab or the unique toxicity spectrum of these drugs in patients with HIV. **Exclusion Criteria related to Medications** *19.* Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment; the following exceptions are allowed: Hormone-replacement therapy or oral contraceptives *20.* Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to start of study treatment *21.* Simultaneous treatment with another investigational agent or simultaneous anticancer treatment outside this trial

	22. Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study *23.* History of allergy to study drug components **Exclusions related to bevacizumab** *24.* Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg) (anti-hypertensive therapy to achieve these parameters is allowable) *25.* Prior history of hypertensive encephalopathy *26.* Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to start of study treatment *27.* History of hemoptysis (≥ one-half teaspoon of bright red blood per episode) within 1 month prior to start of study treatment *28.* Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation) *29.* Current or recent (within 10 days of start of study treatment) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol *30.* Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for > 2 weeks prior to study start - The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to start of study treatment - Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR < 1.5 × ULN and aPTT is within normal limits within 14 days prior to start of study treatment. - Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted. *31.* Core biopsy or other minor surgical procedure, excluding placement of a vascular/pleural access device, within 7 days prior to the first dose of bevacizumab *32.* History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to start of study treatment *33.* Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding *34.* Evidence of abdominal free air not explained by paracentesis or recent surgical procedure *35.* Serious, non-healing wound, active ulcer, or untreated bone fracture *36.* Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection (All patients with ≥ 2+ protein on dipstick

	urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.)
KEY INCLUSION CRITERIA	**Signed Written Informed Consent** *1.* 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 *2.* Subjects must be willing and able to comply with protocoll **Target Population** *3.* Males and Females, ages ≥ 18 years of age *4.* ECOG performance status of 0, 1 and 2 (patients with a decline in performance status due to neurologic symptoms of brain metastasis are eligible for the study up to ECOG 3) *5.* Life expectancy ≥ 12 weeks *6.* Histologically or cytologically documented metastatic non-squamous NSCLC stage IVB (IASLC) [1] *7.* Measurable disease, as defined by RANO-BM (intracranial) and RECIST v1.1 (extracranial) *8.* at least one measurable brain metastasis (tumor diameter: 0.5 to 3 cm) which has not been previously irradiated and is not judged to require immediate local intervention (radiation/surgery) *9.* Known PD-L1 tumor status *10.* no prior cytotoxic/systemic (chemo)therapy regimens for metastatic disease (in this context neo-/adjuvant therapy including immunotherapy is not counted as line of therapy) *11.* The last dose of prior (neo-/adjuvant) systemic anti-cancer therapy or immunotherapy must have been administered ≥ 21 days prior to first dose of study treatment. *12.* The last dose of treatment with any investigational agent or participation in a clinical trial with therapeutic intent must have ended ≥ 28 days prior to first dose of study treatment. *13.* Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first study treatment: *a.* ANC ≥ 1500 cells/µL (without granulocyte colony-stimulating factor support within 2 weeks of test) *b.* WBC counts > 2000/µL *c.* Lymphocyte count ≥ 500/µL *d.* Platelet count ≥ 100,000/µL (transfusion within 2 weeks of test) *e.* Hemoglobin ≥ 9.0 g/dL. Patients may be transfused or receive erythropoietic treatment to meet this criterion.

	14. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 mL/min (using the Cockcroft Gault formula) *15.* Adequate liver function: AST or ALT ≤ 3 × ULN; Serum bilirubin ≤ 1.5 × ULN. With the following exceptions: *a.* Subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL *b.* Subjects with documented liver metastases: AST and/or ALT ≤ 5 × ULN *c.* Subjects with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN. **Reproductive Status** *16.* Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test [minimum sensitivity 25 units per litre (IU/L) or equivalent units of human chorionic gonadotropin (HCG)] within 3 days prior to the start of study drug. *17.* Women must not be breastfeeding *18.* WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment plus 5 half-lives of nivolumab (half-life up to 25 days) plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion.
OUTCOME(S)	**Safety** Safety will be monitored throughout the whole study, with a specific focus on the safety-lead-in phase. • Predefined dose limiting toxicities (DLTs) will be counted and dosing will be adjusted according to the recommendations of the DSMB. • Incidence and intensity of adverse events (AEs) and serious adverse events (SAEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v5.0 **Primary Efficacy Endpoint** Central nervous system (CNS) clinical benefit rate (CBR) 6 months after patient inclusion (pCBR), defined as either • complete response [CR], • partial response [PR] or • stable disease [SD] ≥ 6 months
STATISTICAL ANALYSIS	**Safety** Safety analyses will be performed within the safety population. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All treatment emergent AEs, drug-related AEs, SAEs and drug- related SAEs (will be coded according to MedDRA) and tabulated using worst grade per NCI CTCAE V.5.0 criteria by system organ class and preferred term. Primary efficacy endpoint CBR rate 6 months after study inclusion (pCBR) will be calculated as effect estimate using the intention to treat population. Further, a corresponding exact one-sided 95%-confidence interval (Clopper-Pearson) will be

	calculated. The null-hypothesis pCBR≤0.35 will be rejected if the lower limit of the one-sided 95%-confidence interval is above 0.35. **Secondary endpoints** Time to event endpoints will be presented graphically by using Kaplan-Meier curves. Time distributions, median time to event and event rates at specific time points with corresponding one-sided 95% confidence intervals will be estimated by means of the KM method. Scores of PROs will be calculated according to the manuals and presented by descriptive statistics (N, mean, standard deviation, median, interquartile range, minimum, and maximum) for each visit.
SAMPLE SIZE	Sample size is based on the primary efficacy endpoint. The uninteresting CBR-rate p0 (historical control) was set to 35%. Our desired and expected CBR rate p1 was set to 55%. Alpha was set to 5% (one-sided) and beta to 0.2 (Power 80%). This results in a required sample size of n=37 patients. With a lost-to-follow-up rate of maximal 5% (high burden of patients and closed meshed controls), a total of n=39 patients need to be included.
TRIAL DURATION	Recruitment duration: 2 years and 9 months Treatement: 1 year, all adverse events documented for a minimum of 100 days after the last dose of study medication
PARTICIPATING CENTERS	Uniklinikum Regensburg Universitätsklinikum Augsburg Evangelisches Krankenhaus Hamm Universitätsklinik Mannheim LMU, Klinikum der Universität München Universitätsklinikum Münster Oldenburg, Pius Hospital Klinikum Stuttgart Uniklinikum Gießen Sana Klinikum Offenbach Thoraxklinik Heidelberg

NSCLC mit EGFR-Mutation, metastasiert

AIO-YMO/TRK-0120: Radiation during Osimertinib Treatment: a Safety and Efficacy Cohort Study (ROSE)

AIO-Studie

Studiennummer/-Code:	**AIO-YMO/TRK-0120 / ROSE**
Status:	In Vorbereitung
Rekrutierungszeit:	geplant Q4/2021 bis: Q1/2024
Anzahl Zentren:	geplant: 8-10 aktuell initiiert: 0 aktiv rekrutierend: 0
Weitere Zentren:	sehr erwünscht
Anzahl Patienten:	geplant: 60 aktuell eingeschlossen: 0
Letzte Aktualisierung	Oktober 2021

PRINCIPAL INVESTIGATOR	PD Dr. Amanda Tufman Respiratory Medicine and Thoracic Oncology University of Munich Ziemssenstr. 1 80336 Munich
SPONSOR	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin, Germany Tel: +49 30-8145 344 32, Fax: +49 30-3229329-26 E-Mail: info@aio-studien-ggmbh.de
CONDITION	Stage IV EGFR-mutation positive NSCLC, treatment with osimertinib
DESIGN	Single arm, explorative, multi-center parallel cohort study
Primary objective	To assess the safety of osimertinib treatment continuation during irradiation therapy for palliation or oligoprogressive disease.
Secondary objectives	To assess the efficacy of osimertinib treatment continuation during irradiation therapy for palliation or oligoprogressive disease.
Exploratory objectives	To investigate types of irradiation (conventional vs. stereotactic) and target volumes used. To explore blood- and tissue-based biomarkers in this setting
Primary endpoint	Safety and tolerability (Frequency, time of onset and severity of Adverse Events, grading according to CTCAE V5.0), including pneumonitis, interstitial lung disease, radiation pneumonitis, radionecrosis and cardiac failure (congestive heart failure – CHF) as adverse events of special interest.
Secondary endpoints	• Progression-free survival (PFS), calculated as PFS1, PFS2, PFS3, PFS0 to assess osimertinib treatment continued beyond several progression events entailing radiotherapy, and prior to first radiotherapy • Time to treatment failure (TTF) • Local tumor control • Overall survival (OS) • Quality of Life assessed by EORTC QLQ-C30
INTERVENTION(S)	Osimertinib: according to its marketing authorization, i.e. at daily doses of 80 mg, for a maximum of 12 months within the study. Radiotherapy: according to standard of care.
Exploratory analysis / translational research endpoints	• Blood sample analysis and biomarker assessment • Optional tumor tissue analysis (pre-study FFPE sample) and biomarker correlation with patient baseline characteristics and outcomes • Target volume of irradiation • Type of irradiation (conventional, stereotactic)
BACKROUND/RATIONALE	Many patients with advanced lung cancer require palliative irradiation of metastases to relieve symptoms and prevent local complications. In addition, guidelines recommend local treatment (including radiation) for oligoprogression during TKI treatment. Clinicians are faced with the decision whether to continue TKI therapy during irradiation, a practice for which there

	is little data, or to interrupt the oral treatment for the duration of radiation, which may lead to progression of non-irradiated lesions. For erlotinib and gefitinib there is some data indicating that cranial irradiation as well as stereotactic body irradiation may be carried out safely without discontinuing or interrupting the TKI treatment. There is very limited data on the safety of osimertinib during irradiation, and no evidence-based recommendations around stopping osimertinib for irradiation.
Inclusion criteria	1. Provision of written informed consent prior to any study specific procedures, including screening evaluations that are not SOC. 2. Age ≥ 18 years at time of study entry. 3. Histologically confirmed stage IV NSCLC 4. Ongoing or planned osimertinib treatment according to marketing authorization (first line treatment of tumor positive for an activating EGFR mutation, or later line treatment of tumor positive for EGFR T790M mutation, assessed according to local standard. First line therapy is defined as therapy used to treat advanced disease. Each subsequent line of therapy is preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy. Experimental therapies when given as separate regimen are considered as separate line of therapy. Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.) 5. Clinical indication for palliative radiotherapy of one or more lesions, either for local symptom control of primary tumor or metastasis, or for oligoprogressive metastasis, with conventional or stereotactic strategy. Radiotherapy of metastatic sites can be for bone, solid organ or soft-tissue lesions; initial size of brain metastases should be < 3 cm. Lung lesions should be no more than 5 cm. 6. ECOG performance status 0-2. 7. Life expectancy ≥12 weeks 8. Female subjects should be using highly effective contraceptive measures, and must have a negative pregnancy test and not be breast-feeding prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening: • Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments • Women under 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution. • Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation • Further information in Section **Fehler! Verweisquelle konnte nicht gefunden werden.** and Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.** 9. Male subjects who are sexually active with WOCBP should be willing to use highly effective contraception (see Section **Fehler! Verweisquelle konnte nicht gefunden werden.** and Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**). Men who are azoospermic do not require contraception. 10. 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. 11. Negative COVID-19 test within 1 week prior to starting irradiation if clinically required by current regional COVID-19 outbreak situation.
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. 2. Treatment with an investigational drug within five half-lives of the compound or 3 months, whichever is greater 3. Previous enrolment in the present study.

	4. Any chemotherapy, biologic or hormonal cancer therapy other than EGFR-TKIs used concurrently or within 4 weeks prior to study enrolment, or checkpoint inhibitors within 130 days prior to study enrolment. Hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable. 5. Any unresolved toxicities from prior therapy greater than grade I (exception: alopecia, grade 2 neuropathy) which in the investigator's opinion would jeopardise compliance with the protocol or worsen during irradiation 6. Cardiac side-effects of osimertinib not sufficiently improved by dose reduction as suggested by the label/ German "Fachinformation". 7. In patients with indication for radiotherapy of lung lesions: past medical history of ILD/pneumonitis, radiation pneumonitis grade 2 or greater (CTCAE V5.0) or requiring steroid treatment, or any evidence of clinically active ILD, in particular interstitial pulmonary fibrosis (IPF). 8. Major surgery (as defined by the Investigator) within 4 weeks prior to starting the study; patients must have recovered from effects of preceding major surgery. Note: Local non-major surgery for palliative intent (e.g., surgery of isolated lesions) is acceptable. 9. Congenital long QT syndrome 10. Any of the following cardiac criteria: • Mean resting corrected QT interval (QTc) >470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value • Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block and second degree heart block. • Patient with any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: Serum/plasma potassium < LLN; Serum/plasma magnesium < LLN; Serum/plasma calcium < LLN) , congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes 11. Inadequate bone marrow reserve or organ function (as demonstrated by any of the following laboratory values: • Absolute neutrophil count <1.5 x 10^9/L; • Platelet count <100 x 10^9/L; • Hemoglobin <90 g/L; • Alanine aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; • Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; • Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinemia] or liver metastases; • Serum creatinine >1.5 times ULN concurrent with creatinine clearance <50 mL/min [measured or calculated by Cockcroft and Gault equation]—confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN. 12. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required. 13. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease. 14. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.

	15. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements. 16. Active infection will include any patients receiving treatment for infection. 17. Clinical suspicion of COVID-19 with or without negative COVID-19 test 18. Participants with a resolved or chronic HBV infection are eligible if they are: • Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG] or • Positive for HBsAg, negative for HBeAg but for > 6 months have had transaminases levels below ULN and HBV DNA levels below 2000 IU/mL (i.e., are in an inactive carrier state). 19. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib. 20. Currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of CYP3A4 (at least 3 week prior) (Section **Fehler! Verweisquelle konnte nicht gefunden werden.**). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4. 21. Women who are pregnant or breast-feeding 22. Male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 4 months after the last dose of Osimertinib 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]
TRIAL DURATION	Enrollment: 24 months Total study duration: ~48 months
Sample size estimation	The study objective is exploratory in nature. Therefore, no formal hypothesis test is formulated. Instead, the sample size will be gauged against the objective to observe/acquire meaningful data about the potential toxicities. In this regard, the sample size of N=60 is considered to provide a reasonably reliable estimate. With a sample size of N=60 -assuming that the number of events follows a binomial distribution [B(60,p)]-, events with an incidence rate p > 4,9% will be observed at least once with a 95% probability. Assuming 30% grade 3/4 all-cause AEs during osimertinib* monotherapy, a clinically significant increase in AEs (defined as 48% grade 3 or higher AEs) with simultaneous radiation at any point during osimertinib treatment, will be well within the detection limit of the ROSE trial.
PARTICIPATING CENTERS	8-10
FURTHER CENTERS DESIRED?	yes
NUMBER of PATIENTS	60 (at least 10 per cohort)

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)

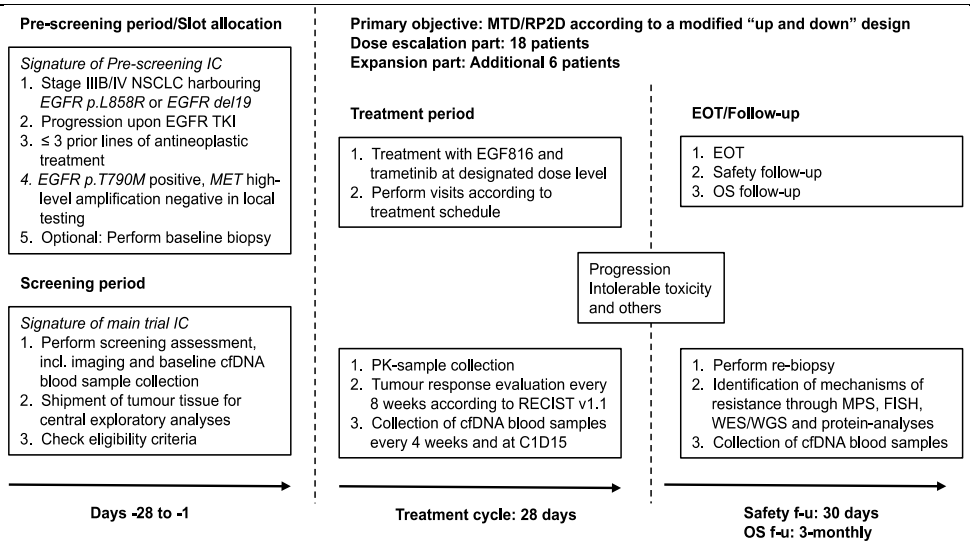
Remark: According to version V02_0 of the protocol, patients may also be eligible if EGFR TKI-treatment naïve, *EGFR* p.T790M-negative at progression while on EGFR TKI therapy or after progression while on osimertinib treatment

AIO-Studie		
Studiennummer/-Code:	AIO-TRK-0216 - EATON	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2018 – 2022	
Weitere Zentren:	Aktiv: Köln, Essen, Würzburg, Frankfurt, Dresden, Barcelona Vall d Hebron, Barcelona IOR	
Patienten:	geplant: 18-24	aktuell eingeschlossen: 13
Zentren:	geplant: ursprünglich 8	aktuell initiiert: 7
Letzte Aktualisierung	Okt 2021	

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 any EGFR TKI Remark: Patients with high-level MET amplification or other secondary EGFR mutations than p.T790M are excluded
Trial design	Phase I, dose escalation, genetically pre-selected, international, multicentre, open-label
Trial rational	Resistance to EGFR TKI treatment inevitably develops upon therapy with first- or second-generation EGFR TKIs (i.e. erlotinib, gerfitinib, afatinib) and third-generation EGFR TKIs (i.e. osimertinib) in first- or second-line. Mechanisms described so far in preclinical models and biopsies involve secondary *EGFR* mutations, *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]. 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 hypothesise 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 third-generation EGFR TKI treatment in first- or second-line.
Summary of the study strategy and aims	The population of interest for this trial is defined as patients with NSCLC harbouring sensitizing *EGFR* mutations, who developed *EGFR* p.T790M-positive or -negative resistance to treatment with EGFR TKIs including osimertinib. A high-level amplification of *MET* as well other EGFR mutations than *EGFR* del19, p.L858R or p.T790M 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 or sequencing methods.

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

<table>
<tr><td></td><td>the highest (already investigated) dose level (i.e. the actual MTD) equal or below the virtual MTD (extension cohort).
No formal statistical sample size calculation was performed for this trial. A total number of 24 patients will be treated.</td></tr>
<tr><td>Treatment regimen and dose levels</td><td>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
<table><tr><th>Dose level</th><th>EGF816 daily dose (mg, QD)</th><th>trametinib daily dose (mg, QD)</th></tr><tr><td>1</td><td>100</td><td>1.0</td></tr><tr><td>2</td><td>100</td><td>1.5</td></tr><tr><td>3</td><td>150</td><td>1.5</td></tr><tr><td>4</td><td>150</td><td>2.0</td></tr></table></td></tr>
<tr><td>Molecular analyses</td><td>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.</td></tr>
<tr><td>Summary of trial procedures</td><td>Flow chart of trial procedures.</td></tr>
</table>



Before signing the Main Trial Informed Consent a slot for participation in the trial should have been allocated for the individual patient. A patient for whom a slot for participation has been requested should be able to start treatment within the next 28 days and presumably fulfil the eligibility criteria. In patients who are undergoing rebiopsy after signature of the Main Trial IC fresh frozen tissue will preferentially 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.

The screening period (d -28 to -1) will only start, once a slot has been allocated to the patient by the sponsor and after the signing of the Main Trial Informed Consent. After the screening period and if the patient meets eligibility criteria, treatment will start at the designated dose level and drug administration schedule. Patients will be treated on a continuous schedule of EGF816 and trametinib. Treatment cycles are defined as 28 days (4 weeks) for the purpose of scheduling procedures and evaluation.

Tumour response evaluation will be performed by CT and/or MRI scans every 8 weeks and assessed according to RECIST v1.1.

Treatment will be conducted until disease progression, occurrence of intolerable toxicity, withdrawal of IC or treatment discontinuation at the discretion of the investigator.

At progression a biopsy should be collected to determine potential mechanisms of acquired resistance (*Section 11.3*).

At baseline, throughout the trial treatment and at progression blood samples will be collected for analysis of circulating cfDNA by MPS.

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.
2. Patients (male or female) ≥ 18 years of age.
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.
4. Presence of at least one measurable lesion according to RECIST v.1.1.
5. ECOG performance status ≤ 2
6. Patients must have NSCLC harbouring *EGFR* p.L858R or *EGFR* del19 as assessed by local testing.
7. Patients must be EGFR TKI treatment naïve (prior chemotherapy treatment is allowed) or must have progressed while on continuous treatment with a first- or second-generation EGFR TKI (*EGFR* p.T790M-negative or -positive) or must have progressed while on continuous treatment with osimertinib (*EGFR* p.T790M-negative or -positive)
8. In patients who have received no prior EGFR TKI treatment, an archival biopsy sample, defined as a sample being obtained prior to any anti-cancer treatment is mandatory. If an archival biopsy fulfilling this criterion is not available, patients must be suitable and willing to undergo baseline biopsy according to the local institution's guidelines (newly obtained biopsy).

	9. In patients who have received prior EGFR TKI treatment, an archival biopsy sample, defined as a sample being obtained after or during progression upon the last anti-cancer treatment is mandatory. 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). 10. In patients who have received prior EGFR TKI treatment, *EGFR* p.T790M mutation status must have been assessed by local testing in the tumour sample fulfilling the requirements of inclusion criterion 9. 11. Patients who have received prior osimertinib treatment, may only be eligible if no standard treatment approach outside this trial is available or feasible (e.g. chemotherapy) 12. Patients who have progressed while on continuous treatment with a first- or second-generation EGFR inhibitor and whose tumour has been tested EGFR p.T790M-negative may only be eligible if no standard treatment approach outside this trial is available or feasible (e.g. chemotherapy). 13. In patients who have received prior EGFR TKI treatment, progression of disease according to RECIST v1.1 while on continuous treatment with an EGFR TKI (e.g. erlotinib, gefitinib, afatinib or osimertinib) must be documented.
Exclusion criteria	1. History of allergic reactions or hypersensitivity to one of the study drugs or to any component of the study drugs 2. Prior treatment with any investigational agent known to inhibit EGFR (mutant or wild-type) 3. Prior treatment with any agent known to inhibit MEK/ERK or other mediators of RAS pathway. 4. Patients with high level *MET* amplification in the archival or newly obtained biopsy sample as determined by local testing. High-level MET amplification is defined as: a) a MET/CEN7 ratio ≥2.0 and/or b) an average MET gene copy number per cell of ≥6.0 [modified Schildhaus et al., 2015]. 5. Patients with EGFR mutations other than *EGFR* del19, p.L858R or p.T790M. 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. 7. Patients with presence or history of carcinomatous meningitis. 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 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 10. Known HIV infection or history of HIV infection independent from the cellular immune status 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 12. Patients who underwent bone marrow or solid organ transplantation, including patients who do not receive any immunosuppressive treatment. 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 14. Any of the following within 6 months prior to first trial drug administration: Myocardial infarction (NSTEMI or STEMI), severe/unstable angina pectoris, symptomatic congestive heart failure (> NYHA II), uncontrolled hypertension, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack, atrial fibrillation of CTCAE Grade ≥ 2, ongoing cardiac dysrhythmias of CTCAE Grade ≥ 2, including corrected QTcF prolongation of > 480 ms, 15. Aortic valve stenosis with mean gradient ≥ 25 mmHg and aortic valve area of ≤ 1.5 cm^2 16. Any other cardiac valve abnormality of more than mild degree/stage 17. Left ventricular ejection fraction (LVEF) of < 50 %

	18. History of congenital long QT-syndrome or Torsades de Pointes 19. History of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED) 20. Unable or unwilling to swallow tablets or capsules 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 22. Patients have received anticancer treatment within the following time frames prior to the first dose of study treatment: a. Conventional cytotoxic chemotherapy: ≤ 4 weeks (≤ 6 weeks for nitrosoureas, mitomycin-C and suramin) b. Biological therapy (e.g., antibodies, excluding PD-1 or PD-L1 antibodies): ≤ 4 weeks c. PD-1/PD-L1 antibodies (e.g., nivolumab, pembrolizumab): ≤ 5 half-times d. Non-cytotoxic anti-cancer therapeutic (e.g., tyrosine kinase inhibitors): ≤ 5 half-times or ≤ 1 weeks (whichever is longer) e. Other investigational agent: ≤ 4 weeks f. Radiation therapy (excluding palliative radiation, e.g., of bone metastases): ≤ 4 weeks g. Major surgery (excluding minor surgical interventions, e.g., vascular device implantation): ≤ 2 weeks 23. Laboratory values as listed below, that cannot be corrected to normal limits within screening : a. Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L b. Haemoglobin (Hb) < 9 g/dL c. Platelets (PLT) < 100 x 10^9/L d. Total bilirubin > 1.5 x upper limit of normal (ULN). For patients with confirmed Gilbert's disease total bilirubin > 2.5 x ULN e. AST and/or ALT > 3 x ULN f. AST and/or ALT > 5 x ULN in patients with liver involvement g. Serum creatinine > 1.5 x ULN h. Measured or calculated creatinine clearance ≤ 45 mL/min i. Serum amylase and/or lipase CTCAE Grade > 2 j. Potassium, magnesium, phosphorus, total calcium (corrected from serum albumin) > ULN 24. Patients receiving treatment with any medication that are known to be a. Strong inhibitors or inducers of CYP3A4/5 b. Substrates of CYP2D6 with narrow therapeutic index c. and that cannot be discontinued at least 7 days prior to the first dose of the study drugs. *d. For further information please refer to Section* ***Fehler! Verweisquelle konnte nicht gefunden werden.*** and the *Concomitant Medication Manual.* 25. Patients with a history of or presence of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis 26. Pregnancy or breastfeeding/nursing women 27. Women of child-bearing potential (for definition see *Section* ***Fehler! Verweisquelle konnte nicht gefunden werden.***) unless they use highly effective methods of contraception during treatment and for four months after withdrawal of study treatment (for methods of contraception see *Section* ***Fehler! Verweisquelle konnte nicht gefunden werden.***) 28. Sexually active males unless they use a condom during intercourse for the time of study treatment and for four months after the withdrawal of study treatment.
Trial duration / timelines	Inclusion first patient (FPFV): 02/2018 Inclusion last patient: 08/2022 Last patient last visit (LPLV): 03/2023

NSCLC mit ALK Translokation metastasiert, 1st-line

AIO-TRK-0219: Advancing Brigatinib Properties in anaplastic lymphoma kinase positive non-small cell lung cancer (ALK+ NSCLC) patients by deep phenotyping (APB)

AIO-Studie	
Studiennummer/-Code:	AIO-TRK-0219 - ABP-2019
Status:	In Rekrutierung
Rekrutierungszeitraum:	Seit Q1 2020, 36 Monate Rekrutierung
Zentren:	geplant: 20 initiiert: 25
Patienten:	geplant: 116 aktuell eingeschlossen: 48
Weitere Zentren:	Ggf. nach Rücksprache weitere Zentren möglich
Letzte Aktualisierung	Oktober 2021

COORDINATING INVESTIGATOR (LKP)	Univ.-Prof. Dr. Michael Thomas, MD Dept. of Thoracic Oncology/Internal Medicine Thoraxklinik at Heidelberg University Röntgenstr. 1 D-69126 Heidelberg E-Mail: Michael.Thomas@med.uni-heidelberg.de
SPONSOR / PROJECT MANAGER	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt Dr. Regina Eickhoff E-Mail: eickhoff.regina@ikf-khnw.de
STUDY PHASE	Phase II trial
STUDY DESIGN	This is a prospective, randomized, open-label, multicenter phase II study.
PLANNED NUMBER OF PATIENTS	116, randomized 1:1 into both treatment arms (58 patients per arm)
STRATIFICATION FACTORS	• Presence of brain metastases vs no presence of brain metastases • ECOG 0-1 vs 2
TOTAL NUMBER OF STUDY SITES	Approx. 20 sites
STUDY POPULATION	Patients are eligible if they have newly-diagnosed histologically confirmed locally advanced (stage III) and not suitable for curative treatment, i.e. R0 operation or definitive chemoradiation, or metastatic (stage IV) ALK$^+$ NSCLC and an age ≥ 18 years.
STUDY AIM	To compare efficacy of brigatinib and other 2nd-generation ALK TKI in 1st and 2nd line and to explore resistance patterns according to treatment and molecular properties of the tumors.
PRIMARY OBJECTIVE AND ENDPOINT	Efficacy of 1st-line treatment, measured as: • Progression-free survival (PFS) of 1st-line treatment (RECIST v1.1)
SECONDARY OBJECTIVES AND ENDPOINTS	Efficacy of 1st and 2nd line treatment, measured as: • PFS of 2nd-line treatment (RECIST v1.1) • TNT 1st line (TNT1, i.e. time-to-next treatment for the 1st line, defined as the time from begin of 1st-line treatment until begin of 2nd-line treatment) • TNT 2nd line (TNT2, i.e. time-to-next treatment for the 2nd line, defined as time from begin of 2nd line until begin of 3rd-line treatment)

	• TNT1/2 (time-to-next treatmemt for the 1st and 2nd line together, defined as time from begin of 1st-line treatment until begin of 3rd-line treatment)
	• Overall survival (OS)
	• Efficacy in the central nervous system (CNS, "brain control") of 1st- and 2nd-line treatment assessed by applying RECIST v1.1 criteria
	  ○ intracranial ORR (iORR)
	  ○ intracranial DOR (iDOR)
	  ○ time to intracranial progression (TTiP), defined as the time from start of 1st-line treatment until the occurrence of a new CNS lesion or progression of pre-existing CNS lesions (adjusted for the two competing events "death" and "extracranial progression inducing a change in ALK inhibitor treatment")
	Quality of life (QoL) as assessed by validated questionnaires:
	• QoL: SF-12 and EORTC-QLQ-BN20 (EORTC-QLQ-BN20 in case of brain metastases, only)
	Safety and tolerability

EXPLORATORY OBJECTIVES	• Typing of *ALK* fusion variants, assessment of *TP53* mutation status and detection of „acquired resistance" mutations via standardized next-generation sequencing (NGS)-based multiplex analysis • Efficacy of treatment according to *ALK* fusion variant and *TP53* status • Molecular resistance patterns after 1st-line failure • Impact of 2nd-line treatment after failure of 1st line • Clinical utility of cerebrospinal fluid ctDNA analysis in "brain-only" progression
TRANSLATIONAL RESEARCH	This clinical trial will be accompanied by a comprehensive translational research program. Tissue and blood sampling for molecular biomarker analyses: • Biopsies are collected at baseline (prior to start of 1st-line treatment); in addition, biopsies of lesions appearing or enlarging under treatment are strongly recommended, especially if a switch in TKI treatment is being considered. FFPE tumor tissue will be subjected to central NGS-based multiplex analysis. Central NGS-based analysis of baseline FFPE biopsies is mandatory for participation in this trial. • Blood samples are taken at baseline (i.e., up to 7 days prior to first administration of study medication, D1-7 days) and with every radiologic assessment with CT/MRI during 1st- and 2nd-line treatment (i.e. two cycles [8 weeks] after start of a new ALK inhibitor, and every 12 weeks [Q12W ±7 days] during continuation of treatment, i.e. at the same time as imaging studies are performed). Analyses will include: • Correlation of systemic and brain efficacy with molecular markers, such as the *ALK* fusion variant and *TP53* status. • Correlation of resistance mechanisms with the compounds used and with molecular markers, such as the *ALK* fusion variant and *TP53* status. • Correlation of site of progression with molecular markers, such as the *ALK* fusion variant and *TP53* status.
RATIONALE	Currently, in Germany several TKI are approved for the treatment of ALK+ NSCLC. Taking advantage of (1) the authorization status and rapid penetration of 2nd-generation ALK TKI in 1st-line treatment in Germany, (2) the broad availability of NGS-based molecular testing for primary biopsies and rebiopsies within the German national Network on Genomic Medicine in Lung Cancer (nNGM), and (3) the trial network available in the German IIT context, this phase II trial is conducted with the aim to generate hypotheses regarding the following key questions:

	a) Is there an optimal upfront treatment among currently available TKI? b) Are there particular resistance patterns associated with each compound? c) What is the additional effect of *ALK* variant status and *TP53* mutations on patterns of acquired resistance, i.e. are there particular compound-specific properties indicating superiority according to the type of *ALK* variant? d) Are there differences in brain control according to the upfront treatment? e) Might exploration of ctDNA (liquid biopsies) improve monitoring of disease and guidance of treatment (assessing resistance mutations, proxys of epithelial-mesenchymal transition [EMT] etc.)? f) Might analysis of cerebrospinal fluid in the same way support clinical decisions (guidance of next-line TKI treatment) in case of "brain-only" progression? In this phase II trial, ALK$^+$ patients are randomized into two arms. The experimental Arm B comprises sequential treatment with brigatinib in 1st line followed by 2nd-line treatment with any ALK TKI according to investigator's choice. In the standard Arm A, patients are treated with any 2nd-generation TKI except for brigatinib in 1st line (currently alectinib or ceritinib) according to investigator's choice, followed by 2nd-line treatment with any ALK TKI also according to physician's choice (see Figure 2). The choice of comparator 2nd-generation TKI in the 1st-line setting as well as the TKI used in 2nd-line treatment is up to the investigator and the latter should ideally take into account mechanisms of acquired resistance (i.e. ALK resistance mutations) as detected by repeat tissue or liquid biopsies at the time of disease progression. If considered appropriate by the treating physician, patients enrolled in Arm A will also be offered the possibility of treatment with brigatinib in the 2nd line, which will be provided by Takeda. Detailed clinical annotation as well as collection of tumor tissue and blood samples for subsequent comprehensive molecular characterization are pivotal in this study. By analyzing the relationship of clinical and molecular parameters with ALK TKI efficacy, as captured by the primary and secondary endpoints of the trial, the data gathered will help optimize treatment of ALK$^+$ NSCLC patients and define the most advantageous position of brigatinib in the treatment scenario of this entity.
INCLUSION CRITERIA	1. Fully informed written consent and any locally-required authorization (EU Data Privacy Directive) given by the patient 2. Male or female ≥ 18 years of age NOTE: There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. Histologically confirmed locally advanced (stage III) and not suitable for curative treatment, i.e. R0 operation or definitive chemo-/radiation, or metastatic (stage IV) ALK$^+$ NSCLC NOTE: Documentation of ALK rearrangement by a positive result of any ALK assay approved in Germany [i.e. positivity for at least one of the three: immunohistochemistry (IHC), NGS, fluorescence *in situ* hybridisation (FISH)] must be available at baseline. Treatment can already be started based on a local ALK$^+$ test result, but subsequent central testing of the baseline biopsy for molecular profiling, incl. determination of *ALK* variant and *TP53* status, should be made possible for all patients. 4. No prior therapy for metastatic ALK$^+$ NSCLC including therapy with ALK inhibitors. However, 1 or 2 cycles of chemotherapy as well as cerebral irradiation before inclusion in the study will be allowed. 5. At least 1 measurable (i.e., target) lesion per RECIST v1.1 6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 7. Have adequate organ function, as determined by: • Total bilirubin ≤1.5x the upper limit of the normal range (ULN) (< 3x the ULN if Gilbert's disease is present)

	• Estimated glomerular filtration rate ≥30 mL/minute/1.73 m^2 (calculated by MDRD or any other validated formula, see Appendix 13.4) • Alanine aminotransferase/aspartate aminotransferase ≤2.5x ULN NOTE: ≤5x ULN is acceptable if liver metastases are present. • Serum lipase ≤1.5x ULN • Platelet count ≥75x 10^9/L • Hemoglobin ≥9 g/dL • Absolute neutrophil count ≥1.5x 10^9/L 8. Willingness and ability to comply with scheduled visit and study procedures 9. Patient willing to participate in accompanying research program 10. Collection of current biopsy during screening must be feasible NOTE: For each patient a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be available for biomarker evaluation. Excisional, incisional or core needle biopsies are appropriate, while fine needle aspirations are insufficient. 11. Women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days prior to randomization. Women must not be breastfeeding. 12. Female patients who: - are postmenopausal for at least 1 year before the screening visit, OR - are surgically sterile, OR - if they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through *4 months* after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. Male patients, even if surgically sterilized (i.e., status post-vasectomy), who: - agree to practice effective barrier contraception during the entire study treatment period and through *4 months* after the last dose of study drug, OR - agree to completely abstain from heterosexual intercourse.
EXCLUSION CRITERIA	1. History or presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis 2. Uncontrolled hypertension (patients with hypertension have to be under adequate treatment for control of blood pressure upon study entry) 3. Systemic treatment with stro ng cytochrome P-450 (CYP) 3A inhibitors, strong CYP3A inducers, or moderate CYP3A inducers or treatment with any investigational systemic anticancer agents, chemotherapy or radiation therapy (except for stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days of randomization 4. Treatment with antineoplastic monoclonal antibodies within 30 days of randomization 5. Major surgery within 30 days of randomization. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed. 6. Current spinal cord compression (symptomatic or asymptomatic) as detected by radiographic imaging. Patients with leptomeningeal disease without cord compression are allowed. 7. Significant or uncontrolled cardiovascular disease, specifically including, but not restricted to the following: • If an acute coronary syndrome has ensued in the past 6 months, successful reperfusion has to be documented and the patient has to be free of symptoms. • New York Heart Association Class III or IV heart failure within 6 months prior to randomization • Any history of clinically significant ventricular arrhythmia

	8. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug 9. Malabsorption syndrome or other gastrointestinal illness or condition that could affect oral absorption of the study drug 10. Active severe or uncontrolled chronic infection, including but not limited to, the requirement for intravenous antibiotics for longer than 2 weeks 11. History of HIV infection. Testing is not required in the absence of history. 12. Chronic hepatitis B (surface antigen-positive) or chronic active hepatitis C infection. Testing is not required in the absence of history. 13. Any serious medical condition or psychiatric illness that could, in the investigator's opinion, potentially compromise patient safety or interfere with the completion of treatment according to this protocol 14. Known or suspected hypersensitivity to brigatinib or other TKI or their excipients 15. Life-threatening illness unrelated to cancer 16. Involvement in the planning and/or conduct of the study (applies to both Takeda staff and/or staff of sponsor and study site) 17. Patient who might be dependent on the sponsor, site or the investigator 18. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities [§ 40 Abs. 1 S. 3 Nr. 4 AMG] 19. 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] 20. Legal incapacity or limited legal capacity 21. Females who are pregnant or breastfeeding 22. Patients who have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days prior to randomization. NOTE: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for 7 days prior to randomization.
STUDY TREATMENT SCHEDULE	<u>1st-line treatment:</u> In the standard arm (Arm A) patients will receive any approved 2nd-generation TKI (currently alectinib or ceritinib) according to investigator's choice. In the experimental arm (Arm B) patients will receive • 90 mg brigatinib QD p.o. for the first 7 days (lead-in) followed by • 180 mg brigatinib QD p.o. afterwards, starting with day 8. <u>2nd-line treatment:</u> In both arms, patients will receive any available ALK TKI according to investigator's choice. Initiation of medication intake will take place after an obligatory washout period of 3 days between the 1st and 2nd line treatment (based on the half-lives of second-generation ALK TKI and in order to allow for a drop in the plasma concentration of the 1st-line TKI to <30%), while treating physicians will also consider additional potentially relevant factors, for example the need to wait even longer for resolution of any previous toxicity. The choice of TKI used in 2nd-line should ideally take into account mechanisms of acquired resistance (i.e. ALK resistance mutations) as detected by repeat tissue or liquid biopsies at the time of disease progression. If considered appropriate by the treating physicians, patients enrolled in Arm A will be offered the possibility of treatment with brigatinib in the 2nd line in the dosage described for the 1st-line experimental Arm B (90 mg brigatinib QD p.o. for the first 7 days of 2nd line [lead-in] followed by 180 mg brigatinib QD p.o. starting with day 8), which will be provided by Takeda.

DURATION OF STUDY TREATMENT	Subjects will continue to be treated with brigatinib or other TKI as long as they derive clinical benefit as determined by the treating physicians (this can include treatment beyond progression per RECIST v1.1 criteria in some cases with oligo-progression and ongoing clinical benefit) or until intolerable toxicity, patient's request to discontinue treatment, or another discontinuation criterion is met. Treatment duration in 1st and 2nd line is not limited to a certain timeframe and will continue until one of the above-mentioned criteria is met.
EFFICACY EVALUATIONS / CRITERIA	CT/MRI with contrast (unless use of contrast media is contraindicated) imaging of chest and abdomen incl. adrenal glands will be performed for all patients. Tumor response is determined based on the Response Evaluation Criteria in Solid Tumors (RECIST v1.1; Eisenhauer et al., 2009; investigator assessment). Baseline tumor evaluation will be performed at screening. Response assessment is recommended according to the standard of care, which should be after two cycles (8 weeks) of treatment in the 1st and 2nd line, and afterwards every 12 weeks (Q12W ±7 days) during active 1st-and 2nd-line treatment, respectively. For 2nd-line treatment, baseline disease assessment should be performed within 30 days prior to start of 2nd-line treatment. Intracranial response evaluation is performed based on RECIST v1.1 criteria. Contrast-enhanced MRI/CT of the brain will be performed at screening for all patients. Due to the higher sensitivity, use of MRI is strongly recommended. In case of brain metastases at baseline as well as in every case of cerebral progression at any later time-point, brain imaging (preferably with MRI) is recommended according to the standard of care, which should be at the time of next scheduled assessment (i.e., 8 weeks after beginning of 1st or 2nd line, and 12 weeks after any other restaging). Thereafter, further brain imaging (preferably with MRI) is recommended every 12 weeks (Q12W ±7 days) during active treatment in the 1st and 2nd line, respectively. In addition, it is recommended to adapt brain imaging intervals according to the location and size of metastases, for example lesions with large size or critical location (e.g. infratentorial) might require more frequent monitoring. For patients without brain lesions in baseline testing, surveillance imaging is recommended according to the same scheme, i.e. an MRI of the brain is recommended at every second time-point of radiologic assessment (that is 20 weeks after beginning of 1st or 2nd line, and every 24 weeks thereafter) in order to facilitate early detection of newly-developed brain lesions that will potentially be amenable to local ablative treatment. After study treatment discontinuation for reasons other than progressive disease, imaging of chest and abdomen incl. adrenal glands is recommended to be performed every 12 weeks (Q12W ±21 days), while imaging of brain is recommended to be performed every 24 weeks (Q24W ±21 days) until progression, death or initiation of another anti-cancer therapy according to standard of care (SOC).
SAFETY EVALUATIONS	Safety assessments will include physical and laboratory examinations, vital signs, performance status, and electrocardiograms. All observed toxicities and side effects will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE, version 4.03) for all patients, and the potential association of each with the study treatment assessed and summarized. Treatment-related serious adverse events rate (SAE) will be determined. AEs and toxicities are assessed on day 1 of every cycle during study treatment and in the safety follow-up.
STATISTICAL METHODS	This is an exploratory phase II trial aiming to generate hypotheses for future trials. Hence, the sample size of n=116 is primarily determined by considerations of feasibility and costs. Besides, in order to plan the duration of the trial, an estimation regarding the expected median PFS of the 1st-line treatment in the two treatment arms is important, but poses a special challenge: recently published interim results from the ongoing phase 3 ALTA-1L (Camidge 2018c) and ALEX (Camidge 2018d, Peters 2017) trials show that the PFS curve of ALK+ NSCLC patients receiving 1st-line brigatinib or alectinib, respectively, vs. crizotinib, forms a

	plateau at the level of about 50%, which causes the observed median PFS times to be a relatively "unstable" measure of treatment efficacy. In contrast, hazard ratios (HR) are generally more robust effect estimates than median PFS times, since they take into account the entire PFS curves under comparison instead of relying on a single time point. For example, the observed median PFS for alectinib was 25.7 months as assessed by the independent radiology review committee of the ALEX trial in 2017 with a HR=0.5 vs. crizotinib (Peters 2017), but "jumped" to 34.8 months (35% change) despite a much smaller HR change to 0.43 (14% change) in this year's investigator-assessed-only update (Camidge 2018d). On the other hand, the median PFS under crizotinib was reported by the investigators as 11.1 months in the first ALEX report (Peters 2017) and 10.9 months in this year's update (Camidge 2018d), i.e. appears to be relatively robust, because it is much shorter and the PFS curves for crizotinib are quite steep at the level of 50%. Therefore, for statistical calculations regarding the ABP trial, we decided to consider the more robust HR of brigatinib and alectinib vs. crizotinib in the ALTA-1L and ALEX studies, together with the more "stable" median estimate of crizotinib PFS, rather than the directly observed, but more "variable" median PFS of alectinib and brigatinib themselves. Aim was to delineate the follow-up times necessary for 1st- and 2nd-line treatment as well as to assess the expected 95% confidence interval (CI) range in the determination of PFS1 as a first exploratory parameter. For these calculations, the HR for PFS of 1st-line alectinib vs. crizotinib was considered 0.45 (the average of the 0.47 and 0.43 as assessed by the investigators in the 2017 and 2018 interim analyses [Peters 2017, Camidge 2018d]), the HR for PFS of 1st-line brigatinib vs. crizotinib was assumed identical to that of 1st-line alectinib vs. crizotinib (based on the very similar observed HR=0.49 (95% CI 0.33-0.74) in the ALTA-1L trial [Camidge 2018c]), and the median PFS under 1st-line crizotinib treatment was considered to be 11 months (i.e. the average of 11.1 and 10.9 months observed by the investigators in the 2017 and 2018 interim analyses of the ALEX trial [Peters 2017, Camidge 2018d]). Consequently, assuming an exponential distribution of PFS, the expected median PFS under 1st-line alectinib treatment was considered to be 24.4 months (11/0.45), and the duration of the ABP trial is proposed based on a follow-up time of 32 months for the last patient, which considers an expected PFS of 24.4 months under 1st treatment plus an expected PFS of about 7 months under 2nd line treatment with a different ALK inhibitor (based on the median PFS of 5.5-6.9 (95% CI 2.9-9.5) months observed with lorlatinib after failure of second-generation ALK inhibitors in the EXP3B/4/5 cohorts of a phase 2 trial [Solomon 2017]). The accrual of the trial is proposed as 36 months based on the expected number of newly-diagnosed ALK^+ patients in the centers expected to participate. In order to quantify the potential degree of evidence regarding PFS1 that can be gained with a number of n=116 patients at hand, we calculated the number of expected events *d*, the expected 95% CI for the median PFS of alectinib and brigatinib in the 1st line (assumed to be equal, as explained above), and the expected 95% CI for the HR of PFS under 1st-line brigatinib vs. alectinib in the ABP trial (assumed to be 1, as explained above), given a constant accrual over a time of 36 months, a follow-up time of 32 months for the last patient, and exponentially distributed PFS times. Under these assumptions, the expected number of PFS events is *d*=87, the expected 95% CI of the median PFS in the 1st line is [16.6 – 34.2 months] (both arms), and the expected 95% CI of the HR for PFS in the 1st line [0.66 – 1.52]. The number of events *d* was calculated using the formula by Schoenfeld (Schoenfeld 1981) and the software ADDPLAN v6.1, the confidence interval calculation for the median PFS was done via bootstrapping using 1,000,000 datasets simulated in R v3.3.3 (http://r-project.org) and a fixed random number seed to yield stable and reproducible results, and the confidence interval for the HR was calculated using the (approximate) formula $\exp(\pm 1.96\sqrt{4/d})$ (Wassmer 2006). A Cox proportional hazards model will be used to assess the primary endpoint PFS. As covariates, the model includes the factor "treatment group" and is adjusted for the presence of brain metastases at baseline (yes vs. no) and

	ECOG (0-1 vs. 2). The treatment groups will be compared at a two-sided α of 0.05, and 95% confidence interval for the hazard ratio will be given. Furthermore, Kaplan-Meier curves will be provided. Primary analysis will be based on the ITT population including all randomized patients. Sensitivity analyses will be conducted for the per-protocol set (patients without major protocol violations) and for predefined subgroups. Analyses of secondary endpoints will be descriptive and will include the calculation of appropriate summary measures of the empirical distributions. For the analysis of Adverse Events, 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.	
INDIVIDUAL STUDY DURATION PER SUBJECT	Subjects who discontinue 1st- or 2nd-line treatment for reasons other than progressive disease will continue to have surveillance imaging until progression, death or initiation of another anti-cancer therapy according to the standard of care. Thereafter, following disease progression, survival follow-up visits will be performed by phone contact or office visit until end of study (EOS).	
PLANNED TRIAL PERIOD	Planned first patient first visit (FPFV)	Approximately Q4 2019
	Last patient first visit (LPFV)	FPFV + 36 months Approximately Q4 2022
	Last patient last visit (LPLV = EOS)	LPFV + 32 months Approximately Q3 2025

Malignes Pleuramesotheliom, Stadien I-III

AIO-TRK/YMO-0419: Nivolumab with chemotherapy in pleural mesothelioma after surgery (NICITA)

AIO-Studie

Studiennummer/-Code:	AIO-TRK/YMO-0419		
Status:	in Rekrutierungsphase		
Rekrutierungszeit:	von: Q1-2020	bis: Q1-2022 (24 Monate)	
Anzahl Zentren:	geplant: 14	aktuell initiiert: 14	aktiv rekrutierend: 12
Weitere Zentren:	Nicht mehr möglich		
Anzahl Patienten:	geplant: 92	aktuell eingeschlossen: 43	
Letzte Aktualisierung	30.09.2021		

STUDY TYPE	Investigator- intiated trial (IIT)
COORDINATING INVESTIGATOR (LKP)	Dr. med. Rajiv Shah Dept. of Thoracic Oncology/Internal Medicine Thoraxklinik at Heidelberg University Hospital Röntgenstr. 1, D-69126 Heidelberg, Germany rajiv.shah@med.uni-heidelberg.de Mentoring LKP (Oncology): Univ.-Prof. Dr. med. Michael Thomas michael.thomas@med.uni-heidelberg.de

	Mentoring LKP (Surgery): PD Dr. med. Martin Eichhorn martin.eichhorn@med.uni-heidelberg.de
TRIAL OFFICE	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 D-60488 Frankfurt am Main, Germany
SPONSOR	Sponsor representative: Prof. Dr. S.-E. Al-Batran Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Germany Project Manager of Sponsor: Dr. Johanna Riedel (Riedel.johanna@ikf-khnw.de) // Christina Kopp (kopp.christina@ikf-khnw.de)
CONDITION	Patients with malignant pleural mesothelioma (MPM) in tumor stages I-III, who have previously undergone cytoreductive surgery by extended pleurectomy/decortication with or without hyperthermic intrathoracic chemoperfusion (eP/D ± HITOC)
DESIGN	Open-label, randomized, multicenter phase II trial
INDICATION	Malignant pleural mesothelioma (MPM) in tumor stages I-III
OBJECTIVE(S)	The primary objective is to determine if addition of nivolumab to adjuvant chemotherapy and subsequent administration of nivolumab mono-agent as maintenance therapy will improve TNT in stage I to stage III MPM patients that were previously subject to extended P/D ± HITOC.
INTERVENTION(S)	Arm A: Four cycles (q4w) of platinum-based adjuvant* chemotherapy i.v. • carboplatin AUC5 or cisplatin 75 mg/m^2 • pemetrexed 500 mg/m^2 Arm B: Four cycles (q4w) of a combination of platinum-based adjuvant* chemotherapy and immunotherapy i.v. • carboplatin AUC5 or cisplatin 75 mg/m^2 • pemetrexed 500 mg/m^2 • nivolumab 480 mg flat-dose followed by up to 12 cycles maintenance immunotherapy • nivolumab 480 mg flat-dose i.v. (q4w) In both arms, treatment will be discontinued upon the Investigator´s decision that patient will not have further benefit from treatment continuation, unacceptable toxicity or patients' request. Active treatment within the experimental arm of the study is limited to 16 months (4 months adjuvant combination therapy + 12 months maintenance immunotherapy).
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	In the context of this trial, tissue and blood samples are collected at indicated time points. These biomaterials will be analyzed in a translational research program. The program will aim to elucidate the effects of immune checkpoint inhibition in pleural mesothelioma patients and to explore potential biomarkers for immunotherapy in this disease. To this end, both blood and tissue samples will be collected during the trial for future analysis with regard to the following aspects: • Characterization of immunological status • Characterization of immunological tumor environment • Exploring the role of genomic features that are associated with MPM
BACKROUND/RATIONALE	Malignant pleural mesothelioma (MPM) is a locally invasive and highly aggressive cancer, and only 10% of the MPM patients live beyond five years. Due to the complex nature of this disease, the low patient number and a lack of randomized controlled trials in this entity, there is no approved standard therapy for the treatment of early-stage malignant pleural mesothelioma.

	Based on retrospective analysis and gained experience in the treatment of MPM, few treatment recommendations have been established, but research on adequate and effective mesothelioma treatment options is still ongoing and urgently needed. Considering the evolving landscape of mesothelioma treatment, it has to be noted that i.) the standard of locoregional treatment is extended pleurectomy/decortication (eP/D) and in specialized centers, if feasible, this is combined with HITOC, ii.) adjuvant chemotherapy might establish a tumor microenvironment with increased tumor immunogenicity, and iii.) inhibition of the immune checkpoint with the PD-1 antibody nivolumab shows promising results in advanced treatment lines. Thus, in the light of these recent developments, the combination of upfront locoregional therapy with adjuvant treatment composed of pemetrexed/platinum-based chemotherapy and additional nivolumab administration and with ongoing nivolumab maintenance after the end of chemotherapy is expected to have a beneficial effect due to synergistic mechanisms.
KEY EXCLUSION CRITERIA	1. Metastatic disease. 2. Patients for which surgery was scheduled as a cytoreductive surgery with curative intent but was then defined as palliative P/D by the operating surgeon. 3. Previous drug therapy against MPM. 4. Post-operative hospitalization > 6 weeks. 5. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways. 6. Inadequate hematological, renal and hepatic functions including the following: a. WBC < 2,000/µL b. Neutrophils < 1,500/µL c. Platelets < 100 x 103/µL d. Hemoglobin <9.0 g/dL e. Serum creatinine >1.5 x ULN unless creatinine clearance ≥ 45 mL/min (measured or calculated using the Cockroft-Gault formula). For application of cisplatin, creatinine clearance must be ≥ 60 mL/min. (measured or calculated using the Cockroft-Gault formula). f. AST/ALT >3.0 x ULN g. Total bilirubin >1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL) 7. Prior organ allograft or allogeneic bone marrow transplantation. 8. Concurrent or prior malignancy requiring or anticipated to require concurrent intervention. 9. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. 10. 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). 11. 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. 12. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or compliance with the study protocol. 13. Pregnant or breast-feeding women. 14. Positive testing for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection. 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.

	15. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV). 16. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidismdue 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. 17. 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. 18. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. 19. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 20. 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].
KEY INCLUSION CRITERIA	1. Fully-informed written consent 2. Males and females ≥ 18 years of age 3. Histologically proven initial diagnosis of malignant pleural mesothelioma of epithelioid subtype (patients can also be included if biphasic histologic subtype has been identified during surgery) 4. Postoperative stage I-III (TNM 8th Edition; pT1-4, pN0-2, cM0). Patients are only included with a completeness of cytoreduction score (CC score) <3 (i.e., residual tumor thickness ≤2.5 cm). 5. Patients must have undergone cytoreductive surgery with curative intent consisting of extended pleurectomy/decortication (eP/D) with or without hyperthermic intrathoracic chemotherapy (HITOC) 6. Surgery conducted ≤12 weeks (≤84 days) before study inclusion and patient recovered from post-surgical complications of P/D or P/D + HITOC 7. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 8. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial. Women must not be breastfeeding. 9. 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. 10. 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 is approximately 25 days. 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. Females must agree to refrain from egg donating (ova, oocytes) during the intervention period and for at least 5 months after last dose of study intervention.
Requirements regarding previous MPM surgery and result of surgery	Cytoreductive surgery should have been performed with the aim of macroscopic complete tumor resection and consisted of extended pleurectomy/decortication (eP/D) or eP/D + hyperthermic intrathoracic chemotherapy (HITOC) as specified in detail: According to the existing ESMO guideline (Baas et al., 2015), extended P/D implies a complete removal of the involved parietal and visceral pleura. If required due to macroscopic tumor infiltration, the diaphragm and pericardium can also be resected in the same procedure but the lung is left in situ: macroscopic complete resection (MCR) is still the goal. HITOC is defined as a 60 minutes intrathoracic lavage at 42°C with cisplatin-based chemotherapeutic agent in the already closed thoracic cavity using four chest tubes and a standardized perfusion system.

	MCR is reached if residual amounts of tumor are less than 1 cm3, but there are differences among surgeons regarding the definition of MCR. Completeness of resection will be further classified at the end of the operation according to the Completeness of Cytoreduction Score (CC score), defined for quantifying amounts of residual tumor after cytoreductive surgery for stage IV ovarian cancer (Rice D, 2012). The completeness of cytoreduction score (CC score): CC0 No residual tumor nodules CC1 Residual tumor nodules <2.5 mm CC2 Residual tumor nodules ≥2.5 mm or ≤2.5 cm CC3 Residual tumor nodules >2.5 cm Only patients with achievement of a CC-score <3 can be included in the trial. Surgery may have been conducted ≤12 weeks (≤84 days) before first drug administration and patient must have recovered (reduction to grade ≤2 for any local or systemic complication) from post-surgical complications of eP/D or eP/D + HITOC before enrollment into the study.
OUTCOME(S)	Primary efficacy endpoint: • Time-to-next-treatment (TNT) defined as time from randomization until initiation of any additional intervention against MPM due to disease progression (any systemic treatment; any locoregional measures [except for prophylactic radiotherapy to prevent procedure-track metastases]; any decision of the Investigator to switch the patient to BSC) Safety endpoints: Safety (according to NCI-CTCAE v 5.0) and tolerability Secondary endpoints: • Progression-free-survival (PFS) [acc. mRECIST for MPM] • Overall survival (OS) • Proportion of patients with Treatment Beyond Progression (TBP), duration of TBP in this population • Quality of life (QoL, based on LCSS-Meso and EQ-5D) Exploratory endpoints: • Biomarker exploration
STATISTICAL ANALYSIS	For the description of the primary endpoint time-to-next-treatment (TNT) a Kaplan-Meier estimator will be used. Moreover, feasibility in terms of toxicity and side effects will be assessed and a descriptive comparison between treatment arms will be conducted. Further analyses will be performed using appropriate descriptive measures and univariate Cox-regressions. 92 patients will be enrolled. With a sample size of n=40 analyzable patients per treatment arm (assuming a 13% drop-out rate), it is possible to adequately describe the tested treatment options.
SAMPLE SIZE	92 patients
TRIAL DURATION	Total study duration: 48 months • Duration of recruitment: 24 months • Maximum treatment duration: 16 months (4 months of chemotherapy in both arms + 12 months maintenance therapy in the experimental arm B) • The follow-up period will end when all study patients have been followed up for at least 8 months after last drug administration (including a safety follow-up period of 100 ± 7 days for all patients which received at least one dose of nivolumab)

Registerstudie NSCLC / SCLC

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

AIO-Studie

Studiennummer/-Code:	AIO-TRK-0315 - CRISP	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2015 - 2023	
Zentren:	geplant: 170	initiiert: 186
Patients included:	7331	
Weitere Zentren:	auf Anfrage	
Letzte Aktualisierung	01.Oktober 2021	

Study type	open, non-interventional , prospective, multi-center clinical research platform
Contact details	Sponsor: AIO-Studien-gGmbH, Berlin, info@aio-studien-ggmbh.de Main Project: Steering Board Spokesperson: Prof. Dr. Frank Griesinger Pius Hospital, Oldenburg, frank.griesinger@pius-hospital.de Satellite Stage I/II/III: Steering Board Spokesperson: PD Dr. Wilfried Eberhardt, University Hospital Essen, wilfried.eberhardt@uni-duisburg-essen.de Satellite SCLC: Steering Board Spokesperson: Dr. Martin Sebastian, University Hospital Frankfurt, sebastian@med.uni-frankfurt.de Concept, Project Management and Analyses: iOMEDICO AG, Freiburg, Annette Fleitz, annette.fleitz@iomedico.com (Main Project) Adrian Binninger, Adrian.binninger@iomedico.com (Satellite Stage I/II/III) Adrian Binninger, Adrian.binninger@iomedico.com (Satellite SCLC)
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) and small cell lung cancer (SCLC). 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 or SCLC. 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. PRO assessment will provide large-scale data on quality of life and anxiety/depression for real-life patients with NSCLC or SCLC in routine practice. In addition, two questionnaires (concerning individual quality of life and patient-caregiver communication) will be validated in German patients with metastatic NSCLC. Furthermore, CRISP will set up a decentralized clinically annotated tissue repository for future collaborative, investigational scientific biomarker testing.
Objectives	To assess molecular biomarker testing, treatment and outcome of patients with NSCLC or SCLC in Germany, in particular: • To collect data on the frequency, methodology and results of molecular biomarker testing before first-line and later-line treatment • To describe types of surgeries, systemic treatments, radiochemotherapies, radiation therapies and sequential treatments thereof applied in real-life practice

	• To assess effectiveness of treatments in regards to response rate, progression-free survival and overall survival • To describe physician-reported factors affecting treatment decision making besides biomarker profiling • To collect key data on specific supportive therapies • To investigate changes in diagnostics, treatment or outcome during the course of the project • 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: Up to 10.000 patients with locally advanced or metastatic NSCLC at the start of palliative first-line systemic therapy or receiving best supportive care. Of all patients recruited, 5,000 patients will be patients with non-squamous cell carcinoma tested for molecular alterations at the start of first-line treatment or patients with squamous cell carcinoma (CRISP patients). The remainder will be patients with untested non-squamous carcinoma (CRISP satellite untested patients stage IIIB/IIIC/IV). Patients included: **7331** (01.October 2021) Satellite Stage I/II/III: Up to 2400 patients with NSCLC stage I, II, stage IIIA, or with NSCLC stage IIIB/C if they are eligible for curative surgery and/or radiochemotherapy, or are receiving best supportive care will be recruited (CRISP satellite I/II/III patients). Satellite Stage II/III started in August 2018. Patients included: **1140** (01.October 2021) Satellite SCLC: Up to 1200 patients with SCLC (limited stage (LD) or extensive stage (ED)) if they are eligible for surgery and/or radio(chemo)therapy and/or systemic therapy, or are receiving best supportive care will be recruited (CRISP satellite SCLC patients). Satellite SCLC started in September 2019. Patients included: **712** (01.October 2021)
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. Target number: 170, 186 Initiated
Inclusion criteria	Patients who meet all of the following criteria are eligible for the project: • Age ≥ 18 years • Able to understand and willing to sign written Informed Consent and to complete patient-reported-outcome assessment instruments Main Project: • Confirmed non-small cell lung cancer (NSCLC) • Informed consent no later than four weeks after start of first-line systemic treatment or no later than four weeks after diagnosis for patients receiving “best supportive care only” • Stage IV, or Stage IIIB/C (UICC8) if patient is ineligible for curative surgery and/or radiochemotherapy • Systemic therapy or best supportive care Satellite Stage I/II/III: • Confirmed non-small cell lung cancer (NSCLC) • Informed consent no later than four weeks after start of first anti-tumor treatment (including surgery and radiotherapy) or no later than four weeks after diagnosis for patients receiving “best supportive care only” (i.e. no anti-tumor treatment = no surgery, radiotherapy or systemic therapy)

	• Stage I, Stage II, Stage IIIA, or Stage IIIB/C (UICC8) if patient is eligible for curative surgery and/or radiochemotherapy • Systemic (chemo)therapy and/or radiation therapy and/or surgery, or best supportive care Satellite SCLC: • Confirmed small cell lung cancer (SCLC) • Informed consent no later than four weeks after start of first anti-tumor treatment or no later than four weeks after diagnosis for patients receiving “best supportive care only” (i.e. no anti-tumor treatment = no surgery, radiotherapy or systemic therapy) • Systemic (chemo)therapy and/or radiation therapy and/or surgery or best supportive care 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. 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) core questionnaire, plus the FACT-L, the lung specific module, 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) will be validated in 1,000 patients with advanced NSCLC each. 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 (Recruitment of up to 6500 patients): First Patient In (FPI) Q4/ 2015 Last Patient In (LPI) Q4/ 2020 Last Patient Out (LPO) Q4/ 2023 Interim analysis Annually Final analysis 2023 CRISP 10000 (Amendment, inclusion of further 3500 Patients) Start Recruitment for another 3 years: Q1/2021 LPI (approx. 10000 patients) Q2/2023 LPO Q2/2026 Final report CRISP 10000 Q4/2027 Satellite Stage II/III (first 800 patients): First Patient In (FPI) Q3/ 2018 Last Patient In (LPI) Q1/ 2020 Last Patient Out (LPO) Q1/ 2023 Interim analysis Annually Final analysis 2023 Satellite I/II/III (additional 1600 patients): Restart of recruitment Q3 2020

	LPI Satellite I/II/III Q3 2023 LPO Satellite I/II/III Q3 2026 Final analysis Satellite I/II/III 12 months after LPO (planned 2027) Satellite SCLC: First Patient In (FPI) Q3/ 2019 Last Patient In (LPI) Q3/ 2023 Last Patient Out (LPO) Q3/ 2025 Interim analysis Annually Final analysis 12 months after LPO (planned Q3 2026) The individual observation time is until death or end of project (LPO). Publication: Various publications during and after the project

Arbeitsgruppe Molekulare und Translationale Onkologie

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

AIO-Studie

Studiennummer/-Code:	AIO-TF-0317 - PROMISE-Last	
Status:	nicht bekannt	
Rekrutierungszeitraum:	Studienstart noch offen	
Weitere Zentren:	sind sehr erwünscht	
Anzahl Patienten:	geplant: 30	aktuell eingeschlossen: nicht bekannt
Anzahl Zentren:	geplant: 3	initiiert: nicht bekannt
Letzte Aktualisierung	November 2021	

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
INTERVENTION(S)	Experimental intervention: 1. Biopsy to establish PDOs, 2. Treatment of the patient with best performing drug in PDO-based drug-screen Control intervention: No control intervention is performed Duration of intervention per patient: 1. Biopsy: 30-60minutes, 2. Treatment after last line therapy (until disease progression) Follow-up per patient: 24 months
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: 1. Patients ≥ 18 years of age. 2. Performance status ECOG 0-2. 3. Histologically confirmed metastatic or locally recurrent colorectal cancer prior last line therapy. 4. Tumor accessible to biopsy and patient willing to undergo biopsy. 5. At least one measurable lesion of disease according to RECIST criteria. 5. Signed informed consent prior to any screening procedures Key exclusion criteria: 1. HIV, HBV or HCV infection. 2. Inadequate end organ function
OUTCOME(S)	Primary efficacy endpoint: Best objective response rate (ORR) per central review in last-line treated subjects (≤5% vs. ≥20%) determined by RECIST criteria Key secondary endpoint(s): Progression-free survival, overall survival, toxicity, quality of life (QoL), predictive value of PDO screens for treatment efficiency, treatment duration and dose intensity Assessment of safety: Patients will be closely monitored for the occurrence of adverse events (AE) and serious adverse events (SAE).

STUDY TYPE	Multicentered, single armed, phase II interventional clinical trial
STATISTICAL ANALYSIS	Efficacy: Objective response rate (≤5% vs. ≥20%, primary end-point) Description of the primary efficacy analysis and population: 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 Safety: Rates of complications, adverse events and serious adverse events will be calculated with 95% confidence intervals for group comparisons. Secondary endpoint(s): Progression-free survival, Toxicity, QoL
SAMPLE SIZE	To be assessed for eligibility: (n = 70) To be allocated to trial: (n = 40) To be analyzed: (n = 30)
TRIAL DURATION	Time for preparation of the trial (months): 6 Recruitment period (months): 24 First patient in to last patient out (months): 48 Time for data clearance and analysis (months): 3 Duration of the entire trial (months): 57 (6 preparation, 48 study, 3 analysis)
PARTICIPATING CENTERS	To be involved (n): 3 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

Studiennummer/-Code:	AIO-STS/TF-0117/ass - NCT-PMO-1603
Status:	Recruiting
Rekrutierungszeitraum:	2018 – 2022
Weitere Zentren:	Not planned
Letzte Aktualisierung	November 2020

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk National Center of Tumor diseases, Heidelberg
CONDITION	• Advanced or recurrent solid tumors harboring DNA repair deficiencies • Relapsed and metastatic solid tumors with homologous recombination DNA repair deficiency
OBJECTIVE(S)	**Primary objective** 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. **Secondary objectives** • 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. • 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. • 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. • Safety/tolerability of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice. • Patient reported outcomes including 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 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 • 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 • Concurrent or previous treatment within 4 weeks in another interventional clinical trial • Treated with an investigational anticancer therapy less than 4 weeks prior to study treatment. Inclusion may be possible after > five half-lives of previous treatment after consultation with the coordinating investigator on a case by case decision. • Prior treatment with PARP inhibitors • Patients with platinum-refractory disease, defined as progressive disease during or immediately after treatment with platinum based chemotherapy • Persistent toxicity (≥Grade 2 according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) caused by previous cancer therapy, excluding alopecia • Clinical signs of active infection (>Grade 2 according to CTCAE version 5.0) • History of HIV infection and immunocompromised patients • Viral active or chronic hepatitis (HBV or HCV)

	• Dementia or significant impairment of cognitive state • Epilepsy requiring pharmacologic treatment • Pregnancy and breast feeding (women) • Inability to take oral medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication • Major surgery within 4 weeks of starting study treatment. Patients must have recovered from any effects of any major surgery. • 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 • Known hypersensitivity to any of the study drugs or other ingredients of the investigational medicinal products • Resting ECG with QTc > 450 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome • Abnormal left ventricular ejection fraction, defined as ejection fraction of <50% on echocardiography • Heart failure NYHA III/IV • Severe obstructive or restrictive ventilation disorder • 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 at least five half-lives. • 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 at least five half-lives(e. g. 5 weeks for enzalutamide or phenobarbital)
KEY INCLUSION CRITERIA	• Provision of a written informed consent • Patients is able to understand and comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations • Progressive locally advanced or metastatic malignancy as determined by local investigator • At least one measurable lesion that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment • Prior administration of at least one standard treatment for primary and/or relapsed malignancy according to current guidelines • Eastern Cooperative Oncology Group Performance Status ≤ 1 • Patients with central venous access device in place (central venous catheter or port-a-cath) • Male or female patient aged ≥ 18 and ≤ 70 years • 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. Postmenopausal or evidence of non-childbearing status is defined as: o Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments

	○ Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the postmenopausal range for women under 50 except in patients with a history of surgical sterilisation (bilateral oophorectomy or hysterectomy) ○ ○ Radiation-induced oophorectomy with last menses >1 year ago ○ Chemotherapy-induced menopause with >1 year interval since last menses ○ Surgical sterilisation (bilateral oophorectomy or hysterectomy) • 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. • 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 by the molecular tumorboard of NCT on the basis of whole-exome/genome sequencing and the presence of “BRCAness”. • Adequate bone marrow, renal, and hepatic function defined by laboratory tests within 14 days prior to study treatment: ○ Hemoglobin ≥ 10 g/dl ○ Neutrophil count ≥ 1,500/mm^3 ○ Platelet count ≥ 100,000/µl ○ Bilirubin ≤ 1.0 x upper limit of normal (ULN) ○ ALT and AST ≤ 2.5 x ULN ○ Alkaline phosphatase ≤ 2.5 x ULN ○ PT-INR/PTT ≤ 1.5 x ULN ○ Albumin ≥ 25 g/l ○ Creatine kinase ≤ 2.5 x ULN ○ Serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 51 ml/min calculation according to Crockroft-Gault)
OUTCOME(S)	Clinical efficacy, determined by disease control rate (DCR) at week 16 after five 21-days cycles of treatment
STUDY TYPE	Multicenter randomized, open-label, phase II study designed to gain evidence of antitumor activity of trabectedin and olaparib in adult patients with (locally) advanced or metastatic solid tumors with defects in DNA damage repair according to the BRCAness classifier
STATISTICAL ANALYSIS	The trial compares olaparib in combination with trabectedin (experimental arm E) versus physician’s choice (control arm C). Primary efficacy endpoint is the disease control rate (DCR) after 5 cycles. Efficacy evaluation involves a two-group comparison of DCR between experimental arm E (DCR_E) and control arm C (DCR_C). The null hypothesis is H_0: $DCR_E - DCR_C \leq 0$. Assuming a DCR_E of 50% for the experimental arm and a DCR_C 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 sample size of 102 patients is deemed adequate for all secondary/exploratory analyses.
TRIAL DURATION	Total trial duration: 46 months Duration of the clinical phase: 34 months The duration of the trial for each patient is expected to be about 5 months, including 42 days safety observation and a continuous follow-up every 12 weeks until end of study (EOS). In case of clinical benefit, it will be longer.

PARTICIPATING CENTERS	1. NCT Heidelberg, Prof. Dr. Richard Schlenk (active) 2. Universitätsklinikum Dresden, Dr. Stephan Richter (active) 3. Charité Berlin, Dr. Sebastian Ochsenreither (approved by EC) 4. Uniklinik Essen, Prof. Dr. Jens Siveke (active) 5. Universitätsmedizin Mainz, Dr. Thomas Kindler (active) 6. Universitätsklinikum Frankfurt, Dr. Sebastian Wagner(active) 7. RBK Stuttgart (Umzug der Klinik Schillerhöhe, Gerlingen), Prof. Dr. Hans-Georg Kopp (active) 8. Universität Tübingen, Dr. Barbara Hermes (active) 9. Universitätsklinikum Freiburg, Dr. Lena Illert (active)) 10. LMU München, PD Dr. Tobias Herold (active)
current number of patients included	73 (21 screening failures)

Registerstudien

AIO-KRK-0413/ass: Retro- und prospektive Erfassung der Rolle von MSI und KRAS für die Prognose beim Kolonkarzinom im Stadium I, II + III sowie prospektiv bei hochsitzendem Rektumkarzinom im Stadium I, II + III (COLOPREDICT PLUS 2.0 - Register)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-KRK-0413/ass - COLOPREDICT PLUS 2.0
Status:	in Rekrutierung
Rekrutierungszeitraum	2013 – 2023
Weitere Zentren:	sind erwünscht
Zentren:	geplant: 200 initiiert: 181
Patienten:	geplant: 8000 aktuell eingeschlossen: 7300
Letzte Aktualisierung	August 2021 Addendum 1: 01-September 2020 (Kooperation Circulate, LKP G. Folprecht, NCT04120701) Addendum 2: 30-August-2021 (Kooperation BNT-001 Studie; NCT04813627)

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

	Klinischer Ansprechpartner: Dr. med.C. Lugnier (0234-509-2398, celine.lugnier@rub.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)
Studiennummer/-Code:	AIO-YMO/TF-0115
Status:	in Rekrutierung
Rekrutierungszeitraum:	2013 - 2023
Weitere Zentren:	sind gewünscht
Letzte Aktualisierung	Oktober 2021

Verantwortlicher Studienleiter nach AMG / Kontaktadresse/	Prof. Dr. med. Michael Quante Klinikum rechts der Isar - Technische Universität München II. Medizinische Klinik, Ismaninger Straße 22, 81675 München michael.quante@tum.de Prof. Dr. med. Michael Quante Universitätsklinikum Freiburg Klinik für Innere Medizin II, Gastrointestinale Onkologie Hugstetter Straße 55, 79106 Freiburg michael.quante@uniklinik-freiburg.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Young-Medical-Oncologist!	

Arbeitsgruppe Weichteilsarkome

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

Studiennummer/-Code:	AIO-STS-0317/ass	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 – 2020	
Weitere Zentren:	sind derzeit leider nicht möglich	
Anzahl Patienten:	geplant: 300	eingeschlossen: 206 davon 23 in Deutschland
Anzahl Zentren:	geplant: 9	initiiert: 9
Letzte Aktualisierung	20.10.2021	

APPLICANT/ COORDINATING INVESTIGATOR	The Scandinavian Sarcoma Group (SSG)/ PD Dr. Peter Reichardt
CONDITION	Patients treated with adjuvant imatinib for 3 years after complete surgical removal of high-risk GIST and who are considered to be at a high risk of GIST recurrence despite 3 years of adjuvant imatinib.
OBJECTIVE(S)	**Primary:** • Recurrence-free survival (RFS) after randomisation. **Secondary:** • Overall survival. • GIST-specific survival. • Adverse events (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0). • Quality of life **Exploratory:** • Effect of tumour site on RFS. • Effect of tumour mutation type on RFS. • Effect of imatinib dose at randomisation on RFS. • To evaluate tumour tissue and blood molecular markers in prediction of GIST recurrence.
INTERVENTION(S)	**Arm A: Imatinib** 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. 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. **Arm B: No imatinib** 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. 2. Not willing to donate tumour tissue and/or blood samples for the study molecular studies.

	3. Presence of a substitution mutation at PDGFRA codon D842 (usually D842V). 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. 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. 6. Neoadjuvant imatinib for a duration that exceeds 12 months. 7. Longer than 4-week break during adjuvant imatinib administration. 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. 9. Patient has received any investigational anti-cancer agents during adjuvant imatinib or between completion of adjuvant imatinib and the date of randomisation. 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 breast cancer (pT1N0M0), a low Gleason score (<8) local (T1 or T2) prostate cancer. Recent existence of any other malignant disease is not allowed. 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). 12. Female patients who are pregnant or breast-feeding. 13. Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, severe chronic renal disease, or active uncontrolled infection). 14. Known diagnosis of human immunodeficiency virus (HIV) infection. 15. Patient with a significant history of non-compliance to medical regimens or with inability to grant reliable informed consent. 16. Patients with chronic or active hepatitis B. 17. Patients that have been committed to an institution by official or judicial order. 18. Patients that are dependent upon the sponsor, the trial site or the investigator.
KEY INCLUSION CRITERIA	1. Age ≥ 18 years. 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). 3. Macroscopically complete surgical resection of GIST (either R0 or R1 resection). 4. Mutation analysis of KIT and PDGFR genes has been carried out. 5. A high risk of GIST recurrence, either 1) gastric GIST with mitotic count >10/50 HPFs, or 2) non-gastric GIST with mitotic count >5/50 HPFs, or 3) non-gastric GIST treated with neoadjuvant imatinib and initially larger than 10 cm 4) tumour rupture Tumour rupture (spillage of the tumour contents into the abdominal cavity) may have occurred either before or at surgery. 6. ECOG performance status ≤ 2. 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.

	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. 9. Patient willing to be followed up at the study site regardless of the result of randomisation. 10. Patient has provided a written, voluntary informed consent prior to study-specific screening procedures.
OUTCOME(S)	**Primary:** • 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. **Secondary:** • Overall survival (the time period between the date of randomisation and the date of death). • 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). • Safety (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0). • Quality of Life (EQ-5D instrument). **Exploratory:** • Effect of the tumour mutation type on RFS. • Effect of tumour site on RFS. • Effect of the imatinib dose at randomisation on RFS. • Tumour tissue and blood molecular markers in prediction of GIST recurrence.
STUDY TYPE	Open-label, 2-arm, prospective, randomised, multicentre phase III trial. Patients diagnosed with GIST who have completed 3 years of adjuvant imatinib, who are free from GIST recurrence after 3 years of adjuvant imatinib, and who have a high risk of recurrence despite 3 years of adjuvant imatinib will be randomly allocated to one of the following 2 arms in a 1:1 ratio: **A.** to further 24 months of adjuvant imatinib (i.e. the planned total duration of adjuvant imatinib is 5 years) **B.** to stop imatinib (i.e. the planned total duration of adjuvant imatinib is 3 years) 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

Chordome, Knochensarkome, fortgeschrittene Erkrankung

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

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-STS-0217/ass - NCT-PMO-1601
Status:	rekrutierend
Rekrutierungszeitraum:	2018– 2022
Weitere Zentren:	nicht geplant
Letzte Aktualisierung	November 2020

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk National Center of Tumor diseases, Heidelberg
CONDITION	locally advanced/metastatic chordoma
OBJECTIVE(S)	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 not amenable to curative treatment with surgery or radiotherapy. The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of complete response (CR) or confirmed partial response (PR) or stable disease (SD) according to RECIST version 1.1. Secondary Objectives include: • Tumor Response rate (TRR) according to RECIST version 1.1 • Progression-free Survival (PFS) • Overall Survival (OS) • Safety/tolerability • Patient reported outcome including 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). • Prior treatment with other CDK4/6 inhibitors • 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])) • Co-therapy with corticosteroidsabove 7.5 mg prednisolone/prednisone equivalent . • 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 • Clinical signs of active infection (>Grade 2 according to CTCAE version 5.0)

	• 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. • Severe neurologic or psychiatric disorder interfering with ability of giving informed consent • Known or suspected active alcohol or drug abuse • Known positivity for HIV, active HAV, HBV, or HCV infection • Cytopenia: platelets <100 G/l, neutrophils <1.0 G/l, hemoglobin <10.0 g/dl • 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 • Uncontrolled electrolyte disorders that can aggravate the effects of a QTc_B-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia) • Participation in other ongoing interventional clinical trials (according to AMG)within 4 weeks prior to study treatment.
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). not amenable to curative treatment with surgery or radiotherapy. • At least one measurable tumor lesion according to RECIST 1.1 criteria • Loss of p16 determined immunohistochemically or CDKN2A/B genomically, presence of CDK4/6 and RB1 determined immunohistochemically or by RNA sequencing. • Age ≥ 18 years, no upper age limit • 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) • • 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). • 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. • 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. • Signed written informed consent • Performance status ≤ 2 according to ECOG/WHO criteria • 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. 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 $p_0 = 0.1$ will be tested against a one-sided alternative, where the desirable level of response is 0.25. 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 25 in the second stage (only if first stage was positive) Total sample size: minimum 18 patients; maximum 43 patients
TRIAL DURATION	Total trial duration: 48 months Duration of the clinical phase: 36 months
PARTICIPATING CENTERS	1. Universitätsklinikum Heidelberg, Prof. Dr. Richard Schlenk 2. Universitätsklinikum Essen, Dr. Rainer Hamacher 3. Universitätsklinikum Ulm, Dr. Verena Gaidzik
CURRENT NUMBER OF PATIENTS INCLUDED	22 (10 screening failures)

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	
Studiennummer/-Code:	AIO-STS/TF-0117/ass - NCT-PMO-1603
Status:	Recruiting
Rekrutierungszeitraum:	2018 – 2022
Weitere Zentren:	Not planned
Letzte Aktualisierung	November 2021

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk National Center of Tumor diseases, Heidelberg
CONDITION	• Advanced or recurrent solid tumors harboring DNA repair deficiencies • 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

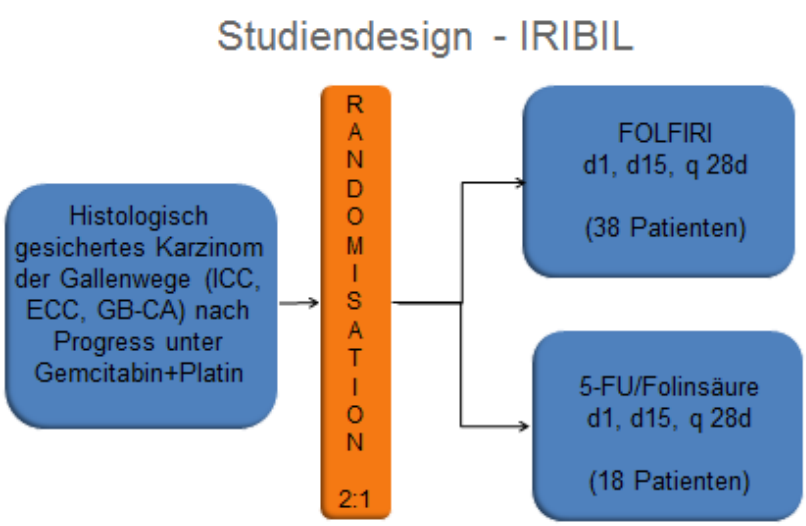
Biliäre Tumoren – 2nd-line

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: a randomized open-label phase 2 study (IRIBIL)

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)	
Studiennummer:	AIO-YMO/HEP-0316	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 – 224	
Patienten	geplant: 23	aktuell eingeschlossen: 10
Zentren	geplant: 1	initiiert:1
Weitere Zentren:	sind leider nicht möglich!	
Letzte Aktualisierung	Okt. 2021	

Verantwortlicher Studienleiter nach AMG	Prof. Dr. Oliver Waidmann
Studienziele	Primäres Studienziel: Progressionsfreie Überleben (PFS) Sekundäre Studienziele: Gesamtüberlebenszeit (OS) Zeit bis zur Tumorprogression (RECIST V1.1) Ansprechrate (RECIST V1.1) Sicherheit Lebensqualität (EORTC QLQ-C30 Fragebogen)
Zielparameter	Beurteilung der Wirksamkeit und Sicherheit einer Chemotherapie mit 5-FU, Folinsäure und Irinotecan (FOLFIRI) im Vergleich zur Chemotherapie mit 5-FU und Folinsäure bei Patienten mit metastasierten oder lokal fortgeschrittenen, nicht operablen Tumoren des biliären Systems (Gallengangs-, Gallenblasen- sowie Papillenkarzinome), die eine progrediente Erkrankung unter einer Erstlinienchemotherapie mit Gemcitabin- und platinhaltigen Chemotherapie zeigten.
Patientenzahl	Geplant: 23 Patienten mit FOLFIRI behandelt (Arm A) Bereits eingeschlossen: 10 Arm A (Stand Okt 2021), 4 Arm B (geschlossen) (in 1 Zentrum)
Rekrutierungs-zeitraum	Erster Patient eingeschlossen: August 2017 Rekrutierungsdauer: 72 Monate Therapiedauer: 12 Monate Follow-up-Dauer: alle 6 Wochen bis Tod Studienende: August 2024 Gesamtdauer: 7 Jahre
Haupt-Einschlusskriterien	Einschlusskriterien • Vorherige Einwilligung nach erfolgter Aufklärung vor Einleitung einer studienspezifischen Maßnahme • Patienten mit histologisch-gesichertem inoperablem oder metastasiertem Karzinom der Gallenwege und der Gallenblase.

	• 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 • Alter ≥ 18 Jahre • ECOG Performance-Status 0-2 (Appendix 21.2) • Adäquate Knochenmarks, Leber- und Nierenfunktion: Neutrophile > 1.500/mm³ Hämoglobin > 9 g/dl Thrombozyten > 75 x 10^9/l INR ≤ 1,5 Gesamtbilirubin ≤ 2 mg/dl ALT und AST < 5x ULN Kreatinin < 1,5 x ULN • Child-Pugh Stadium A bei Vorliegen einer Leberzirrhose • Bei Frauen im gebärfähigen Alter ist ein negativer Serum-Schwangerschaftstest erforderlich, der innerhalb von 7 Tagen vor Randomisierung durchgeführt worden sein muss • 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: • Resektabler Primärtumor ohne Nachweis von Fernmetastasen • Vorhergegangene Radiatio oder Radiochemotherapie, transarterielle Chemoembolisation (TACE), Radiofrequenzablation (RFA) oder selektive intraarterielle Radiotherapie (SIRT) innerhalb der letzten 3 Monate außer Radiatio von symptomatischen Knochenfiliae • Begleitende photodynamische Therapie oder intraduktale Radiofrequenzablation innerhalb der letzten 8 Wochen • Child Pugh Status B oder C (> 6 Punkte) bei Vorliegen einer Leberzirrhose (Appendix 21.3) • Massiver, nicht kontrollierbarer Aszites • Vorherige systemische Chemotherapie außer Gemcitabin und Platinderivat (Cisplatin, Carboplatin oder Oxaliplatin) • Herzinsuffizienz > NYHA-Klasse 2 • Bekannte Hirnmetastasen, die nicht klinisch kontrolliert sind • Vorhergegangene Organ- oder Stammzelltransplantation • Aktive, unkontrollierte relevante Infektion > CTCAE Grad 2, ausgenommen einer chronischen Hepatitis C-Virusinfektion (Appendix 21.5) • Größere chirurgische Eingriffe innerhalb der letzten 4 Wochen vor Beginn der Chemotherapie, Portimplantation ist erlaubt • Bekannte oder vermutete Allergie gegen 5-FU, Folinsäure, Irinotecan • Eine andere gleichzeitig oder innerhalb der letzten 3 Jahren bestehende Krebserkrankung (Ausnahmen: Zervixkarzinom in situ, behandeltes Basalzellkarzinom, oberflächliches Harnblasenkarzinom) • Drogenmissbrauch, medizinische, psychologische oder soziale Einschränkungen, die die Studienteilnahme behindern können • 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 • Schwangerschaft oder stillende Frau • 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 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 Medianes PFS FOLFIRI: 4 Monate Überwachungsdauer: 12 Monate Withdrawal rate: 0.03 Type I error (alpha): 0.10 (1-sided) Type II error (beta = 1 – power): 0.20 Power: 80% Patientenzahl FOLFIRI: 23

NSCLC, limitiert oder local fortgeschritten

AIO-YMO/TRK-0319: Thoracic Radiotherapy plus Durvalumab in Elderly and/or frail NSCLC stage III patients unfit for chemotherapy- Employing optimized (hypofractionated) radiotherapy to foster durvalumab efficacy (TRADEhypo)

AIO-Studie

Studiennummer/-Code:	AIO-YMO/TRK-0319 - TRADEhypo	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2020 – 2021	
Weitere Zentren:	nicht mehr möglich	
Zentren:	geplant: 20	initiiert: 16
Patienten:	geplant: 88	aktuell eingeschlossen: 22
Letzte Aktualisierung	30.09.2021	

STUDY TYPE	Investigator- initiated trial (IIT)
PRINCIPAL INVESTIGATOR	Dr. Farastuk Bozorgmehr (Farastuk.Bozorgmehr@med.uni-heidelberg.de) (LKP) Prof. Dr. Stefan Rieken (Deputy LKP) Univ.-Prof. Dr. Michael Thomas (Mentoring LKP)
TRIAL OFFICE	Department of Thoracic Oncology/ Internal Medicine Thoraxklinik at Heidelberg University Hospital Röntgenstr.1 69126 Heidelberg Germany
SPONSOR	Sponsor representative: Prof. Dr. S.-E. Al-Batran Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Germany Project Manager of Sponsor: Dr. Johanna Riedel (Riedel.johanna@ikf-khnw.de) / Christina Kopp (kopp.christina@ikf-khnw.de)
DESIGN	Randomized, open-label, multicenter, phase II trial with safety stop-and-go lead-in phase
INDICATION	Locally advanced, unresectable NSCLC (stage III) not eligible for sequential chemo-/radiotherapy
OBJECTIVE(S)	Primary objective: To evaluate the safety and tolerability of either conventionally fractionated (CON-group) or hypofractionated (HYPO-group) thoracic radiotherapy in combination with durvalumab. Primary efficacy objective: To investigate the efficacies of either mode of fractionation of radiotherapy in combination with durvalumab with respect to the response rates in patients with unresectable stage III NSCLC, who are not suitable for chemotherapy. Secondary objectives: To determine further parameters for efficacy, safety, and quality of life in both treatment arms. Exploratory objectives: Analyses of concomitant “Vulnerability assessment” (G8 screening questionnaire); Biomarker exploration.

INTERVENTION(S)	Durvalumab
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Radiation-induced tumor-specific immune effects can explain events of tumor regression upon radiation treatment both within and beyond the irradiated fields and the immune system can be further stimulated by administration of a PD-L1 blocking antibody such as durvalumab. The translational research planned to be conducted on these samples (tumor tissue, blood and stool) aims to elucidate the immune-related mechanisms behind these observations.
BACKROUND/RATIONALE	Based on the PACIFIC study, sequential treatment with durvalumab after chemoradiotherapy has become the new standard treatment for locally advanced, unresectable NSCLC. However, an estimated proportion of more than 20% of patients with this diagnosis is not subjected to such a combined modality treatment due to age and/or comorbidities and receives radiotherapy only. Now, when combining durvalumab therapy with radiotherapy, the immune-promoting characteristics of radiotherapy are expected to boost the efficacy of the checkpoint inhibitor, thereby improving response in these otherwise potentially undertreated patients. Moreover, in the case of early concomitant application, combination of local radiotherapy with systemic immunotherapy is hypothesized to particularly increase efficacy on the control of distant micrometastases. In addition, hypofractionated treatment considerably increases convenience and practicability for the patient due to the shorter duration time of radiotherapy. However, safety of concurrent application of radiotherapy, in particular in a hypofractionated scheme, and checkpoint inhibitors is a concern as both therapy modalities by themselves can cause severe pneumonitis. Therefore, a prospective clinical trial is warranted that investigates the feasibility of hypofractionated radiotherapy in combination with PD-1/PD-L1 blockade and evaluates the efficacy of this treatment. The trial aims to i) determine the safety and tolerability of the combination of immunological and radiological treatment in the first-line setting for stage III NSCLC patients only prone to radiotherapy, ii) increase the efficacy of radiotherapy by utilizing its immune-sensitizing effect when combining it with durvalumab, and iii) to collect tumor tissue as well as blood and stool samples to be able to explore the immunological mechanisms responsible for checkpoint inhibitor efficacy and immune-promoting effects of radiotherapy, gain insight into the tumor-host biology, and identify novel biomarkers. <u>Hypothesis:</u> It is hypothesized that TRT combined with concurrent durvalumab administration in patients with unresectable stage III NSCLC, who are not amenable to sequential radio-/chemotherapy 1. is safe and feasible, 2. will improve treatment efficacy by a synergistic effect of checkpoint inhibition and the photon-induction of immunostimulatory pathways, 3. will have an effect on the immunological characteristics of the tumor, the microenvironment, and the systemic immune response, such as upregulation of PD-L1 or secretion of stimulatory cytokines and recruitment and priming of immunocompetent cells, which might then mediate the “abscopal effect” beyond the irradiated targets.
KEY EXCLUSION CRITERIA	1. 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. 2. History or current radiology suggestive of interstitial lung disease. 3. Any concurrent chemotherapy, investigational product (IMP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer related conditions (eg, hormone replacement therapy) is acceptable. 4. Prior thoracic radiotherapy within the past 5 years before the first dose of study drug.

	5. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: o Intranasal, inhaled, topical steroids, or local steroid injections (e.g. intra articular injection) o Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent o Steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication) 6. Active or prior documented autoimmune or inflammatory disorders (except inflammatory bowel disease [e.g. ulcerative colitis or Crohn's disease]; including diverticulitis [with the exception of diverticulosis], celiac disease, systemic lupus erythematosus, Sarcoidosis, or Wegener's syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis). The following are exceptions to this criterion: o Patients with vitiligo or alopecia o Patients with hypothyroidism (e.g., following Hashimoto's disease) stable on hormone replacement o Any chronic skin condition that does not require systemic therapy o Patients without active disease in the last 5 years may be included but only after consultation with the study physician. 7. Oxygen-dependent medical condition.
KEY INCLUSION CRITERIA	1. Histologically documented diagnosis of unresectable stage III NSCLC. 2. Fulfills <u>at least one</u> of the following criteria: • Performance status (PS) ≥ 2 (ECOG scale) • ECOG 1 <u>and</u> CCI ≥ 1 • Age ≥ 70 years 3. Non-feasibility of sequential chemo-/radiotherapy 4. FEV1 ≥ 40% (Best/Soll) 5. DLCO or DLCO/VA (Hb-corrected, if available) ≥ 40% (Best/Soll) 6. FVC or VC ≥ 70% (Best/Soll) 7. Adequate organ function.
OUTCOME(S)	<u>Primary endpoint:</u> Toxicity, defined by the occurrence of treatment-related pneumonitis grade ≥ 3 <u>Primary efficacy endpoint:</u> Objective response evaluated at 12 weeks (3 months) after first durvalumab administration according to RECIST 1.1 criteria <u>Secondary endpoints:</u> • Occurrence of treatment-related AEs and SAEs according to CTCAE V5.0 • Abnormal values of laboratory parameters • PFS according to RECIST 1.1 • Duration of Clinical Benefit (Duration of CR, PR, SD) according to RECIST 1.1 • MFS • OS • QoL (FACT-L)
STATISTICAL ANALYSIS	The analysis of the primary efficacy endpoint objective response is based on the ITT population. We assume that we can demonstrate that the ORR in both treatment arms is higher than 0.42, i.e. the null hypotheses for arm HYPO and CON are defined as H_0^{HYPO}: $\pi^{HYPO} \leq 0.42$ and H_0^{CON}: $\pi^{CON} \leq 0.42$, which are tested against the alternatives H_1^{HYPO}: $\pi^{HYPO} > 0.42$ and H_1^{CON}: $\pi^{CON} > 0.42$,

	respectively, where π^{HYPO} and π^{CON} denotes the actual ORR in arm A and B, respectively. The null hypotheses H_0^{HYPO} and H_0^{CON} will both be assessed at one-sided significance levels of α=0.10 each, using an optimal Simon's two-stage design, ensuring a power of 1-β=0.8 for each comparison with the planned sample size of n=40 patients per group. After n=18 patients have been enrolled to the respective treatment arm HYPO or CON, an interim analysis for the respective arm will be conducted. If among 18 patients, the number of patients who have achieved a response is 8 or lower, the respective null hypothesis will be prematurely accepted and the respective treatment arm will be terminated. Otherwise, the trial will continue until n=40 patients have been enrolled to the respective treatment arm. If the number of responders is 20 or less, the null hypothesis will be accepted, otherwise, it will be rejected. All analyses of safety endpoints are based on the Safety Population. A safety interim assessment based on the primary safety endpoint, occurrence of a pneumonitis grade ≥ 3, is conducted after 18 patients have been enrolled to the HYPO-group. If the number of patients with a pneumonitis grade ≥ 3 is 1 or less, regimen assessment will continue with the interim efficacy analysis. If among 18 patients, the number of patients with a pneumonitis grade ≥ 3 is 2 or more, recruiting patients to the HYPO-treatment arm will be stopped.
SAMPLE SIZE	88 Patients
TRIAL DURATION	Duration of recruitment: 20 months starting from FPI Maximum treatment duration per subject: 12 months Individual follow-up: ≥ 3 months after last administration of study drug
TREATMENT, DOSAGE AND ADMINISTRATION	• Durvalumab: fixed dose of 1,500 mg as an IV infusion over 1 hour, on day 1, to be repeated every 4 weeks (Q4W) for a maximum of 12 months • Thoracic radiation therapy (TRT) is started within 72 hours after start of durvalumab treatment. **CON group:** Patients receive conventional fractions of 30 x 2 Gy (60 Gy) within 6 weeks (+9 days) of thoracic radiotherapy in combination with durvalumab treatment. **HYPO group:** Patients receive hypofractionated thoracic radiotherapy consisting of 20 x 2,75 Gy (55 Gy) within 4 weeks (+9 days) in combination with durvalumab treatment. A safety stop-and-go phase will precede full enrollment in the HYPO-group. Toxicity will be evaluated with a 6+6 design that is based on the statistical assumption that ≤1 events in n = 18 patients conforms to a non-toxicity scenario, with "event" being defined as the occurrence of pneumonitis grade ≥ 3.
SAFETY ASSESSMENTS	Safety assessments will include physical examinations, performance status (ECOG), clinical laboratory profile and continuous assessments of adverse events. All observed toxicities and side effects will be graded according to NCI CTCAE v5.0 for all patients and the degree of association of each with the procedure assessed and summarized. • Rate of treatment-related Grade 3 and 4 pneumonitis, • treatment related serious adverse events rate, and • frequency of abnormal laboratory parameters

	will be determined. **Safety Lead-In phase (stop-and-go design):** A safety lead-in phase with stop-and-go design will precede full enrollment into the HYPO-group. Toxicity will be evaluated with a 6+6 design that is based on the statistical assumption that ≤1 events in n=18 patients conforms to a non-toxicity scenario, with “event” being defined as the occurrence of pneumonitis grade ≥ 3.

NSCLC mit EGFR-Mutation, metastasiert

AIO-YMO/TRK-0120: Radiation during Osimertinib Treatment: a Safety and Efficacy Cohort Study (ROSE)

AIO-Studie

Studiennummer/-Code:	**AIO-YMO/TRK-0120 / ROSE**		
Status:	In Vorbereitung		
Rekrutierungszeit:	geplant Q4/2021		bis: Q1/2024
Anzahl Zentren:	geplant: 8-10	aktuell initiiert: 0	aktiv rekrutierend: 0
Weitere Zentren:	sehr erwünscht		
Anzahl Patienten:	geplant: 60	aktuell eingeschlossen: 0	
Letzte Aktualisierung	Oktober 2021		

PRINCIPAL INVESTIGATOR	PD Dr. Amanda Tufman Respiratory Medicine and Thoracic Oncology University of Munich Ziemssenstr. 1 80336 Munich
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Thorakale Onkologie	

Malignant Pleural Mesothelioma, stage I-III

AIO-TRK/YMO-0419: Nivolumab with chemotherapy in pleural mesothelioma after surgery (NICITA)

AIO-Studie

Studiennummer/-Code:	AIO-TRK/YMO-0419		
Status:	in Rekrutierungsphase		
Rekrutierungszeit:	von: Q1-2020	bis: Q1-2022 (24 Monate)	
Anzahl Zentren:	geplant: 14	aktuell initiiert: 14	aktiv rekrutierend: 12
Weitere Zentren:	Nicht mehr möglich		
Anzahl Patienten:	geplant: 92	aktuell eingeschlossen: 43	
Letzte Aktualisierung	30.09.2021		

STUDY TYPE	Investigator- intiated trial (IIT)
COORDINATING INVESTIGATOR (LKP)	Dr. med. Rajiv Shah Dept. of Thoracic Oncology/Internal Medicine Thoraxklinik at Heidelberg University Hospital Röntgenstr. 1, D-69126 Heidelberg, Germany rajiv.shah@med.uni-heidelberg.de Mentoring LKP (Oncology): Univ.-Prof. Dr. med. Michael Thomas michael.thomas@med.uni-heidelberg.de Mentoring LKP (Surgery): PD Dr. med. Martin Eichhorn martin.eichhorn@med.uni-heidelberg.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Thorakale Onkologie	

Metastasiertes Kolorektales Karzinom

AIO-KRK/YMO-0519: Prospective, randomized, open, multicenter Phase II trial to investigate the efficacy of trifluridine/tipiracil plus panitumumab versus trifluridine/tipiracil plus bevacizumab as first-line treatment of metastatic colorectal cancer (FIRE-8)

AIO-Studie

Studiennummer/-Code:	AIO-KRK/YMO-0519 – FIRE-8		
Status:	aktiv		
Rekrutierungzeit:			
Anzahl Patienten:	geplant: 153	aktuell eingeschlossen: 0	
Anzahl Zentren:	geplant: 40	initiiert:	1
Weitere Zentren:	Derzeit keine weiteren Zentren		
Letzte Aktualisierung	Okt. 2021		

Sponsor	Charité, Universitätsmedizin Berlin Charitéplatz1, 10117 Berlin

Coordinating investigator	Prof. Dr. med. Dominik Modest Charité -Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie am Campus Virchow Klinikum (CVK) Augustenburger Platz 1, 13353 Berlin
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Kolon-/Rektum-/Dünndarmtumoren	

Pankreaskarzinom – Operable Patienten

AIO-YMO/PAK-0218/ass: Prognostic role of circulating tumor DNA in resectable pancreatic cancer (PROJECTION)

AIO-assoziierte Studie		
Studiennummer/-Code:	AIO-YMO/PAK-0218/ass	
Status:	Rekrutiert	
Rekrutierungszeitraum:	Q4/2020 – Q4/2022	
Zentren:	geplant: 6	initiiert: 5
Patienten:	geplant: 132 (Max 200)	aktuell eingeschlossen: 20
Weitere Zentren:	Nicht geplant.	
Letzte Aktualisierung	15.10.21	

STUDY TYPE	Non-interventional, exploratory
PRINCIPAL INVESTIGATOR	Dr. Benedikt Westphalen Medizinische Klinik und Poliklinik III, Klinikum der Universität München Marchioninistr. 15, 81377 München
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Pankreaskarzinom!	

Registerstudie - Patienten mit Barrett-Metaplasie im Ösophagus

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)
Studiennummer/-Code:	AIO-YMO/TF-0115
Status:	in Rekrutierung
Rekrutierungszeitraum:	2013 - 2023
Weitere Zentren:	sind gewünscht
Letzte Aktualisierung	Oktober 2021

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:	Prof. Dr. med. Michael Quante Klinikum rechts der Isar - Technische Universität München II. Medizinische Klinik, Ismaninger Straße 22, 81675 München michael.quante@tum.de Prof. Dr. med. Michael Quante Universitätsklinikum Freiburg Klinik für Innere Medizin II, Gastrointestinale Onkologie Hugstetter Straße 55, 79106 Freiburg michael.quante@uniklinik-freiburg.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. 2. Bestimmung der Inzidenz der Entwicklung von LG-IEN, HG-IEN und AEG ausgehend von einem BE 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. 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 Bereits eingeschlossen: Anzahl Studienpatienten: 851 (Stand 19.08.2021) Anzahl Studienvisiten: 1156 (Stand 19.08.2021)
Rekrutierungzeitraum	01/2013 – 12/2023
Weitere teilnehmende Zentren erwünscht?	Ja Rekrutierung weiterer Studienzentren ist in Prozess Stand zum 18.10.2020 : initiiert: 23, davon geschlossen: 5, geplante Initiierungen: 1
Haupt-Einschlusskriterien Key inclusion criteria	Alter zwischen 18 und 80 Jahren Überwachungsendoskopie bei Patienten mit bereits diagnostiziertem Barrett-Ösophagus ohne bisher bekannter LG-EIN, HG-IEN oder AEG (Barrett-Ösophagus sollte anhand der Prag-Klassifikation ausgemessen sein und mindestens C0M1 sein) unterschriebene Einwilligungserklärung
Haupt-Ausschlusskriterien Key exlusion criteria	andersartige Tumorerkrankung (unabhängig der Therapie) fehlende Zustimmungsfähigkeit zur Studie Kontraindikation zur Biopsie-Entnahme (Thrombozytopenie < 50.000/µl, Quick < 60%, pTT > 50 sec) Patienten in reduziertem Allgemeinzustand

Therapieschema Scheme of therapy	**Studienablauf:** 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 Criteria for evaluation	Die histologische Begutachtung erfolgt nach histopathologischem Goldstandard mit leichter zeitlicher Verzögerung im Institut für Pathologie am Klinikum rechts der Isar, sowie durch einen Referenzpathologen (PD Dr. med M Vieth, Klinikum Bayreuth). Ein vom pathologischen Befund der Routine-Biopsie abweichender Befund wird in einem Nachtrag zum originalen Befund dem behandelnden Arzt (Gastroenterologen) mitgeteilt. Weiterhin werden zu Studienzwecken RNA, DNA und Protein von den Proben zur weiteren Analyse isoliert.
Rationale	In den letzten Jahrzehnten hat sich gezeigt, dass das Adenokarzinom des gastroösophagealen Übergangs (AEG) die Tumorentität mit der am schnellsten wachsenden Inzidenz in der industrialisierten Welt ist. Die Prognose des AEG ist hinsichtlich des Langzeitüberlebens sehr limitiert, da der Tumor bei Diagnosestellung häufig kurativ nur noch durch eine radikale Operation behandelt werden kann. Auch nach der kurativ intendierten Operation ist die 5-Jahresüberlebensrate mit ca. 20% niedrig. Der Barrett-Ösophagus (BE) ist der wichtigste Risikofaktor für die Entwicklung eines AEG. Man geht davon aus, dass das Plattenepithel des Ösophagus im distalen Bereich durch chronischen Reflux von Mageninhalt alteriert und durch präkanzeröses, spezialisiertes, intestinal-metaplastisches Zylinderepithel ersetzt wird. Ein BE wird, älteren Daten nach, bei ca. 10% aller Refluxpatienten diagnostiziert und zeigt in weiteren 10% eine Entartungstendenz so dass eine Inzidenz der Entstehung von AEG aus BE mit ca. 0,5-1%pr Jahr (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. Derzeit ist die Surveillance-Endoskopie die einzig etablierte Methode der Überwachung der Barrett-Patienten. Obwohl hierdurch für Erkrankte die Prognose hinsichtlich des Gesamtüberlebens verbessert werden konnte, gerät die Surveillance-Strategie aufgrund des enormen Aufwands und der hohen Kosten sowie des pro Patienten kalkulierten, niedrigen Gesamtrisikos ein AEG zu entwickeln zunehmend in die Kritik. Somit besteht der dringende Bedarf nach eindeutigen Markern oder Prognosekriterien, um die Wahrscheinlichkeit - aber auch die Ursache - der Entwicklung einer LG-IEN oder HG-IEN aus dem BE zu beurteilen. Identifizierung von neuen 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

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

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)	
Studiennummer/-Code:	AIO-YMO/PAK-0215 - PDAC, PaCaReg	
Rekrutierungszeitraum:	Rekrutierung gestartet 10/2018 geplant von/bis: nicht festgelegt	
Anzahl Zentren:	geplant: nicht festgelegt	initiiert: 6
Anzahl Patienten:	geplant: nicht festgelegt	aktuell eingeschlossen: 54
Weitere Zentren:	Offen für weitere Zentren	
Letzte Aktualisierung	Oktober 2020	

Studienleitung	Dr. med. Thomas Ettrich Universitätsklinikum Ulm, Klinik für Innere Med. I 89081 Ulm, Tel. 0731-500 44774, thomas.ettrich@uniklinik-ulm.de Mentoring Investigator: Univ.-Prof. Dr. Thomas Seufferlein Universitätsklinikum Ulm, Klinik für Innere Medizin I
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)
Sekundäre Zielgrößen	• Registrierung aller Patienten mit neu diagnostiziertem PDAC an den beteiligten Zentren • Erfassung der definitiven Tumorstadien (TNM-Klassifikation, CRM, UICC-Stadium) • Erfassung klinischer Parameter bei Erstdiagnose und im Verlauf (Tumoransprechen, krankheitsfreies Überleben, progressionsfreies Überleben, Gesamtüberleben, Überleben in Abhängigkeit vom Tumorstadium) • Erfassung epidemiologischer, Patienten-bezogener Basisdaten • Korrelation von Lebensqualität und Therapiekonzept • Asservierung von Biomaterial der Patienten für die Evaluation prognostischer und prädiktiver Biomarker (Tumorgewebe, Blut/ Plasma) in der Biobank der Klinik für Innere Medizin I des Universitätsklinikums Ulm sowie dem Institut für Pathologie der Universität Ulm/Biobank des Comprehensive Cancer Centers Ulm (CCCU)

Einschlusskriterien	• Zytologisch oder histologisch gesichertes duktales Adenokarzinom des Pankreas • Alter ≥ 18 Jahre • Schriftliches Einverständnis zur Teilnahme an der Studie
Ausschlusskriterien	• Papillenkarzinome • Neuroendokrine Neoplasien des Pankreas • PDAC-spezifische Vortherapie, außer Tumorresektion • Schwere neurologische oder psychiatrische Störungen die eine Einwilligungsfähigkeit beeinträchtigen • 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 Tumore der Schilddrüse

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

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 2021

Art der Studie Study Type	Retrospective and prospective registry study
Kontaktadresse/ Kontaktperson:	Prof. Dr. Dr. Matthias Kroiß LMU Klinikum Medizinische Klinik und Poliklinik IV Endokrinologie/Diabetologie Ziemssenstr. 1 80336 München Tel.: 089/4040-52221 Email: matthias.kroiss@med.lmu.de

	Prof. Dr. C. Spitzweg Medizinische Klinik und Poliklinik IV Endokrinologie/Diabetologie Marchioninistr. 15 81377 München Tel.: 089/4040-73012 Email: christine.spitzweg@med.lmu.de Studiensekretariat: J. Putz Tel.: 089/4400-52414 Email: jacqueline.putz@med.lmu.de
Studienziele/ Objectives	<u>Primary objectives:</u> Prospective collection of histopathologic, clinical, clinical chemical and imaging data and biomaterial of newly diagnosed patients with rare malignant tumors of the thyroid (anaplastic thyroid carcinoma, ATC; medullary thyroid carcinoma, MTC; radioiodine refractory thyroid carcinoma, RDTC; poorly differentiated thyroid carcinoma, PDTC) and parathyroid glands (PaTC). The aim is to improve diagnosis and treatment of patients by definition of - Parameters and biomarkers for diagnosis. - Parameters and biomarkers of treatment response and side effects - Parameters for risk stratification. - Parameters and biomarkers for follow-up <u>Secondary objectives:</u> Establishment of - cooperative structures for rare malignant tumors of the thyroid. - a clinical cancer registry for rare malignant tumors of the thyroid at the natio European centers. - Structures to facilitate translational research. - Structures to enable future prospective clinical trials. Collaborative evaluation of data collected retrospectively in individual centers.
Zielparameter/ Objectives	overall survival, disease free survival, time to progression, time to recurrence
Patientenzahl Number of patients	not restricted; current recruitment (10/2021): 268 ATC, 645 MTC, 263 RDTC, 82 PaTC
Rekrutierungzeitraum von/bis period of	retrospective: 2000 – 2013 prospective: 2014 – 2023 (planned interim evaluation)
Weitere teilnehmende Zentren erwünscht? More centres?	current centers (10/2021): - Universitätsklinikum Würzburg - Universitätsklinikum Augsburg - Universitätsklinikum Düsseldorf - Klinikum der Goethe-Universität Frankfurt/Main - Universitätsklinikum Gießen und Marburg – Standort Marburg - Universitätsmedizin Göttingen - Universitätsklinikum Greifswald - Endokrinologische-Nuklearmedizinische Gemeinschaftspraxis Heidelberg - Universitätsklinikum Leipzig - Universitätsklinikum Magdeburg - Universitätsklinikum Schleswig-Holstein - Standort Lübeck - Helios Kliniken Schwerin - Diakonie Klinikum Stuttgart

	- Universitätsklinikum Freiburg - Universitätsspital Zürich additional centers are invited to participate
Haupt-Einschlusskriterien 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 / Key exlusion criteria	inability to provide informed consent
Therapieschema Scheme of therapy	standard of care; investigational therapies
Tumorevaluierung 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.
Statistik statistics (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.

ZNS-KRK-Register: Metastasiertes kolorektales Karzinom / alle Stadien und Therapielinien

AIO-YMO/ZNS/KRK-0219: Prospektive Sammlung von Patienten- und Tumordaten sowie von Tumorgewebe und Liquid Biopsies (Blut und/oder Liquor) bei Patienten mit mKRK und ZNS-Metastasen (GECCObrain)

AIO-Studie

Studiennummer/-Code:	AIO-YMO/ZNS/KRK-0219 - GECCObrain
Status:	in Vorbereitung
Rekrutierungszeitraum:	2019 - 2024
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	31.10.2020

STUDY TYPE	Register mit Biobank
PRINCIPAL INVESTIGATOR	PD Dr. Marlies Michl Medizinische Klinik und Poliklinik III und CCC München[LMU] Klinikum der Universität München – Großhadern Marchioninistr. 15 81377 München
TRIAL OFFICE	Studiensekretariat der AG Onkologie Medizinische Klinik und Poliklinik III und CCC München[LMU] Klinikum der Universität München – Großhadern Marchioninistr. 15 81377 München
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe ZNS-Tumoren/Meningeosis	

Versorgungsforschung

AIO-KRK/YMO-0520/ass: CancerCovid - „Ressourcenallokation für die Krebsmedizin im Kontext von SARS-CoV-2. Nationale Studie zur Auswirkung der Pandemie mit SARS-CoV-2 auf die Versorgung von Patienten mit Tumorerkrankungen (Kolorektales Karzinom)"

Subprojekt 2 Onkologie: *"Quantitative Analyse der Auswirkungen von Allokation verfügbarer Ressourcen auf Patienten mit kolorektalem Karzinom (KRK)."*

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-KRK/YMO-0520/ass - CancerCovid
Status:	Datenerhebung wurde begonnen
Rekrutierungszeitraum	Zeitraum der Datenerhebung 01.01.2019 bis 31.12.2020
datenerhebende Zentren:	erwünscht
Zentren:	AIO- und Darmzentren
Daten:	retro- und prospektive Erhebung von Behandlungs- und Versorgungsdaten
Letzte Aktualisierung	Oktober 2021

Verantwortlicher Studienleiter	Prof. Dr. med. Anke Reinacher-Schick Abteilung für Hämatologie, Onkologie und Palliativmedizin St. Josef-Hospital Bochum Klinikum der Ruhr-Universität Tel.: 0234-509-3591, Fax-Nr.: 0234-509-3592 E-Mail: onkologie@klinikum-bochum.de Prof. Dr. med. Andrea Tannapfel Institut für Pathologie der Ruhr-Universität Bochum Zentrale Gewebebank Bürkle-de-la-Camp-Platz 1, 44789 Bochum Tel.: 0234-302-4800, Fax-Nr.: 0234-302-4809 E-Mail: andrea.tannapfel@rub.de
Weitere Mitarbeiter SP 2	Dr. med. Celine Lugnier, YMO, celine.lugnier@rub.de Dr. med. Anna-Lena Kraeft, anna-lena.kraeft@rub.de Eleni Kourti, YMO, e.kourti@klinikum-bochum.de Abteilung für Hämatologie, Onkologie und Palliativmedizin St. Josef-Hospital Bochum Klinikum der Ruhr-Universität Tel.: 0234-509-3591, Fax-Nr.: 0234-509-3592
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Kolon-/Rektum-/Dünndarmtumoren	
Die kostenneutrale Laufzeitverlängerung wurde genehmigt.	

Arbeitsgruppe ZNS-Tumoren/Meningeosis

NSCLC ohne onkogenen Treiber, metastasiert

AIO-TRK-0220/ass: Breaking the big Five Barriers of Brain Metastasis: A prospective phase II, open-label, multi-center trial of combined nivolumab, ipilimumab and bevacizumab together with 2 cycles of induction chemotherapy in patients with non-squamous non-small-cell lung cancer (NSCLC) metastatic to the brain (Break B5-BM NSCLC Trial)

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-TRK-0220/ass - CA209-7WF / Break B5-BM-NSCLC**		
Status:	in Vorbereitung		
Rekrutierungszeit:	von: 04.21 bis: 10.23		
Anzahl Zentren:	geplant: 10	aktuell initiiert:7	aktiv rekrutierend:7
Weitere Zentren:	sind aktuell leider nicht möglich		
Anzahl Patienten:	geplant: 39	aktuell eingeschlossen: 5	
Letzte Aktualisierung	29.10.2021		

PRINCIPAL INVESTIGATOR	Dr. Daniel Heudobler Department of Internal Medicine III University Hospital Regensburg Franz-Josef-Strauß-Allee 11 93053 Regensburg, Germany Tel: +49-941-944-4800 Fax: +49-941-944-5502 E-mail: daniel.heudobler@ukr.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Thorakale Onkologie	

Registerstudie

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

AIO-assoziierte Studie

Studiennummer/-Code:	
Status:	In Rekrutierung
Rekrutierungszeitraum:	Seit 2011, unbegrenzt
Weitere Zentren:	erwünscht
Letzte Aktualisierung	Oktober 2021

Art der Studie	Registerstudie
Projektleiter, wissenschaftlicher Leiter	Dr. med. Stefan Habringer Prof. Dr. med. Ulrich Keller Arbeitsgruppe ZNS-Lymphome der Charité Universitätsmedizin Berlin

	(Im Kompetenznetz Maligne Lymphome (KML) und in der German Lymphoma Alliance (GLA)) Charité Universitätsmedizin Berlin, Campus Benjamin Franklin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie Hindenburgdamm 30, 12203 Berlin Tel: 030 450 513447, Fax: 030 8445 2896 E-Mail: stefan.habringer@charite.de; E-Mail: ulrich.keller@charite.de
Datenmanagement	Frau Michaela Deparade Charité Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie (CBF) Hindenburgdamm 30, 12203 Berlin Tel: 030 450 513404 , Fax: 030 8445 2896 E-Mail: michaela.deparade@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: • Bestrahlung • intrathekale Therapie • systemische Chemotherapie. 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; 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). Prospektive Studien zur Therapie der SZNSL, die über den palliativen Ansatz hinausgehen, fehlen weitgehend.
	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). 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 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 und Thiotepa 80% des Serumspiegels, Carmustin 50–80%, Etoposid 5%, AraC 6–22%, Melphalan 10%; Wiebe 1992). 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). 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 HDMTX 4 g/m^2 (Tag 1) Ifosfamid 2 g/m^2 (Tag 3-5)

	Depocyte 50 mg ith. (Tag 6) Dexamethason 2x4 mg (Tag 6-10) 1-2 Zyklen HDAraC 3 g/m^2 (Tag 1-2) Thiotepa 40 mg/m^2 (Tag 2) Depocyte 50 mg ith. (Tag 3) Dexamethason 2x4 mg (Tag 3-7) gefolgt von einer Hochdosischemotherapie mit: BCNU 400 mg/m^2 (Tag -5) Thiotepa 2x5 mg/kg (Tag -4 bis -3) Etoposid 150 mg/m^2 (Tag -5 bis -3) und autologer Stammzelltransplantation. 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.
Beobachtungsziel	Diese Therapiebeobachtung ist eine prospektive Studie (prospektives Register). Aus diesem Grund werden weder diagnostische noch therapeutische Maßnahmen vorgeschrieben. 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: • Welche Therapieansätze werden verfolgt? • Wie ist das klinische Ergebnis der verschiedenen Behandlungsoptionen? • Wie ist die Frequenz schwerer unerwünschter Ereignisse bei den jeweiligen Therapieansätzen? 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 die Diagnosestellung nicht mehr benötigt, gebeten.
Auswahl der Prüfärzte	Die Beobachtungsstudie soll in Kliniken, Ambulanzen und bei niedergelassenen onkologisch tätigen Ärzten durchgeführt werden. Mit Meldung eines Patienten werden die personenbezogenen Daten des den Patienten einschließenden Arztes erfasst und in Form einer Listendokumentation zusammengestellt.
Patienten	Alle Patienten mit einem systemischen Lymphom und ZNS-Befall (einschließlich transformierter indolenter Lymphome und Mantelzelllymphome, jedoch kein Burkitt- oder lymphoblastisches Lymphom) können und sollen in die Untersuchung aufgenommen werden unabhängig davon, welche Therapieoptionen genutzt werden und unabhängig davon ob es sich um eine Erstlinienbehandlung, die Behandlung eines Rezidives oder um eine Erhaltungstherapie bei SZNSL handelt. Mit der Durchführung der Beobachtungsstudie ist keine Intervention hinsichtlich Auswahl und Durchführung des konkreten Therapieschemas, der Diagnostik und Untersuchungsfrequenz während und nach der Behandlung verbunden.
Patientenzahl	Es wird geschätzt, dass ca. 20 Patienten pro Jahr prospektiv eingeschlossen werden. Aktuell sind **275** Pat. eingeschlossen (Stand Oktober 2021).

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.

ZNS-KRK-Register: Metastasiertes kolorektales Karzinom / alle Stadien und Therapielinien

AIO-YMO/ZNS/KRK-0219: Prospektive Sammlung von Patienten- und Tumordaten sowie von Tumorgewebe und Liquid Biopsies (Blut und/oder Liquor) bei Patienten mit mKRK und ZNS-Metastasen (GECCObrain)

AIO-Studie

Studiennummer/-Code:	AIO-YMO/ZNS/KRK-0219 - GECCObrain	
Status:	nicht bekannt	
Rekrutierungszeitraum:	2019 - 2024	
Weitere Zentren:	sind sehr erwünscht	
Patienten:	geplant: 200	aktuell eingeschlossen: nicht bekannt
Letzte Aktualisierung	Nov. 2021	

STUDY TYPE	Register mit Biobank
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SPONSOR	Entfällt bisher Anschubfinanzierung über eigene Drittmittel
DESIGN	Prospektive Sammlung von Patienten- und Tumordaten sowie von Tumorgewebe und Blut (ggf. Liquor, wenn vorhanden)
INDICATION	Alle Patienten mit kolorektalem Karzinom und ZNS-Metastasen
OBJECTIVE(S)	Charakterisierung des sehr besonderen und seltenen Metastasierungsweges ins ZNS
INTERVENTION(S)	Keine

OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Genom-/Genexpressions-Analysen an Gewebe und Liquid Biopsies
BACKROUND/ RATIONALE	Nur etwa 2-4% aller KRK-Patienten entwickeln im Laufe ihrer Erkrankung ZNS-Metastasen. Umgekehrt handelt es sich bei nur 5% aller histologisch untersuchten ZNS-Metastasen um Adenokarzinom-Metastasen aus dem Kolorektum. Somit liegt die Inzidenzrate von ZNS-Metastasen beim KRK deutlich unter der bei anderen soliden Malignomen wie beispielsweise dem Lungen-, Mamma- oder Nierenzell-Karzinom oder Malignen Melanom. ZNS-Metastasen scheinen beim mKRK am häufigsten bei jüngeren Patienten aufzutreten (Altersklasse von 50 bis 65 Jahre) aufzutreten, was deutlich unter dem medianen KRK-Erkrankungsalter von 72 Jahren (Männer) bzw. 75 Jahren (Frauen) in epidemiologischen Registern liegt. Epidemiologische Analysen zeigen, dass die Inzidenz von ZNS-Metastasen beim KRK in den letzten Dekaden angestiegen ist. Ein Grund hierfür liegt möglicherweise in der höheren Detektionsrate durch den Fortschritt in diagnostischen Verfahren und in der Verfügbarkeit immer präziserer neuroradiologischer Bildgebungstechnik. Ein weitaus wichtigerer Grund wird in den optimierten Therapiestrategien des zugrundeliegenden Primärtumors und dessen Fernmetastasen vermutet. Diese ermöglichen längere Überlebenszeiten und lassen den Patienten das Entstehen der ZNS-Metastasierung als Spätmanifestation der Systemerkrankung erleben. Unterstrichen wird diese Annahme durch die Beobachtung, dass die Zeitspanne von (m)KRK-Erstdiagnose bis zur Diagnose der ZNS-Metastasierung über die Zeit zugenommen hat, was sich möglicherweise durch den Fortschritt der Systemtherapien und lokalen Metastasentherapien erklären lässt. Obwohl das kolorektale Karzinom eines der häufigsten Malignome darstellt, ist bis heute nur wenig bekannt über die Genese und die Therapiemögichkeiten von kolorektalen ZNS-Metastasen. Denn, im Gegensatz zu anderen seltenen Metastasenlokalisationen, sind Patienten mit ZNS-Metastasen aufgrund ihrer ungünstigen Prognose und Therapierbarkeit grundsätzlich von der Teilnahme an großen klinischen KRK-Studien ausgeschlossen und somit in prospektiven Studienpopulationen nicht repräsentiert. Aus diesen Gründen und aufgrund der Seltenheit ist die Initiierung von randomisierten prospektiven Therapiestudien nicht zu erwarten. Die wenigen Daten zu diesem Thema stammen bisher aus retrospektiven post-mortem-Studien oder aus Abteilungen für Neurochirurgie und Strahlentherapie, die die Ergebnisse einer untersuchten Therapiemethode an einem stark selektionierten Patientenkollektiv beschreiben. Der Großteil dieser Publikationen ist deskriptiv und fokussiert auf klinische Angaben. Translationale Aspekte fehlen oft gänzlich. Hier möchte das KRK-ZNS-Register anzusetzen. Es wird der Tatsache gerecht, 1) dass es sich um ein sehr seltenes Patientenkollektiv handelt (Stichwort: “rare cancers”) 2) Im Hinblick auf 1) und dass es vermutlich zeitnah keine prospektive (randomisierte) Studie für kolorektale ZNS-Metastasen geben wird, ist ein prospektives multizentrisches Register mit klinischen Angaben und Biobank aus wissenschaftlicher Sicht gerechtfertigt 3) Patienten können individuell und nach dem aktuellen und bestverfügbaren Therapiestandard behandelt werden. Die Behandlung in einer Therapiestudie ist ebenso zu jedem Zeitpunkt möglich und kein Ausschlusskriterium für die Aufnahme in das Register
KEY EXCLUSION CRITERIA	- Zweitmalignom (außer Basaliom, in den letzten 10 Jahren) - Fehlende Zustimmung des Patienten oder dessen gesetzlichen Betreuers

KEY INCLUSION CRITERIA	- >18 Jahre - Histologisch gesichertes kolorektales Karzinom - Bildgebender oder histolopathologischer Nachweis einer ZNS-Metastasierung
SAMPLE SIZE	N = 200 (gerne mehr)
TRIAL DURATION	5 Jahre
METHODIK	Digitales Register über m4 (Bitcare München)

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