STUDIENKURZPROTOKOLLE

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Impressum

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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

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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.**

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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).

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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

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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 – 2021	
Anzahl Zentren:	geplant: 134	initiiert: 134
Weitere Zentren:	sind leider nicht möglich	
Anzahl Patienten:	geplant: 790	aktuell eingeschlossen: 330 (Stand 10/2020)
Letzte Aktualisierung	Oktober 2020	

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:

	o Women with axillary node metastasis as predominant tumor site o Women with papillary adenocarcinoma of the peritoneal cavity o Men with poorly diff. ca. with midline distribution o Squamous cell carcinoma in cervical lymph nodes o Poorly diff. neuroendocrine tumors o Men with blastic bone metastases and elevated PSA o Isolated inguinal adenopathy o 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

CUP - palliative Therapie - 2nd-line

AIO-CUP-0119/ass: A phase II, open-label, non-randomized, multi-center study evaluating the efficacy and safety of nivolumab plus ipilimumab in patients with cancer of unknown primary site who are relapsed after or refractory to platinum-based chemotherapy (CheCUP)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-CUP-0119/ass - CheCUP
Status:	in Rekrutierung, Rekrutierungsbeginn Dezember 2019
Rekrutierungszeit:	2019 - 2021
Anzahl Zentren:	geplant: 11 initiiert: 9 aktiv rekrutierend: 8
Weitere Zentren:	leider nicht möglich
Anzahl Patienten:	geplant: 194 aktuell eingeschlossen: 20
Letzte Aktualisierung	8.10.2020

SHORT TITLE	Nivolumab/Ipilimumab in second line CUP-syndrome
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
CLINICAL TRIAL CODE	CheCUP
EUDRACT NO.	2018-004562-33
INDICATION	CUP-syndrome, relapsed/refractory to platinum-based chemotherapy ICD10: C80.0
OBJECTIVES	Primary

	To compare the efficacy of nivolumab plus ipilimumab in subjects with high vs. Intermediate/low TMB poor-prognosis CUP (non-specific subset) who are resistant or refractory to platinum-based first-line chemotherapy Secondary To evaluate the efficacy of nivolumab plus ipilimumab in subjects with poor-prognosis CUP (non-specific subset) who are resistant or refractory to platinum-based first-line chemotherapy
PHASE	II
INVESTIGATIONAL MEDICINAL PRODUCT(S)	Nivolumab and Ipilimumab
STUDY POPULATION	Inclusion Criteria Signed Informed Consent Form Able and willing to comply with the study protocol Age ≥ 18 years at time of signing Informed Consent Form Histologically-confirmed disseminated or advanced unresectable CUP diagnosed according the criteria defined in the 2015 ESMO Clinical Practice Guidelines for CUP. Acceptable disease histology includes: – Adenocarcinoma of unknown primary site (ACUP) – Poorly differentiated adenocarcinoma of unknown primary site – Poorly differentiated carcinoma of unknown primary site – Squamous cell carcinoma of unknown primary site (SCUP) At least one lesion that is measurable according to RECIST v1.1 Availability of a tumor FFPE block either fresh or archival if obtained ≤ 6 months at Screening that is sufficient for generation of a TruSight Oncology 500 (TSO500) panel at the central reference pathology laboratory Availability of test reports confirming local CUP diagnosis. If test reports confirming local CUP diagnosis are not available, an FFPE block must be submitted that is sufficient to allow for central confirmation of CUP diagnosis Disease relapse or progression after at least three cycles of a platinum-based standard chemotherapy. There is no upper limit of prior treatments received. ECOG performance status of 0 - 2 Life expectancy ≥ 12 weeks Eligible for immune checkpoint inhibitor Adequate hematologic and end-organ function For women of childbearing potential and men capable of reproduction: 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 for women and 7 months for men, respectively after the last dose of study treatment. Recovery from significant toxicity from platinum-doublet therapy to Grade ≤ 1, except for alopecia and for neurosensory toxicity, which must be ≤ 2 Recovery from active infections requiring intravenous antibiotics, with antibiotic therapy ceased for ≥ 7 days prior to planned start of therapy Exclusion Criteria Subjects with any of the specific non-CUP neoplasms identified in the ESMO CUP guidelines, including: – Non-epithelial cancer – Extragonadal germ-cell tumor Subjects belonging to any of the following subsets of CUP with favorable prognoses: – Poorly differentiated carcinoma with midline distribution – Women with papillary adenocarcinoma of the peritoneal cavity – Women with adenocarcinoma involving only the axillary lymph nodes – Squamous cell carcinoma restricted to cervical lymph nodes – Poorly and well differentiated neuroendocrine tumors – Men with blastic bone metastases and elevated PSA – Subjects with a single, small tumor potentially resectable and/or amenable to radiotherapy with curative intent

	– Colon cancer-type CUP Known presence of brain or spinal cord metastasis (including metastases that have been irradiated), as determined by CT or magnetic resonance imaging (MRI) evaluation during screening History or known presence of leptomeningeal disease Uncontrolled or symptomatic hypercalcemia (serum calcium ≥ 2.9mmol/L) Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis, current alcohol abuse, or cirrhosis Known human immunodeficiency virus (HIV) infection Positive for hepatitis C virus (HCV) antibody at screening Positive for hepatitis B surface antigen (HBsAg) at screening Active tuberculosis at Screening 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 (including active ventricular arrhythmia requiring medication), or unstable angina 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 CUP within 5 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 Prior allogeneic stem cell or solid organ transplantation 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 Treatment with investigational therapy within 28 days prior to initiation of study treatment Known allergy or hypersensitivity to any component of the immunotherapy, including history of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins and to Chinese hamster ovary cell products or other recombinant human or humanized antibodies for nivolumab and ipilimumab. Subjects with an active, known or suspected autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, myocarditis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents, or other immuno-suppressive medications within 14 days of study treatment. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents for adults, or > 0.25 mg/kg daily prednisone equivalent for adolescents are permitted, in the absence of active autoimmune disease. Subjects who received 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 All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 5) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

	Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment initiation might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 5). Subjects must not have received a live / attenuated vaccine within 30 days of first treatment. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the last dose of study treatment or intention of fathering a child within 7 months after the last dose of study treatment.
SAMPLE SIZE	To be screened: 700 To be enrolled 194 (97 subjects with high and intermediate/low TMB, respectively) To be analyzed: 194
TRIAL DURATION	Total trial duration: 36 months Duration of clinical phase: 24 months Beginning of the preparation phase: 10/2018 FSI (first subject in): 10/2019 LSI (last subject in): 10/2021 LSO (last subject out): [10/2022] DBL (database lock): [Q3 2022] Statistical analyses completed: [Q4 2022] Trial report completed: [Q4 2022]
STATISTICAL ANALYSIS	This is a non-randomized biomarker trial. Tumor mutational burden (TMB) is considered as biomarker. Subjects showing high TMB are considered biomarker-positive. A total of 194 subjects with 191 events are required to detect a hazard ratio of 0.65 for biomarker positive vs biomarker negative subjects with 80% power at the two-sided significance level of 5%. Median progression-free survival in the studied subject population is assumed to be 2.3 months, and 15% of subjects are expected to be biomarker-positive. Biomarker-positive subjects are expected to have a favorable prognosis. Assuming a hazard ratio of 0.65 for biomarker-positive versus biomarker-negative subjects and exponentially distributed survival, median survival times are 2.18 and 3.35 months for biomarker-negative and biomarker-positive subjects, respectively. Subjects will be recruited in a 1:1 ratio, i.e. biomarker-positive subjects will be enriched, which means that approximately 700 subjects need to be assessed for their TMB status. There will be a 24 months recruitment period and a minimal follow-up time of 12 months. The primary analysis will be performed by testing the null hypothesis of no difference in PFS between both biomarker groups using a log-rank test at a significance level of 5%. <u>Primary endpoint:</u> • Progression-free survival (PFS) <u>Secondary endpoints:</u> • Overall survival (OS) • Overall response rate (ORR) • Duration of clinical benefit (DCB) Safety endpoints: • Incidence, nature and severity of adverse events (AEs) • Incidence and reasons for any dose reductions, interruptions, or premature discontinuation of any component of study treatment • Clinically significant laboratory values and vital signs
FINANCING	Bristol-Myers Squibb

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: 10
Weitere Zentren:	Nicht geplant (single center trial)
Letzte Aktualisierung	10/2020

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: 10
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:	geplant: nicht definiert	initiiert: 12
Patienten:	geplant: 1000	aktuell eingeschlossen: s.u.
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	Oktober 2020	

Art der Studie Study Type	Retrospective and prospective registry study
Kontaktadresse/ Kontaktperson:	Prof. Dr. Dr. Matthias Kroiß Tel.: 089/4400-52221, Email: matthias.kroiss@med.lmu.de LMU Klinikum der Universität München Medizinische Klinik und Poliklinik IV Lehrstuhl Endokrinologie/Diabetologie Ziemssenstraße 1, 80336 München Studiensekretariat (UK Würzburg): Ramona Walter-Ruckstetter, Tel.: 0931/201-39717 Email: Walter_R@ukw.de
Die Synopse finden Sie unter den Kurzprotokollen der Arbeitsgruppe Young-Medial-Oncologists	

Registerstudie

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 2020

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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 2020: 3996 (davon > 1460 aus Deutschland) Phäochromozytom: Oktober 2020: 4339 (davon ca. 600 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 Lanet 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-assoziierte Studie		
Studiennummer/-Code:	AIO-HEP-0417/ass	
Status:	In Rekrutierung	
Rekrutierungszeitraum:	Seit Q3/2019, 12 Monate Rekrutierung	
Zentren	geplant: 10	aktuell initiiert: 11
Patienten	geplant: 30	aktuell rekrutiert: 13
Weitere Zentren:	sind leider nicht mehr möglich	
Letzte Aktualisierung	Oktober 2020	

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	IKF Klinische Krebsforschung 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 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 • Patient is awaiting liver transplantation (LTx) • Prior history of Grade ≥ 2 hepatic encephalopathy • Pericardial effusion, uncontrollable pleural effusion, or clinically significant ascites • Autoimmune disease requiring systemic treatment

KEY INCLUSION CRITERIA	• Histologically confirmed diagnosis of HCC • Child-Pugh Classification score ≤ 6 • Candidate for local ablation (via either RFA or MWA) • High risk patient (Presence of ≤ 5 tumor nodules with diameters ≤ 5cm [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 RFA / MWA will allow conversion / downstaging of borderline candidates for local ablation. This will be displayed by an ORR of 30% (measured before RFA / MWA, compared to baseline). • We hypothesize that peri-interventional treatment with pembrolizumab will increase TTR, recurrence free survival and overall survival after RFA / MWA. Safety: • We hypothesize that combination of RFA / MWA with peri-interventional administration of pembrolizumab is safe and well tolerated.
STUDY TYPE	Interventional, single-arm, open-label, multicenter
STATISTICAL ANALYSIS	This is an explorative phase II study. There is no formal sample size calculation. The primary endpoint is ORR and the number of 30 patients will allow to observe the expected ORR of 30% (0.3) with 90% confidence interval (CI) extending from 0.18 to 0.45 and 95% confidence interval extending from 0.16 to 0.48. There is no full interim analysis planned for this study, due to the small sample size and the relatively short recruitment period. However, single objectives may be analyzed as soon as sufficient events are available for analysis as detailed in the Statistical Analysis Plan (SAP).
SAMPLE SIZE	n=30
TRIAL DURATION	max. 42 months from FPI to LPO (consisting of 12 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-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: 4 aktiv rekrutierend: 1
Weitere Zentren:	sind erwünscht
Anzahl Patienten:	geplant: 104 aktuell eingeschlossen: 4
Letzte Aktualisierung	09.10.2020

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 not suitable for resection or liver transplantation (> 3 tumors > 3 cm or one tumor > 5 cm) 3. Availability of Biopsy for translational research 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 first treatment 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	
Status:	in Vorbereitung	
Rekrutierungszeitraum:	Studienstart Q2 2020 – Q3 2022	
Zentren:	geplant: 10	initiiert: 6
Paytienten:	geplant: 100	eingeschlossen: 9
Weitere Zentren:	Interessierte Zentren können sich auf die Wartliste setzen lassen	
Letzte Aktualisierung	November 2020	

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. ≥ 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). <u>Safety considerations</u> 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:	erste Zentren initiiert	
Rekrutierungszeitraum:	Q3 2020 – Q3 2022	
Weitere Zentren:	sind sehr erwünscht	
Zentren:	geplant: 25	initiiert:
Patienten:	geplant: 84	aktuell eingeschlossen: 0
Letzte Aktualisierung	27.10.2020	

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: o Invasion of a segmental portal vein or hepatic veins. 2. Patients with advanced liver disease as defined below: o Encephalopathy; o Untreatable Ascites. 3. Any contraindications for hepatic embolization procedures: o Known hepatofugal blood flow; o Known porto-systemic shunt; o Impaired clotting test (platelet count < 70 Thsd/L, INR > 1.25); o Renal failure/insufficiency requiring hemo-or peritoneal dialysis; o Known severe atheromatosis; o 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: o Congestive heart failure > New York Heart Association (NYHA) class 2; o Active coronary artery disease (CAD) (myocardial infarction ≥ 6 months prior to study entry is allowed);

	o Cardiac arrhythmias (Grade > 2 NCI-CTCAE Version 5.0) which are poorly controlled with anti-arrhythmic therapy or requiring pace maker; o Uncontrolled hypertension; o 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: 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) 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: o Patients with vitiligo or alopecia o Patients with hypothyroidism (e.g. following Hashimoto syndrome) 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 o 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: o Hemoglobin ≥ 9.0 g/dL, absolute neutrophil count ANC ≥1.5 x 10^9/L (> 1500 per mm^3), platelets ≥ 75 x 109/L (>75,000 per mm^3); o Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN); o AST (SGOT), ALT (SGPT) ≤ 2.5 x institutional ULN unless liver metastases are present, in which case it must be ≤5x ULN; o 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: o Patients with HBV or HCV infection should be monitored for viral levels during study participation; o 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; o 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, 1st-line

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

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-HEP-0218/ass // IMMUNIB	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2019 bis voraussichtlich 2020	
Zentren:	geplant: 15	initiiert: 13
Patienten:	geplant: 50	aktuell eingeschlossen: 42
Weitere Zentren:	sind leider nicht möglich	
Letzte Aktualisierung	Oktober 2020	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1, 30625 Hannover Tel.: +49 176 1 532 9590 Email: vogel.arndt@mh-hannover.de
TRIAL OFFICE	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26, 60488 Frankfurt/Main Christiane Jöckel Tel: +49 69 / 7601-4595 Email: joeckel.christiane@ikf-khnw.de
SPONSOR	IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26, 60488 Frankfurt/Main
CONDITION	Multinodular, advanced stage hepatocellular carcinoma (HCC) in first line therapy
OBJECTIVE(S)	Primary efficacy endpoint: Objective response rate (ORR) according to RECIST 1.1 Primary safety endpoint: Safety (according to NCI-CTCAE v 4.03) and tolerability Secondary endpoints: • ORR according to iRECIST • Time-to-progression (TTP) • Progression free survival (PFS) • Overall survival (OS) • Translational research program
INTERVENTION(S)	• Lenvatinib peroral qd (8 mg for patients with body weight <60kg and 12 mg for patients with body weight ≥ 60kg) • Nivolumab i.v. q2w (240mg fixed dose IV)
KEY EXCLUSION CRITERIA	• Previous systemic therapy in the first-line setting. • Patients on a liver transplantation list or with advanced liver disease as defined below: o Encephalopathy o Untreatable Ascites. • Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

	• Prior organ allograft or allogeneic bone marrow transplantation. Local therapies ongoing or completed <4 weeks prior to the baseline scan.
KEY INCLUSION CRITERIA	• Unresectable, multinodular tumour, not eligible for resection or local ablation • Histologically confirmed diagnosis of hepatocellular carcinoma • Has a Child-Pugh Classification score ≤ 6 for assessed liver function within 7 days before allocation (Appendix 4: Child-Pugh Score) – patients with BCLC stage B can be included if they are no longer eligible for local ablation (i.e. after progress under local concept) • At least one measurable site of disease as defined by RECIST 1.1 criteria with spiral CT scan or MRI. • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. • Life expectancy of at least 12 weeks.
OUTCOME(S)	The primary efficacy endpoint is: • Objective response rate (ORR) according to RECIST 1.1 based on the ITT population The primary safety endpoint is: • Safety (according to NCI-CTCAE V 4.03) and tolerability
STUDY TYPE	Open-label, single-arm, multicenter phase II trial
STATISTICAL ANALYSIS	The present trial is designed as an explorative, single-arm phase II study which aims to estimate the therapeutic efficacy of an experimental combination regimen. ORR analysed according to the ITT principle is the primary efficacy endpoint. The efficacy assumptions are derived from historical data. Descriptive analysis will be performed according to the study specific SAP.
SAMPLE SIZE	n=50
TRIAL DURATION	➢ Duration of recruitment: 13 months ➢ Maximum treatment duration will be 18 months (estimated 5 months median treatment duration) ➢ The individual follow-up period will end when all study patients have been followed for at least 6 months from their date of enrolment
PARTICIPATING CENTERS	15 sites planned

HCC, fortgeschrittenes Stadium, 2nd-line

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-Studie

Studiennummer/-Code:	**AIO-HEP-0320/ass_CaboRISE**
Status:	aktiv
Rekrutierungszeit:	Studienstart Q4 2020, Rekrutierungszeit 12 Monate
Anzahl Zentren:	geplant: 10 aktuell initiiert: 3 aktiv rekrutierend: 1
Weitere Zentren:	sind sehr erwünscht – ein weiteres Zentrum gesucht
Anzahl Patienten:	geplant: 40 aktuell eingeschlossen: 1 (FPI 12.10.2020)
Letzte Aktualisierung	10/2020

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. 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 3 months • 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) <u>Translational Research:</u> 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 LenvAtinib Treatment (AURORA)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO- HEP-0419/ass - AURORA	
Status:	erste Zentren initiiert	
Rekrutierungszeitraum:	Q3 2020 – Q2 2021	
Weitere Zentren:	sind sehr erwünscht	
Zentren:	geplant: 10	initiiert:
Patienten:	geplant: 45	aktuell eingeschlossen: 0
Letzte Aktualisierung	27.10.2020	

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. History of encephalopathy in past 12 months. 9. 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. 10.Baseline QTcF >500 ms. 11.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. 12.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. 13.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. 14.Treatment with investigational systemic therapy within 28 days prior to initiation of study treatment.

	15.Prior cabozantinib use. 16.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. 17.Patients who have 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].
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 despite of lenvatinib treatment OR patients must have had their treatment interrupted for at least 1 administration due to toxicity. 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. 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-to-Treatment-Failure <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 in relation to other salvage options after lenvatinib pre-treatment. Since the efficacy of Cabozantinib in lenvatinib experienced patients 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: o 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: o combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: ▪ oral ▪ intravaginal ▪ transdermal o progestogen-only hormonal contraception associated with inhibition of ovulation: ▪ oral ▪ injectable ▪ implantable o intrauterine device (IUD) o intrauterine hormone-releasing system (IUS) o bilateral tubal occlusion o vasectomised partner (medical assessment must be present and done) o 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, adjuvant

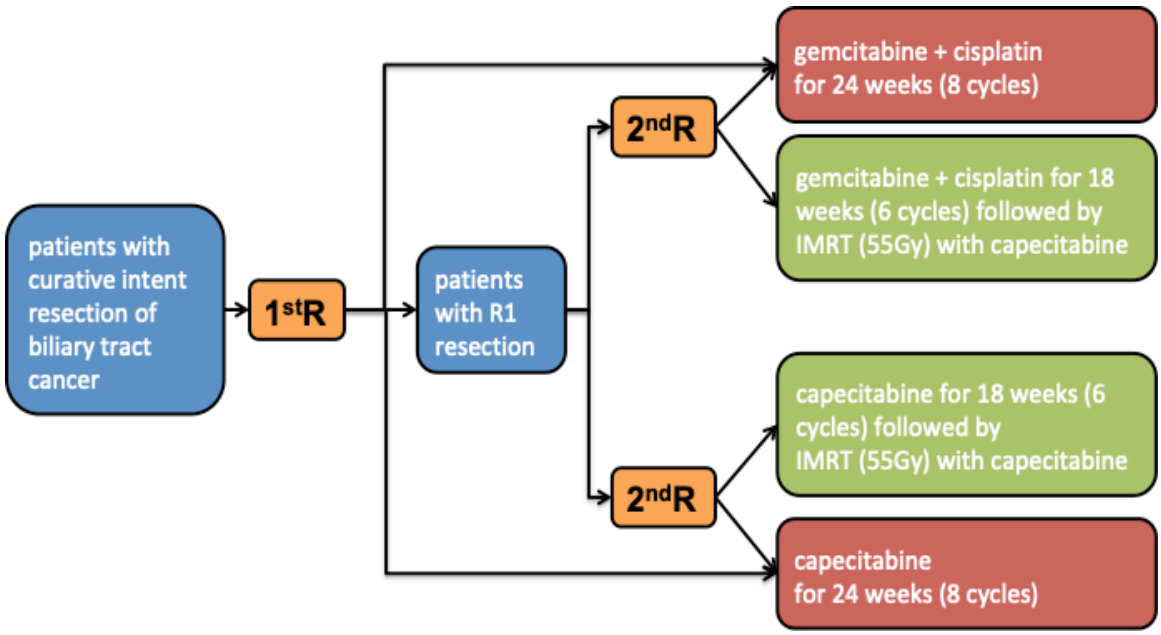
AIO-HEP-0112: Adjuvant chemotherapy with gemcitabine and cisplatin compared to standard of care (currently in stage 2 capecitabine) after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1). A randomized, multidisciplinary, multinational AIO/DGAV/DGVS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

AIO-Studie

Studiennummer:	AIO-HEP-0112 - ACTICCA-1
Status:	in Rekrutierung
Rekrutierungszeitraum:	ab 2014
Zentren:	60 sites in Australia/Austria/Denmark/Germany/The Netherlands/UK
Patienten:	577 pts included/534 pts randomized
Weitere Zentren:	sind leider nicht möglich
Letzte Aktualisierung	10.10.2020

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 Current status as of 13/10/2019: 472 pts included/436 pts randomized
Study duration	Stage 1 analysis currently ongoing 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). **Arm AR: Gemcitabine/cisplatin followed by chemoradiation and observation** Therapy will be administered on days 1 and 8 every 3 weeks for 18 weeks (6 cycles), with cisplatin (25 mg per square meter of body-surface area) and gemcitabine (1000 mg per square meter) (Valle, Wasan et al. 2010), followed by chemoradiation with a total dose of 45Gy to elective nodal area and 55Gy to R1 delivered as a simultaneous integrated boost in 25 daily fractions over 5 weeks with concomitant capecitabine at 1330 mg per square meter of body-surface area per day (665 mg per square meter, twice daily) on radiotherapy days (5 days per week). **Arm BR: Capecitabine followed by chemoradiation and observation** Therapy will be administered from day 1 to 14 every 3 weeks for 18 weeks (6 cycles), with capecitabine 2500 mg per square meter of body-surface area per day (1250 mg per square meter, twice daily) followed by chemoradiation with a total dose of 45Gy to elective nodal area and 55Gy to R1 delivered as a simultaneous integrated boost in 25 daily fractions over 5 weeks with concomitant capecitabine at 1330 mg per square meter of body-surface area per day (665 mg per square meter, twice daily) on radiotherapy days (5 days per week). **Radiotherapy** Radiotherapy should start not more than 6 weeks after day 1 of cycle 6. A contrast enhanced liver protocol CT must be obtained for treatment planning in custom immobilisation. A linear accelerator with at least 6 MV should be used, capable of daily image guidance and IMRT delivery. Radiation therapy will be given daily, five times weekly. On-line imaging prior to each fraction of radiotherapy is mandatory.

	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.

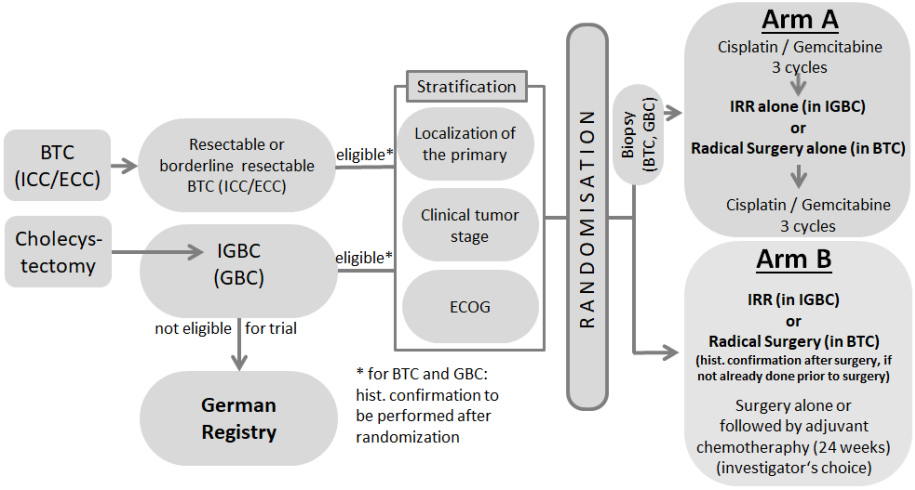
CCA, neoadjuvant

AIO-HEP-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, die Hälfte der Zentren ist initiiert, Rekrutierung ist angelaufen	
Rekrutierungszeitraum:	Q2/2019, 4 Jahre Rekrutierung	
Zentren:	geplant: 50	initiiert: 23
Patienten:	geplant: 330	aktuell eingeschlossen: 10
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	23.10.2020	

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. <u>Safety Objectives</u> • 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)	<u>Arm A (gemcitabine plus cisplatin)</u> 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 <u>Arm B (standard postoperative management)</u> 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.

AIO-HEP-0120: Neoadjuvante Therapie mit Bintrafusp alfa bei Patienten mit operablem Krebs der Gallenwege (NEOBIL)

AIO-Studie

Studiennummer/-Code:	AIO-HEP-0120 - NEOBIL		
Status:	in Vorbereitung		
Rekrutierungszeit:	18 Monate		
Anzahl Zentren:	geplant: 10	aktuell initiiert: 0	aktiv rekrutierend: 0
Weitere Zentren:	Leider nicht mehr möglich		
Anzahl Patienten:	geplant: 24	aktuell eingeschlossen: 0	
Letzte Aktualisierung	Oktober 2020		

Leiter der klinischen Prüfung (LKP)	Prof. Dr. Oliver Waidmann Medizinische Klinik 1 Universitätsklinikum Frankfurt Theodor-Stern-Kai 7 60590 Frankfurt
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Strasse 8 14057 Berlin
Indikation	Behandlungsnaive Patienten mit der Diagnose eines operablen Gallengangskrebses, bestätigt durch Histopathologie.
Studiendesign	Einarmige, multizentrische, offene, therapeutisch explorative Phase-II-Studie
Studiendauer	Rekrutierung: 18 Monate. Behandlungsdauer: 10 Wochen mit anschließender Nachsorge bis zum Studienabschluss.
Anzahl Prüfzentren	10
Geplante Fallzahl	24
Prüfmedikation/Dosierung	Bintrafusp alfa (alternativer Name: MSB0011359C, M7824) wird für zwei Zyklen mit 1200 mg q2w dosiert.
Primäres Studienziel	Hauptziel dieser Studie ist die Untersuchung der Wirksamkeit einer präoperativem Behandlung mit Bintrafusp alfa (M7824, MSB0011359C) im Bezug auf die pathologisch gemessene Remission bei Patienten mit Gallengangskrebs

Sekundäres Ziel	Zu den sekundären Zielen gehören explorative Ziele, wie weitere Durchführbarkeitsdaten (z.B. Sicherheitsdaten, zusätzliche Wirksamkeitsdaten) sowie ein translationaler Forschungsteil, der Veränderungen in der Immunaktivität der Patienten untersucht. Hierfür werden Blutuntersuchungen und Gewebeanalysen vor und nach der Behandlung mit Bintrafusp alfa durchgeführt.
Translationale Forschung	• Biomarker-Untersuchung zur Vorhersage der Tumorantwort (Infiltration von Immunzellen, Zunahme von immunverwandten Genen) in archivierten Tumorgewebeproben und resezierten Tumorproben. • Vollblutproben werden vor und nach der Behandlung für die Analyse flüssiger Biomarker entnommen.
Rationale	Die einzige kurative Therapie bei Gallengangskrebs (BTC) ist die Resektion. Die Rezidivraten sind jedoch mit einer medianen rezidivfreien Überlebenszeit (RFS) von 18 Monaten mit adjuvanter Chemotherapie sehr hoch. Bintrafusp alfa ist ein bifunktionelles Fusionsprotein, das auf TGF-β und PD-L1 abzielt und in einer Phase-I-Studie der Zweitlinientherapie von BTC vielversprechende Aktivität gezeigt hat. Der neoadjuvante Behandlungsansatz ist aktuell kein Standard bei Gallengangskrebs, aber eine akzeptierte und häufig angewandte Behandlungsstrategie bei anderen resektablen und grenzwertig resezierbaren Krebsarten wie Lungen-, Magen- und Rektalkrebs.
Einschlusskriterien	1. Schriftliche Einverständniserklärung vor Beginn der studienspezifischen Screening-Untersuchung. 2. Histologisch bestätigte Diagnose eines BTC. Zytopathologie ist nicht ausreichend. 3. Von einem Tumorboard inklusive eines hepatobilären Chirurgen bestätigte und auf die Leber begrenzte resektable Erkrankung. 4. Patient erklärt sich bereit und ist in der Lage an Visiten, Untersuchungen und der Behandlung inklusive der Nachbeobachtung gemäß Prüfplan samt aller damit verbundenen Anforderungen für die Dauer der Studie teilzunehmen. 5. Alter ≥ 18 Jahre 6. Leistungsstatus ECOG 0-1 7. Normale Organ- und Knochenmarkfunktion definiert als: a. Hämatopoetisch: absolute Neutrophilenzahl ≥1,500/mm3, Thrombozytenzahl ≥ 100,000/mm3, b. Hämoglobin ≥9 g/dL c. Normales International Normalized Ratio (INR), PT ≤ 1.5 x ULN und aktivierte partielle Thromboplastinzeit (aPTT) ≤ 1.5 x ULN d. Leber: AST ≤5 x ULN, ALT ≤ 5 x ULN, und Bilirubin ≤ 3.0 x ULN. e. Niere: Kreatininspielgel ≤1.5 x ULN oder geschätzte Kreatinin Clearance ≥ 30 mL/min gemäß der Cockcroft-Gault Formel (oder der lokalen institutionellen Standardmethode) 8. Besondere Erkrankungen und Komorbiditäten: a. Maximales Child Pugh-Stadium A bei Patienten mit Zirrhose. b. HIV: mindestens 4 Wochen auf ART stabil, keine dokumentierten Hinweise auf Multiresistenz, Viruslast von <400 Kopien / ml und CD4 + T-Zellen ≤ 350 Zellen / µL. c. HBV-Infektion: Teilnehmer an einer stabilen Dosis einer antiviralen Therapie, HBV-Viruslast unterhalb der Bestimmungsgrenze. 9. Frauen im gebärfähigen Alter müssen innerhalb von 7 Tagen vor der ersten IMP-Dosis einen negativen Serumschwangerschaftstest durchführen lassen

Ausschlusskriterien	1. Metastisierung 2. Vorherige Operation, systemische Therapie, Strahlentherapie, Radiochemotherapie, transarterielle Chemoembolisation (TACE), Radiofrequenzablation (RFA) oder selektive intraarterielle Strahlentherapie (SIRT) zur Behandlung von CCA. HINWEIS: Die Laparoskopie für diagnostische Verfahren ist zulässig. 3. Drogen- oder Alkoholabhängigkeit, medizinischer oder psychischer Zustand, der die Teilnahme des Patienten an der Studie beeinträchtigen kann. 4. Teilnahme an einer anderen klinischen Studie mit einem Prüfpräparat (unabhängig von der Verwendung, kurativen, prophylaktischen oder diagnostischen Absicht) innerhalb von 30 Tagen vor der Registrierung. 5. Schwangerschaft oder Stillzeit von Frauen 6. Regulatorische und ethische Kriterien: • Patienten, die inhaftiert sind oder unfreiwillig auf gerichtliche oder behördliche Anordnung in einer Anstalt untergebracht sind (§ 40 Abs. 1 S. 3 Nr. 4 AMG). • Patienten, die nicht in der Lage sind, Wesen, Bedeutung und Tragweite der klinischen Prüfung zu erkennen und daher unfähig sind, ihren Willen hiernach auszurichten (§ 40 Abs. 1 S. 3 Nr. 3a AMG). 7. IMMUNOSUPRESSANTEN: „Derzeitige Verwendung von immunsuppressiven Medikamenten, AUSSER für Folgende: a. intranasale, inhalative, topische Steroide oder lokale Steroidinjektion (z. B. intraartikuläre Injektion); b. Systemische Kortikosteroide in physiologischen Dosen ≤ 10 mg / Tag Prednison oder Äquivalent; c. Steroide als Prämedikation für Überempfindlichkeitsreaktionen (z. B. CT-Scan-Prämedikation). “ 8. AUTOIMMUNKRANKHEIT: „Aktive Autoimmunerkrankung, die sich bei Erhalt eines immunstimulierenden Mittels verschlechtern kann. Patienten mit Diabetes Typ I, Vitiligo, Psoriasis oder Hypo- oder Hyperthyreoseerkrankungen, die keine immunsuppressive Behandlung benötigen, sind berechtigt. “ 9. VORHERIGE MALIGNE KRANKHEIT: “Innerhalb der letzten 3 Jahre mit Ausnahme von a. oberflächlicher /nicht-invasiver Blasenkrebs oder Basal- oder Plattenepithelkarzinom in situ, behandelt mit kurativer Absicht; b. endoskopisch resezierte GI-Krebserkrankungen, die auf die Schleimhautschicht beschränkt sind und in > 1 Jahr nicht erneut auftreten.” 10. INFEKTIONEN: „Aktive Infektion, die eine systemische Therapie erfordert.“ 11. IMPFUNG: „Patient hat innerhalb von 30 Tagen vor der ersten Verabreichung der Studienintervention einen Lebendimpfstoff erhalten oder wird diesen erhalten. Saisonale Grippeimpfstoffe, die kein Lebendvirus enthalten, sind zulässig.“ 12. HYPERSENSITIVITÄT FÜR BINTRAFUSP ALFA: „Bekannte schwere Überempfindlichkeit [Grad ≥ 3 NCI CTCAE 5.0]) gegen das Prüfpräparate oder Komponenten in der Zusammensetzung, Anaphylaxie in der Anamnese oder kürzlich innerhalb von 5 Monaten aufgetretenes unkontrollierbares Asthma. 13. KARDIOVASKULÄRE ERKRANKUNG: „Klinisch signifikante (d.h. aktive) Herz-Kreislauf-Erkrankung: zerebraler Gefäßunfall / Schlaganfall (< 6 Monate vor der Registrierung), Myokardinfarkt (< 6 Monate vor der Registrierung), instabile Angina pectoris, Herzinsuffizienz (≥ New York Heart Association Classification Class II) oder schwerwiegende Herzrhythmusstörungen, die Medikamente erfordern. “ 14. BLUTUNGEN: „Blutungsdiathese in der Anamnese oder kürzlich aufgetretene schwerwiegende Blutungsereignisse (d. H. Blutungsereignisse vom Grad ≥ 2 im Monat vor der Behandlung).

	15. Andere schwere akute oder chronische Erkrankungen: „einschließlich einer medikamenteninduzierten interstitiellen Lungenerkrankung (ILD) oder eines Teilnehmers, bei dem in der Vergangenheit eine medikamenteninduzierte Pneumonitis aufgetreten ist, für die oralen oder intravenösen Steroide erforderlich waren“ und/oder andere Krankheiten, die in der der Meinung des Prüfers die Teilnahme an der Studie oder die Fähigkeit zur konsequenten Teilnahme an dem Studienverfahren beeinträchtigen.
Statistiken Primärer Analysenplan	Alle im eCRF aufgezeichneten Daten, die die Probe, die Wirksamkeit und die Sicherheit beschreiben, werden deskriptiv analysiert. Kategoriale Daten werden in Kontingenztabellen mit Häufigkeiten und Prozentsätzen dargestellt. Kontinuierliche Daten werden mit mindestens den folgenden Angaben zusammengefasst: Stichprobengröße, Median, Quartile, Mittelwert, Standardabweichung (Standardfehler), Minimum und Maximum. Time-to-Event-Messungen werden mit Kaplan-Meier-Techniken analysiert. Die im chirurgisch resezierten Tumor gemessene Major Pathologic Response (MPR) wird gemäß der folgenden Regressionsbewertung bewertet: Die histopathologische Untersuchung wird gemäß der an das Cholangiokarzinom angepassten Becker-Klassifikation durchgeführt. Das Ansprechen auf eine neoadjuvante Behandlung wird anhand des Becker-Scores bestimmt. MPR wird durch einen Becker-Grad von 1 (1a oder 1b) definiert, mindestens <10% des lebensfähigen Tumors.
Stichprobengröße	Spontane Regression (MPR), ist bei Patienten mit Gallengangskrebs sehr selten, und wir gehen davon aus, dass MPR bei weniger als 5% der Patienten (P0) auftritt. Aufgrund von jüngsten histopathologisch bestätigten Ergebnissen bei Patienten mit nicht-kleinzelligem Lungenkarzinom (NSCLC) und radiologischen Befunden bei Patienten mit Gallengangskrebs gehen wir bei Patienten, die vor der Resektion mit Bintrafusp alfa behandelt wurden, von einem MPR von 30% (P1) aus. Eine Stichprobengröße von 24 Patienten erreicht eine Power von 95%, um einen Unterschied (P1-P0) von 0,25 unter Verwendung eines einseitigen Binominal-Tests festzustellen. Das Zielsignifikanzniveau beträgt 0,05. Das tatsächliche Signifikanzniveau, das durch diesen Test erreicht wird, beträgt 0,0298. Es wird davon ausgegeangen das der Bevölkerungsanteil der Nullhypothese 0,05 beträgt.

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: 3
Patienten:	geplant: 50	aktuell eingeschlossen: 0
Letzte Aktualisierung	12 Oktober 2020	

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 BTC not amenable to curative treatment (tumor resection or ablation)* * will soon be amended as follows: 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. ➢ Prior chemotherapy with gemcitabine and cisplatin (exception: capecitabin or gemcitabine and cisplatin in the adjuvant setting, last infusion has to be ≥ 6 months prior inclusion). ➢ Prior radiotherapy treatment before the first dose of any study drug. ➢ History of allogenic organ transplantation. * *will soon be amended as follows:*

	➢ *Presence of peritoneal carcinomatosis or brain metastases.* ➢ *Exclusion criterion "Prior chemotherapy with gemcitabine and cisplatin (exception: capecitabin or gemcitabine and cisplatin in the adjuvant setting, last infusion has to be ≥ 6 months prior inclusion)" will be removed.*
KEY INCLUSION CRITERIA	➢ Histologically documented diagnosis of intrahepatic, non-resectable BTC and available tumor tissue (block or at least 4 slides) for translational research. ➢ 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 * *<u>will soon be amended as follows</u>:* ➢ *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*.
OUTCOME(S)	<u>Primary endpoint:</u> Objective response rate (ORR) according to RECIST 1.1 <u>Secondary endpoints:</u> • Safety (rate of adverse events) • Duration of response (DoR) • Progression free survival (PFS) • Overall survival (OS) <u>Exploratory:</u> 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-HEP-0116: A randomized phase II trial of nal-IRI and 5-Fluorouracil compared to 5-Fluorouracil in patients with cholangio- and gallbladder carcinoma previously treated with gemcitabine -based therapies (NALIRICC)

AIO- Studie		
Studiennummer/-Code:	AIO-HEP-0116 - NALIRICC	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2017 - 2019	
Zentren:	geplant: 20	initiiert: 18
Patienten:	geplant: 100	aktuell: 90 rand.
Weitere Zentren:	nicht möglich	
Letzte Aktualisierung	Oktober 2020	

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Study design	open label, randomized, multicenter phase II trial
Start date	FPI Dec-2017
Duration of study	Enrollment: 24 months, total study duration ~32 months (incl. follow-up)
Indication	Advanced, unresectable and metastatic cholangio- and gallbladder carcinoma (CCA) after failure of gemcitabine-based therapies.
Target population	Patients with advanced, unresectable and metastatic cholangio- and gallbladder carcinoma eligible for treatments after failure to respond to a gemcitabine-based treatment.
Total number of sites	20
Primary objective	To assess the efficacy of nal-IRI in gemcitabine pre-treated patients with CCA.
Secondary objectives	To assess further efficacy variables as well as safety, tolerability and quality of life measures of nal-IRI for CCA.
Planned sample size	N=100 total (n=50 per treatment arm)

Inclusion criteria	1. Written informed consent incl. participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations 2. Age ≥ 18 years at time of study entry 3. Histologically or cytologically confirmed, non-resectable, locally advanced or metastatic cholangiocarcinoma or gall bladder carcinoma 4. Measurable or assessable disease according to RECIST 1.1 5. Documented disease progression after prior gemcitabine or gemcitabine containing therapy, in locally advanced or metastatic setting. Examples of permitted therapies include, but are not limited to: a) Single agent gemcitabine b) Any one gemcitabine-based regimen, with or without maintenance gemcitabine 6. ECOG performance status 0-1 7. Adequate blood count, liver-enzymes, and renal function: • ANC > 1,500 cells/µL without the use of hematopoietic growth factors; and • Platelet count ≥ 100 x 109/L (>100,000 per mm3) and • Hemoglobin > 9 g/dL (blood transfusions are permitted for patients with hemoglobin levels below 9 g/dL) • Serum total bilirubin ≤ 3x upper normal limit (ULN) (biliary drainage is allowed for biliary obstruction; elevated bilirubin should be caused by obstruction not impaired liver function as assessed by albumin and INR values): • Albumin levels ≥ 3.0 g/dL • 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 • AST (SGOT)/ALT (SGPT) ≤ 5 x institutional upper limit of normal • Serum Creatinine ≤ 1.5 x ULN and a calculated glomerular filtration rate ≥ 30 mL per minute 8. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of treatment. 9. Subject is willing and able to comply with the protocol (including contraceptive measures) for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
Exclusion criteria	1. Active CNS metastases (indicated by clinical symptoms, cerebral oedema, steroid requirement, or progressive disease); patient should have been off steroids for at least 28 days prior to starting study therapy 2. Clinically significant gastrointestinal disorder including bleeding, inflammation, occlusion, or diarrhoea > grade 1 3. History of any second malignancy in the last 5 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years. 4. Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumour fever may be enrolled), which in the

	investigator's opinion might compromise the patient's participation in the trial or affect the study outcome. 5. Premalignant hematologic disorders, e.g. myelodysplastic syndrome 6. Pre-esxisting lung disease 7. Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment 8. History of hypersensitivity to any of the study drugs or any excipient (nal-IRI, other liposomal products, fluropyrimidines or leucovorin) 9. Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy 10. Severe non-healing wounds, ulcers or bone fractions 11. Evidence of bleeding diathesis or coagulopathy 12. Major surgical procedures, except open biopsy, nor significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgical procedure during the course of the study except for surgery of central intravenous line placement for chemotherapy administration. 13. Medication that is known to interfere with any of the agents applied in the trial. 14. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are:implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner]. 15. Known Gilbert-Meulengracht syndrome 16. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results 17. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 5 half-lifes of previously used trial medication, whichever is of longer duration. 18. Previous enrollment or randomization in the present study (does not include screening failure). 19. Previous enrollment in the NIFE trial [AIO-YMO/HEP-0315] 20. Involvement in the planning and/or conduct of the study (applies to both Baxalta staff and/or staff of sponsor and study site) 21. Patient who might be dependent on the sponsor, site or the investigator 22. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 23. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
Investigational agents and active comparators	• IRINOTECAN LIPOSOME (MM-398, nal-IRI) • 5-Fluorouracil, • leucovorin (calcium folinate)
Treatment schedule	<u>Experimental intervention (Arm A):</u> • nal-IRI 80 mg/m^2 as a 1.5 hour infusion • 5-FU 2400 mg/m^2 as 46 hour infusion • leucovorin 400 mg/m^2 as 0.5 hour infusion • Cycle q2w

	Control intervention – standard arm (Arm B): • 5-FU 2400 mg/m^2 as 46 hour infusion • leucovorin 400 mg/m^2 as 0.5 hour infusion • Cycle q2w In both study arms treatment continues until progressive disease or intolerable toxicity or withdrawal of consent. **Key study procedures (and routine procedures):** • Tumor assessment according to standard of care Q6W • Monitoring of serum tumor markers (Ca19-9, CEA, CRP) before and during therapy. • Blood sampling of 35 mL Q6W for translational research
Primary endpoint	Progression-free survival
Secondary endpoints	• Overall survival • Objective response rate (ORR) • Safety (type, grade and frequency of AEs/SAEs) • QoL – EORTC QLQ C30
Exploratory objectives and endpoints	To assess prognostic biomarker in the serum and in tumor tissue and correlation with survival and response to treatment: • Ca-19-9, CEA, CRP serum levels before the beginning of treatment and during treatment. • Immunohistochemistry of Carboxylesterase (CES) 1 and 2 before treatment • Whole blood and plasma will be collected to potentially identify factors that may correlate with tumour response, sensitivity or resistance to nal-IRI.
Randomization procedure	1:1 Stratified permutated block randomization will be applied to ensure balanced prognostic groups. The stratification parameter will be tumor localization: • Intrahepatic CCA (ICCA) • Extrahepatic CCA (ECCA) • Gallbladder CA (GB)
Rationale Hypothesis	Cholangio-/ Gallbladdercarcinoma (CCA) is an epithelial cancer originating from the bile ducts with features of cholangiocyte differentiation. CCA are rare tumours comprising only 3% of gastrointestinal tumours and having an overall incidence of less than 2/100 000 (Berqquist A et al. 2015). However, they are the second most common primary hepatic malignancies, accounting for approximately 20% of the deaths from hepatobiliary cancer, which cause 13% of the total cancer mortality worldwide. Epidemiologic studies suggest its incidence is clearly increasing in Western countries during the last decades (Plentz RR et al. 2015, Berqqist A et al. 2015). The only curative option for patients with CCA is surgical resection. Unfortunately, most CCA remain clinically silent until the advanced stages. At advanced stage, CCA has a devastating prognosis. There are only limited numbers of studies about the systemic treatment options for biliary cancers. The combination of cisplatin with gemcitabine is the standard first-line chemotherapy for patients with unresectable CCA (Valle J et al. 2010; Okusaka T et al. 2010).

	So far, no standardized second-line therapy has been established due to the lack of prospective, randomized controlled trials. However, a systematic review and meta-analysis of phase II data and retrospective analyses recently provided weak evidence for second-line chemotherapy to prolong median progression-free (PFS) and overall survival (OS) (Lamarca A et al. 2014). In clinical practice, a combination of 5-fluorouracil (5-FU)-based chemotherapy alone or in combination with either irinotecan or oxaliplatin is most commonly administered rather than best supportive care (BSC). Regarding therefore this clinical standard from an ethical point of view, an evaluation of novel therapies within clinical trials requires a control against a 5-FU treatment rather than BSC. Nanoliposomal irinotcean (Nal-Iri) significantly improves overall and progression-free survival and response rate (RR) in combination with 5-FU compared to 5-FU alone in patients with metastatic pancreatic cancer after failure of gemcitabine treatment providing a rationale for potential efficacy in CCA as well (Chen LT et al. 2015). **Research hypothesis:** We hypothesize that the addition of nal-IRI to 5-FU improves progression-free survival (PFS) compared to 5-FU in patients with advanced, unresectable and metastatic cholangio- and gallbladder carcinoma after failure to respond to a gemcitabine treatment.
Safety data	• Treatment Emergent Adverse Events according to CTC 4.03 • Frequency of abnormal laboratory parameters
Sample size estimation	Assumptions: The median PFS achieved with a combination of nal-IRI with 5-FU is estimated to be 3 months. The historical median PFS for 5-FU/FA is 1.5 months. The experimental therapy arm would be rated as insufficiently active, if the true median PFS is shorter than 3 months, as this corresponds to the efficacy of 5-FU alone. On the other hand, the experimental therapy would be considered to be a highly promising candidate for further development, if the true median PFS is 3 months or longer. Patient accrual is conducted for 24 month; treatment and follow-up are estimated to be 7 month on average per patient. With these assumptions a two-sided logrank test with an overall sample size of 99 subjects (49 in the control group and 50 in the experimental group) achieves a 90.3% power at a 5% significance level to detect a hazard ratio of HR=0.5 when the control group median survival time is 1.5 month. The study lasts for 31 month of which subject accrual (entry) occurs in the first 24 month. The proportion dropping out is 0.004 (equals 5% per year). In order to achieve balanced treatment arms it is proposed to recruit **N=100** patients into the study. For the final efficacy analysis a total of 96 observed events are required.
Study plan / time lines	First Patient In (FPI): Q4/2017 Last Patient In (LPI): after approx. 24 months Last Patient Last Visit (LPLV): after approx. 27 months End of follow-up period after LPLV: after approx. 31 months Study report: after approx. 42 months Publication: after approx. 45 months

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

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)	
Studiennummer:	AIO-YMO/HEP-0316 - IRIBIL	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 – 2019	
Patienten	geplant: 56	aktuell eingeschlossen: 13
Zentren	geplant:	initiiert:
Weitere Zentren:	sind leider nicht möglich!	
Letzte Aktualisierung	Okt. 2020	

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, 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:	Initiated
Rekrutierungszeitraum:	28.10.2020-28.10.2021, First patient in planned in October 2020
Weitere Zentren:	Open for participation
Zentren:	planned: 40 initiated: 7
Patienten:	200 patients (approximately 40 patients per disease type) enrollments: 0
Letzte Aktualisierung	October 2020

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School (MHH) Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover Tel.: +49 176 1 532 9590 Email: vogel.arndt@mh-hannover.de
TRIAL OFFICE	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Bianca Zäpf Tel: +49 69 / 7601-4636 Email: zaepf.bianca@ikf-khnw.de
SPONSOR	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
CONDITION	All participants are patients diagnosed with hepatocellular cancer (HCC) or intra-/extrahepatic cholangiocellular carcinoma (CCA) or gallbladder carcinoma (GBCA) or pancreatic cancer (PanCa) or esophagogastric cancer (EC/GC).
OBJECTIVE(S)	The objectives of this study are to assess the distribution of mutations (incl. TMB and MSI status) in systemically treated patients with locally advanced or metastatic HCC, intra- and extrahepatic CCA, GBCA, PDAC and gastric cancer. Another important objective is to evaluate whether and how many patients are treated by their investigators based on their genomic profiles. Additionally, we aim to evaluate the heterogeneity of targetable alterations in paraffin specimen vs. cfDNA.
INTERVENTION(S)	Biobanking, Genetic Analysis via FoundationOne CDx Liquid and FoundationOne CDx Solid Tumors (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 Endpoint: - Frequency of targetable* mutations (incl. TMB and MSI status) in the pooled patient population (primary). Secondary Endpoints: - Frequency of targetable* mutations (incl. TMB and MSI status) per disease group. - Number of patients receiving therapies based on their genomic profiles - Number of differences (heterogeneity) in targetable alterations in paraffin specimen vs. cfDNA *defined as alternations with actionability excluding K-RAS as its frequency is well described in the literature and it is very frequent in some diseases like pancreatic cancer.
STUDY TYPE	PLATON is a prospective, multicentre, observational cohort study with biobanking. The study does not define any medical intervention and does not evaluate the efficacy or safety of the treatment decision made by the investigator.
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: 12 months Maximum duration of trial: 24 months
PARTICIPATING CENTERS	Initiation is ongoing - 40 sites are planned

Interdisziplinäre Arbeitsgruppe Hodentumoren

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 2022
Patienten:	geplant: 70 – 75 Pat. in Deutschland (420 international) aktuell eingeschlossen: 38 in D
Zentren:	12 Zentren in Deutschland
Weitere Zentren:	Vorerst nicht geplant
Letzte Aktualisierung	Oktober 2020

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: Prof. Dr. med. Anja Lorch 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 Univ.-Prof. Dr. med. Anja Lorch FÄ Hämatologie und Onkologie anja.lorch@usz.ch
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 38 Patienten in D eingeschlossen)

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

AIO-Studie		
Studiennummer/-Code:	AIO-KRK-0212 - PanaMa	
Status:	Rekrutierung	
Rekrutierungszeitraum	2014 – 2020	
Zentren:	geplant:	initiiert: 88
Patienten:	geplant: 272 rand.	aktuell: 258 rand.
Weitere Zentren:	Leider nicht mehr möglich	
Letzte Aktualisierung	Oktober 2020	

Study design	Phase II, randomized, multi-center, open-label, parallel-group	
National Coordinating investigator	Prof. Dr. med. Dominik Paul Modest	
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534435; Fax: +49 30 322932926	
Translational research committee	Prof. Dr. Stefan Kasper, Prof. Dr. Dominik Modest, Prof. Dr. Sebastian Stintzing, Dr. Tanja Trarbach.	
Quality of life committee	Dr. T. Trarbach	
Status:	• 88 Study Sites initiated • 383 Patients enrolled • 258 Patients randomized	
Duration of study	Duration of accrual Final Analysis of primary study endpoint with 218 events: End of FU (observation period of at least 24 months after randomization for each patient): End of study:	84 months 88 months after start of enrollment 108 months after start of enrollment 24 months after last randomization
Total number of centers	Approx. 95	
Study population	Patients with metastatic colorectal cancer (wild-type RAS) in palliative first-line therapy	

Primary objective	To assess the efficacy of panitumumab plus 5-FU/ FA as maintenance after an induction treatment of 12 weeks with mFOLFOX6 plus panitumumab in the first-line treatment of RAS wild-type metastatic colorectal cancer patients compared to 5-FU/ FA maintenance alone in terms of progression-free survival.
Secondary objectives	To compare maintenance arms with respect to: • Time from randomization until failure of treatment strategy (death/ progression) • Progression-free survival of re-induction • Objective response after 12 weeks of induction chemotherapy • Objective best response during maintenance and re-induction • Overall survival measured from time of randomization and from time of registration • Safety • Health and skin related Quality of life
Exploratory objectives	• Translational research parameters as defined in the respective section • Central review of CT/MRI scans • Depth of response (during induction and maintenance therapy)
Planned sample size	Approx. 400 patients will be enrolled to reach the planned number of 272 randomizations.
Inclusion criteria	• Signed written informed consent • Male or female ≥ 18 years of age • Histologically proven metastatic colorectal cancer • Molecular testing showing RAS wild-type in colorectal carcinoma cells • Life expectancy > 12 weeks • At least one measurable lesion according to RECIST 1.1 • Adequate bone marrow, liver, kidney, organ and metabolic function o Bone marrow function o leukocyte count > 3.0 × 109/L o ANC > 1.5 x 109/L o platelet count ≥ 100 × 109/L o hemoglobin ≥ 9 g/dL or 5.59 mmol/L (may be transfused or treated with erythropoietin to maintain/ exceed this level) o Hepatic function o Total bilirubin ≤ 1.5 × UNL o ALT and AST ≤ 2.5 × UNL (or ≤ 5 × UNL in presence of liver metastases) o AP ≤ 5 × UNL o Renal function o Creatinine clearance ≥ 50 mL/ according to Cockroft-Gault formula or serum creatinine ≤ 1.5 × UNL o Metabolic function o Magnesium ≥ lower limit of normal o Calcium ≥ lower limit of normal • ECOG performance status 0 - 1 • Women of child-bearing potential must have a negative pregnancy test
Exclusion criteria	• Previous treatment for colorectal cancer in the metastatic setting with the exception that patients with urgent need of immediate treatment (high tumor load, symptoms) may have received one cycle of any FOLFOX regimen (no capecitabine!) in case of yet unconfirmed RAS status. • Previous EGFR-targeting therapy • < 6 months after end of adjuvant therapy (previous chemoradiation for rectal cancer is accepted for inclusion into the trial and does not account as adjuvant therapy) • Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids

	• Chronic inflammatory bowel disease • Peripheral neuropathy ≥ NCI-CTCAE V 4.03 grade 2 • Other previous malignancies with the exception of a history of previous curatively treated basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix or other curatively treated malignant disease without recurrence after at least 5 years of follow-up • Significant disease that, in the investigator's opinion, would exclude the patient from the study • History of cardiac disease; defined as: o Congestive heart failure > New York Heart Association (NYHA) class 2 o Active coronary artery disease (myocardial infarction more than 6 months prior to start of study treatment is allowed) o Cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted) o Uncontrolled hypertension (defined as blood pressure > 160 mmHg systolic and/or > 90 mmHg diastolic on medication) • Patients with interstitial lung disease, e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan • Known HIV, hepatitis B or C infection • Known hypersensitivity reaction to any of the study components • Radiotherapy, major surgery or any investigational drug 21 days before registration • Pregnancy or lactation or planning to be pregnant during treatment and 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 at least an additional 6 months after the end of treatment • Known alcohol or drug abuse • Any condition that is unstable or could jeopardize the safety of the patient and his compliance in the study
Treatment scheme	<u>Induction chemotherapy</u> 6 cycles mFOLFOX6 plus panitumumab for 12 weeks Panitumumab 6mg/kg BW mFOLFOX6: 85 mg/m² Oxaliplatin 2h d1 400 mg/m² folinic acid 2h d1 2400mg/m² 5-FU over 46 h d1 -2 Q2w <u>Maintenance</u> Patient with CR, PR and SD after 12 weeks of induction treatment, will be randomized in a 1:1 ratio to receive either 5-FU/FA + panitumumab q2w (arm A) or 5-FU/FA alone q2w (arm B) until tumor progression. Patient with curative resection within 12 weeks of induction therapy do not qualify for randomization. <u>Re-induction:</u> After tumor progression, a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression <u>Concomitant therapy:</u> Prophylactic management program for panitumumab-related acute and late skin toxicities (see section 6.5.2, 6.5.3)
Primary parameter	Progression-free survival during maintenance therapy defined as time from randomization until disease progression or death, whatever occurs first.
Secondary parameters	• Time from randomization until failure (death/ progression) of treatment strategy

	• Progression-free survival of re-induction • Objective response after 12 weeks of induction chemotherapy • Objective best response during maintenance and re-induction • Overall survival measured from time of randomization and from time of registration • Safety • Health and skin related Quality of life
Exploratory parameters	Translational research analysis in tumor tissue, circulation tumor cells, circulating tumor DNA and blood cells. These investigations will include DNA, RNA, immunohistochemistry, FISH, Sequencing from tumor/or blood cells as well as evaluations of laboratory markers (tumor markers). Central review of CT/MRI scans for resectability, volumetry and further related parameters (i.e. depth of response etc.)
Study procedures	After the initial screening procedure, eligible patients will be registered for study participation. The patient receives chemotherapy consisting of 6 cycles mFOLFOX6 plus panitumumab every 2 weeks. Patients showing CR, PR or SD after induction therapy and qualifying for subsequent maintenance treatment and re-induction treatment with all potential drug components, will be randomized to receive a maintenance regimen of 5-FU/FA + panitumumab or 5-FU/FA alone until tumor progression. After tumor progression a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression. Tumor assessments will be performed 12 weeks after treatment start with induction therapy and every 8 weeks during maintenance therapy and re-induction. All patients will have an end of treatment visit 4 weeks (+ 7 days) after the last dose of the study agent. Thereafter, all patients will be followed up for survival every 3 months.
Randomization procedure	Permuted block randomization will be applied to guarantee balanced group numbers throughout enrollment period. To increase homogeneity between treatment arms, randomization will be stratified by 1. Response to induction therapy at time of randomization (CR/PR vs. SD) 2. Prior oxaliplatin-containing adjuvant therapy (yes vs. no) 3. Planned starting dose of panitumumab for maintenance therapy, if patient will be assigned to arm A (full dosage vs. reduced dosage) Randomization will be performed in the subgroup of patients achieving CR, PR or SD 12 weeks after start of induction therapy qualifying for maintenance treatment and re-induction treatment with all potential drug components.
Sample size calculation	With a total number of 218 events (progressions or death, whichever occurs first), a logrank test for testing superiority of progression-free survival with a 10% one-sided significance level will have 80% power to reject the null-hypothesis if the true median progression-free survival times in patients treated with maintenance alone and maintenance plus panitumumab are 7.5 and 10 months, respectively. A total of approx. 400 patients eligible for induction therapy should be accrued for randomisation of 272 patients needed to reach the required number of events.
Planned interim analysis	No confirmatory interim analyses for efficacy with the aim to stop the trial prematurely are foreseen within this study protocol.

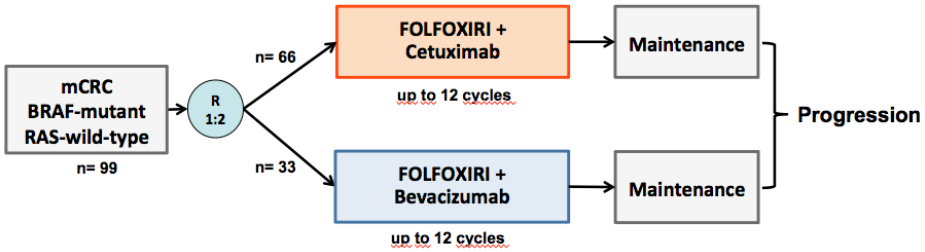
AIO KRK-0116: Randomised study to investigate FOLFOXIRI plus Cetuximab vs. FOLFOXIRI plus bevacizumab as first-line treatment of BRAF-mutated metastatic colorectal cancer (FIRE-4.5)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0116 - FIRE-4.5	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2016 - 2020	
Zentren:	geplant: 150	initiiert: 150
Patienten:	geplant: 108	aktuell eingeschlossen: 101
Weitere Zentren:	Aktuell keine neuen Zentren benötigt	
Letzte Aktualisierung	12.10.2020	

Study Type	Randomisierte, multizentrische Phase-II Studie
Verantwortlicher Studienleiter nach AMG	Klinikum der Universität München Marchioninistraße 15, 81377 München Vertreten durch: Prof. Dr. med. Volker Heinemann
Objectives	Primäres Studienziel: Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 under treatment with FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab. Sekundäre Studienziele: • Progression-free survival (PFS) from randomisation • Overall survival (OS) from randomisation • Investigation of early tumour shrinkage (ETS) and depth of response (DpR) • Study of molecular biomarkers for prediction of sensitivity and secondary resistance of an anti-EGFR treatment with cetuximab (including tumour biopsies and liquid biopsies from blood samples) • Investigation of progressive analysis of tumour marker evolution (CEA and CA 19-9) • Recording of the safety and tolerance (NCI-CTCAE version 5.01 criteria) of the treatment
Objectives	- Objective response rate (ORR) - Progression-free Survival (PFS) and Overall Survival (OS) - Safety and Toxicity
Number of patients	Geplant: 99 Patienten Bereits eingeschlossen: 68 (Oktober 2019)
Key inclusion criteria	- Histologically confirmed, UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer, mCRC), primarily non-resectable or surgery refused by the patient - RAS wild-type tumour status (KRAS and NRAS exons 2, 3, 4) (proven in the primary tumour or metastasis) - BRAF-mutated (V600E) tumour (proven in primary or metastasis) o Age ≥18 years o ECOG performance status 0-1 - Patient's written declaration of consent obtained - Presence of at least one measurable reference lesion according to the RECIST 1.1 – criteria (chest X-ray in two planes or chest CT and abdominal CT 4 weeks or less before randomisation)

	- Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of the tumour material. - Adequate haematopoietic function: o Leukocytes ≥ 3.0 x 10^9/L with neutrophils ≥ 1.5 x 10^9/L o Thrombocytes ≥ 100 x 10^9/L, o Haemoglobin ≥ 5.6 mmol/L (equivalent to 9 g/dL) - Adequate hepatic function: o Serum bilirubin ≤ 1.5 x upper limit of normal (ULN), o ALAT and ASAT ≤ 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT ≤ 5 x ULN) - INR < 1.5 and aPTT < 1.5 x ULN (patients without anticoagulation). Therapeutic anticoagulation is allowed if INR and aPTT have remained stable within the therapeutic range for at least 2 weeks. - Adequate renal function: o Serum creatinine ≤ 1.5 x ULN or creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50ml/min. - Adequate cardiac function: ECG and echocardiogram with a LVEF of ≥55% - No previous chemotherapy for metastatic disease. One cycle (cycle 0) of either FOLFOX, FOLFIRI, or FOLFOXIRI is allowed prior to randomisation. - Time since last administration of any previous adjunctive chemotherapy >6 months - Any significant toxicities of previous treatments must have subsided to grade 0
Key exlusion criteria	- Grade III or IV heart failure (NYHA classification) - Myocardial infarction, unstable angina pectoris, balloon angioplasty (PTCA) with or without stenting within the past 12 months before randomisation - Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study - Additional cancer treatment (chemotherapy, radiation, immune therapy or hormone treatment) during the study treatment. Treatments that are conducted as part of an anthroposophic or homeopathic treatment approach, e.g. mistletoe therapy do not represent an exclusion criterion). - Previous chemotherapy for the colorectal cancer with the exception of adjunctive treatment, completed at least 6 months before entering the study. - Participation in a clinical study or experimental drug treatment within 30 days prior to study inclusion or within a period of 5 half-lives of the substances administered in a clinical study or during an experimental drug treatment prior to inclusion in the study, depending on which period is longest or simultaneous participation in another clinical study while taking part in the study - Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, cetuximab, irinotecan, bevacizumab, oxaliplatin, and chemically related substances and/or hypersensitivity to any of the excipients of any of the aforementioned substances - Known hypersensitivity to CHO (Chinese hamster ovary cells) - cellular products or other recombinant human or humanised antibodies - Patients with confirmed cerebral metastases. In case of clinical suspicion of brain metastases, a cranial CT or MRI must be performed to rule out brain metastases before study inclusion. - History of acute or subacute intestinal occlusion or chronic inflammatory bowel disease or chronic diarrhoea. - Symptomatic peritoneal carcinosis - Severe, non-healing wounds, ulcers or bone fractures - Patients with active infection (including confirmed HIV and/or HBV/HCV infection). In case of clinical suspicion of the presence of HIV or HBV/HCV infection, the latter should be ruled out before study inclusion. - Requirement for immunisation with live vaccine during the study treatment. - Uncontrolled hypertension - Marked proteinuria (nephrotic syndrome) - Arterial thromboemboli or severe haemorrhage within 6 months prior to randomisation (with the exception of tumour bleeding before tumour resection surgery)

	- Haemorrhagic diathesis or tendency towards thrombosis - Known DPD deficiency (specific screening not required) - Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required) - History of a second malignoma during the 5 years before inclusion in the study or during participation in the study, with the exception of a basalioma, spinalioma or cervical carcinoma in situ, if these were treated curatively. - Known history of alcohol or drug abuse - A significant concomitant disease which, especially chronic hepatic or renal disease, chronic inflammatory or autoimmune diseases, in the investigating physician's opinion, rules out the patient's participation in the study - Absent or restricted legal capacity
Scheme of therapy	**FOLFOXIRI plus bevacizumab up to 12 cycles** one cycle (cycle duration 14 days) consists of: • Irinotecan 150 mg/m² iv, 30 - 90 min. day 1 • Folinic acid (racemic) 400 mg/m² iv, 120 min. day 1 • Oxaliplatin 85mg/m² day 1 • 5-FU 3000 mg/m² iv over 48 h days 1-2 • Bevacizumab 5 mg/kg BW iv over 30 to 90* min day 1 **FOLFOXIRI plus cetuximab up to 12 cycles** one cycle (cycle duration 14 days) consists of: • Irinotecan 150 mg/m² iv, 30 - 90 min. day 1 • Folinic acid (racemic) 400 mg/m² iv, 120 min. day 1 • Oxaliplatin 85mg/m² day 1 • 5-FU 3000 mg/m² iv over 48 h days 1-2 • Cetuximab initially 400 mg/m² with infusion rate of ≤5 mg/min., subsequently 250 mg/m² iv with infusion rate of ≤10 mg/min.days 1+8 **Study design**  **Primary Objective:** Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 during treatment with FOLFOXIRI plus bevacizumab versus FOLFOXIRI plus cetuximab.
Criteria for evaluation	After treatment week 8, 16, 24 and every 12 treatment weeks thereafter tumor response evaluation according to RECIST 1.1
Rationale	The question of the right treatment for BRAF-mutated colorectal cancer is currently the subject of scientific discussion. No clinical data are available to date for treatment with FOLFOXIRI plus bevacizumab. A retrospective analysis of 10 patients with BRAF-mutated tumours was able to show that it is possible to achieve a response (ORR) in 90% (9 patients), a median PFS of 12.8 months and a median OS of 23.8 months [Masi G et al Lancet Oncol 2010]. A validation study based on 15 patients was able to confirm the efficacy in BRAF-mutated patients of FOLFOXIRI plus bevacizumab, which resulted in a tumour response of 60%, a median PFS of 9.1 months and a median OS of 24.1 months [Loupakis F. et al Eur J Cancer 2014]. Furthermore, retrospective data from the TRIBE study are available, which suggest greater efficacy of FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab in 28 patients with BRAF-mutated tumours [Cremolini C et al Lancet Oncol 2015]. In this case, it was

	possible to demonstrate response rates of 56% versus 42%, median PFS times of 7.5 months versus 5.5 months and median OS times of 19.0 months versus 10.7 months, repectively [Cremolini C et al Lancet Oncol 2015]. However, none of the differences reached the significance level, owing to the small number of cases. Given the study design, it is not possible to make any statement concerning the additional benefit of bevacizumab in combination with FOLFOXIRI. A pooled retrospective assessment of the TRIP and MCBETH studies is available for colorectal tumour patients treated with FOLFOXIRI plus anti-EGFR antibodies [Salvatore L et al Annaös of Oncology (2014) 25 (suppl_4)]. Only RAS/BRAF wild-type patients were assessed in this case. The response rates were around 82% versus 71 in comparison of anti-EGFR plus FOLFOXIRI with FOLFOXIRI plus Bevacizumab. PFS and OS data were not presented.
Statistik	This is a randomised, phase II trial, intended to study the efficacy of the two regimens - FOLFOXIRI plus cetuximab or FOLFOXIRI plus bevacizumab - as part of first-line treatment with reference to the endpoint of tumor response (ORR according to RECIST 1.1) in patients suffering from BRAF-mutant colorectal cancer. The efficacy of FOLFOXIRI plus cetuximab will be assessed as promising if: • The null hypothesis (ORR in the FOLFOXIRI plus cetuximab arm ≤ 55%) can be rejected at a significance level of 0.1 and • Response (ORR) in the FOLFOXIRI plus cetuximab arm is greater than in the FOLFOXIRI plus bevacizumab arm. Hence, the hypotheses to be tested are: • H0: ORR (arm B) ≤ 55% • H1: ORR (arm B) ≥70% Since an ORR of ≥70% is expected in the FOLFOXIRI plus cetuximab arm, 53 patients are required in the FOLFOXIRI plus cetuximab arm in order to reject the null hypothesis with a power of 80% at a significance level of 0.1 (two-stage design according to Fleming with 20 patients in the first stage and 53 patients in the second stage). The null hypothesis would be rejected if at least 17 out of the first 20 patients (85%) or at least 33 patients (62.5%) in the second stage (total evaluable n=53) show a tumour response according to RECIST 1.1 (partial (PR) or complete response (CR)) and, at the same time, response (ORR) in the FOLFOXIRI plus cetuximab arm is numerically greater than in the FOLFOXIRI plus bevacizumab arm. If less than 12 patients of the first 20 patients show tumor response according to RECIST 1.1 the study would be terminated due to “futility”. 27 further patients are used as a control arm with the standard recommended therapy of FOLFOXIRI and bevacizumab according to Loupakis et al. (TRIBE study) to investigate efficacy and safety of both study arms.

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

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0117	
Status:	Rekrutiert	
Rekrutierungszeitraum:	09/2018 – erweitert bis 09/2021 (geplant)	
Zentren:	geplant: 35	initiiert: 33
Patienten:	geplant: 196	bereits eingeschlossen: 60
Weitere Zentren:	Sehr erwünscht - auf Anfrage	
Letzte Aktualisierung:	Oktober 2020	

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 35 sites
Primary objective	To assess the rates of progression-free survival at six months calculated from the start of treatment in elderly / frail elderly patients with metastatic colorectal cancer undergoing a 1st line treatment.
Secondary objectives	To compare the treatment arms with respect to: **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 will be recruited.
Target population	Elderly or frail elderly patients with metastatic colorectal cancer scheduled to undergo palliative 1st line chemotherapy
Inclusion Criteria	1. To enter this trial the oncologist has to confirm, that the patient was in his or her opinion not a candidate for standard full-dose combination therapy. Moreover, the oncologist has to state the reason for entering the trial (Advanced age alone versus both age and frailty). As an operational definition for frailty the G8 screening tool will be used upon inclusion of the patient in a standardized manner. Briefly, G8 is an established screening tool that includes seven items from the Mini Nutritional Assessment (MNA) and an age-related item (<80, 80 to 85, or 85 years). The total score can range from 0 to 17. The result on the G8 is considered abnormal if the score is ≤14, indicating a geriatric risk profile. 2. Patients have to have histologically confirmed mCRC with unidimensionally measurable inoperable advanced or 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 ≤ 1 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 > 5 years 3. Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 Days 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) 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 entry. 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. 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.
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, the study will be carried on to the phase-III part of the trial. Description of the terms and conditions to expand the current trial are not part of this protocol. Briefly, a potential phase-III study should aim at showing non-inferiority of 5-FU / aflibercept regarding 6-months PFS rate as primary endpoint. This would allow to include all patients from the phase-II part in the phase-III study in order to save time and patients.
Randomization and stratification procedures	After the initial screening procedure, eligible patients will be randomized in a ratio of 1:1 to receive either mFOLFOX7 or Aflibercept + mLV5FU2. 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 2.15.2 (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 In summary, with 88 evaluable patients in the 5-FU / aflibercept arm and an accrual of 24 months the lower limit of the 95% confidence limit for the 6 months PFS is 42.4%. Randomization of a total 176 patients will be stratified by G8 score and ECOG and will be performed on a 1:1-basis. Assuming a 10% drop out rate a total of 196 patients need to be recruited. Stratification factors: G8 score ≤14 versus 15-17 & 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: 196 Location of sites: Germany

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)

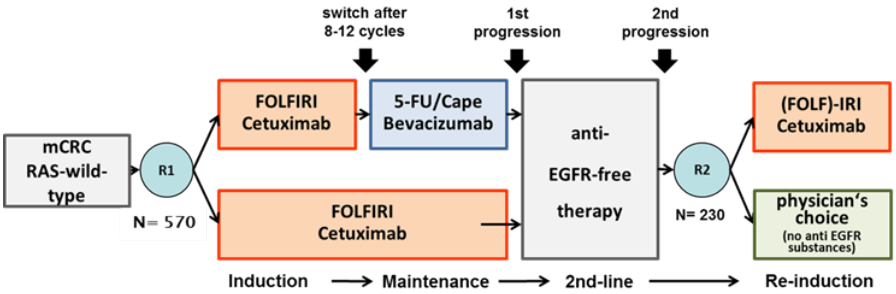
AIO-Studie

Studiennummer/-Code:	AIO-KRK-0114 - FIRE-4	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2015 - 2024	
Zentren:	geplant: 170 (in D und A)	initiiert: 140
Patienten:	geplant: 670	aktuell eingeschlossen: 660
Weitere Zentren:	Aktuell keine neuen Zentren benötigt	
Letzte Aktualisierung	12.10.2020	

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 und FOLFIRI mit CR, PR oder SD >6 Monate angesprochen haben

	Sekundäre Studienziele: • 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 592 Patienten 3rd-line 37 Patienten (Stand: Okt. 2019)
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.

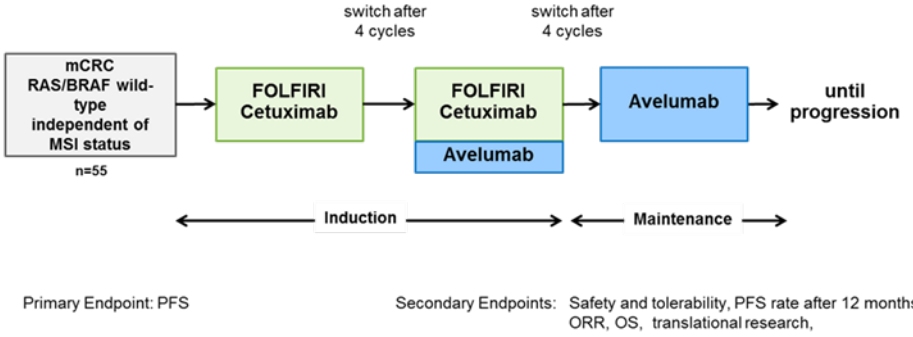
AIO KRK-0118: Avelumab added to FOLFIRI plus Cetuximab followed by Avelumab maintenance in patients with previously untreated RAS wild-type colorectal cancer. The phase II FIRE-6-Avelumab study

AIO-Studie		
Studiennummer/-Code:	AIO-KRK-0118 - FIRE-6	
Status:	Start der Rekrutierung für Q1/2019 geplant	
Rekrutierungszeitraum	2019 - 2020	
Zentren:	geplant: 15	initiiert: 15
Patienten:	geplant: 55	aktuell eingeschlossen: 23
Weitere Zentren:	sind derzeit nicht möglich	
Letzte Aktualisierung	12.10.2020	

Study Type	Einarmige, multizentrische Phase-II Studie
Verantwortlicher Studienleiter nach AMG	Klinikum der Universität München Marchioninistraße 15, 81377 München Vertreten durch: Prof. Dr. med. Sebastian Stintzing
Objectives	<u>Primäres Studienziel:</u> Progression Free Survival (PFS) according to RECIST v1.1 <u>Sekundäre Studienziele:</u> • Safety and tolerability (acc. to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters (oxygen saturation) and feasibility of the regimen) • Progression-free survival (PFS) according to immune-modified RECIST (imRECIST) • Response Rate (RR) according to RECIST v1.1 and (imRECIST) • Progression Free Survival Rate after 12 months of treatment (PFSR@12) (acc. to RECIST v1.1) • Overall survival (OS) • Translational research (PD-L1, PD-1 expression, TIL´s within the tumor specimen, neutrophil/leukocyte ratio and use of antibiotics as predictive marker for avelumab)
Objectives	- Progression-free Survival (PFS) - Objective response rate (ORR) and Overall Survival (OS) - Safety and Toxicity
Key inclusion criteria	- Histologically confirmed, UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer), metastases primarily non-resectable or surgery refused by the patient - RAS wild-type tumour status (KRAS and NRAS exon 2, 3, 4) (proven in the primary tumour or metastasis) - Age ≥18 - ECOG performance status 0-1 - Patients suitable for chemotherapy administration - Patient's written declaration of consent obtained - Estimated life expectancy > 3 months - Presence of at least one measurable reference lesion according to the RECIST 1.1 criteria - Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of tumour material. Molecular profiling of blood samples is optionally performed.

	- Females of childbearing potential (FCBPs) and men must agree to use highly effective contraceptive measures (Pearl index <1) or practice true abstinence from any heterosexual intercourse (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject) for the duration of the study treatment and for at least 6 months after the last administration of study medication. A woman will be considered as being of childbearing potential unless she is at least 50 years old and moreover has gone through menopause for at least 2 years or has been surgically sterilised. - Adequate bone marrow function: - Leukocytes ≥ 3.0 x 109/L with neutrophils ≥ 1.5 x 109/L - Thrombocytes ≥ 100 x 109/L - Haemoglobin ≥ 5.6 mmol/L (equivalent to 9 g/dL) - Adequate hepatic function: - Serum bilirubin ≤ 1.5 x upper limit of normal (ULN) - ALAT and ASAT ≤ 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT ≤ 5 x ULN) - INR < 1.5 and aPTT < 1.5 x ULN (patients without anticoagulation). Therapeutic anticoagulation is allowed if INR and aPTT have remained stable within the therapeutic range for at least 2 weeks. - Adequate renal function: - Creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50 mL/min - Adequate cardiac function: ECG and echocardiogram with a LVEF of ≥ 55% - No previous chemotherapy for metastatic disease. Patient with need of immediate treatment (high tumour load, symptoms) may have received one application of FOLFIRI prior to study entry. - Time interval since last administration of any previous neoadjuvant/adjuvant chemotherapy or radiochemotherapy of the primary tumour in curative treatment intention ≥ 6 months. - Any relevant toxicities of prior treatments must have resolved - Patient affiliated to a public health insurance coverage
Key exlusion criteria	- Proof of a RAS mutation (KRAS or NRAS, exons 2, 3, 4 in the tumor (proven in the primary tumor or metastasis) or absence of testing for RAS mutation - Primarily resectable metastases and the patient wishes for resection - ≥ Grade II heart failure (NYHA classification) - Myocardial infarction, balloon angioplasty (PTCA) with or without stenting, and cerebral vascular accident/stroke within the past 12 months before start of study treatment, unstable angina pectoris, serious cardiac arrhythmia according to investigator's judgement requiring medication. - Pre-existing pulmonary fibrosis or immune pneumonitis - Active autoimmune disease that might be negatively affected by an immune checkpoint inhibitor. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible. - Prior organ transplantation, including allogeneic stem cell transplantation - Current use of immunosuppressive medication, except for the following: - Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); - Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication). - Pregnancy (absence of pregnancy to be ascertained by a negative beta hCG test) or breast feeding - Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study - Additional cancer treatment (chemotherapy, radiation, immunotherapy or hormone treatment) during the study treatment in first-line (treatments that are conducted as part of an anthroposophic or homeopathic treatment approach, e.g. mistletoe therapy do not represent an exclusion criterion)

	- Previous chemotherapy for the colorectal cancer with the exception of adjuvant treatment, completed at least 6 months before entering the study - Toxicity > Grade 1 that has not yet resolved, attributed to a previous treatment or measure for treatment of the CRC. However, alopecia (all grades) and oxaliplatin-induced neurotoxicity ≤ Grade 2 are acceptable. - Participation in a clinical study or experimental drug treatment within 30 days prior to study inclusion or within a period of 5 half-lives of the substances administered in a clinical study or during an experimental drug treatment prior to inclusion in the study, depending on which period is longest or simultaneous participation in another study while taking part in the study - Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, capecitabine, cetuximab, irinotecan, avelumab and chemically related substances and/or hypersensitivity to any of the components in the formulations of the aforementioned substances, including known hypersensitivity reactions to monoclonal antibodies NCI CTCAE Grade ≥ 3. - Known hypersensitivity to Chinese hamster ovary cell (CHO) – cellular products or other recombinant human or humanised monoclonal antibodies - Patients with known brain metastases. In case of clinical suspicion of brain metastasis a cranial CT or MRI must be performed to rule out brain metastasis before study inclusion. - History of acute or subacute intestinal occlusion, inflammatory bowel disease, immune colitis or chronic diarrhoea - Symptomatic peritoneal carcinosis - Severe, non-healing wounds, ulcers or bone fractures - Patients with active infection requiring systemic therapy - Known history of testing positive for HIV or known acquired immunodeficiency syndrome. - Active or chronic Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive; serologic tests required). - Requirement for immunisation with live vaccine under the study treatment. - Haemorrhagic diathesis or known thrombophilia - Known DPD deficiency (specific screening not required) - Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required) - History of a second primary malignancy during the past 5 years before inclusion in the study or during participation in the study, with the exception of a basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ, if these were treated curatively. - Known history of alcohol or drug abuse - Any other severe acute or chronic concomitant disease or medical condition including psychiatric conditions (including recent i.e. within the past year or active suicidal ideation or behavior) or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. - Absent or restricted legal capacity
Scheme of therapy	All eligible patients will receive cetuximab and FOLFIRI until the first follow up examination for the first 4 cycles (2 months). Patients with a cycle 0 of FOLFIRI will also receive 4 cycles of FOLFIRI plus cetuximab within the study. Patients that have not progressed will receive FOLFIRI and cetuximab in combination with avelumab from the fifth cycle onwards for a total of 4 cycles until the second follow up examination. Having not progressed for a total of 8 cycles, patients will then switch to avelumab single agent maintenance until progression of the disease. Study treatment will therefore be discontinued if one of the following events occur: • Progressive disease (according to RECIST 1.1)

	• Intolerable toxicity • Withdrawal of consent **Initial regimen (4 cycles):** **FOLFIRI plus cetuximab (administration to local standard)** One cycle (cycle duration 14 days) consists of: Irinotecan 180 mg/m² iv — day 1 Folinic acid (racemic) 400 mg/m² iv — day 1 5-FU 400 mg/m² bolus — day 1 5-FU 2400 mg/m² iv over 46h — day 1-2 Cetuximab initially 400 mg/m²; subsequently 250 mg/m² iv — day 1 + 8 **Switch after 4 cycles:** **FOLFIRI Cetuximab (administration to local standard) plus Avelumab (for 4 cycles)** One cycle (cycle duration 14 days) consists of: Irinotecan 180 mg/m² iv — day 1 Folinic acid (racemic) 400 mg/m² iv — day 1 5-FU 400 mg/m² bolus — day 1 5-FU 2400 mg/m² iv over 46h — day 1-2 Cetuximab 250 mg/m² iv — day 1 + 8 Avelumab at a dose of 10mg/kg IV — day 1 **Maintenance (starting at cycle 9) until progression:** Avelumab at a dose of 10mg/kg IV day 1 (repeat every 14 days) Study design **FIRE-6 Avelumab Study** **Phase-II Design** 
Criteria for evaluation	During treatment tumor response will be assessed by the investigator according to RECIST v1.1 (MRI (or CT scan if MRI is unavailable) of the chest, abdomen, pelvis and all other sites of disease) every 4 cycles (8 weeks ±7 days) CT and/or MRI scans will be independently reviewed. The results ot the central review will not have an impact on the study treatment.
Rationale	Inhibition of the PD-1/L1 axis has shown to improve survival as single agent in a variety of tumor types (e.g. melanoma and lung cancer) (Robert, Long et al. 2014, Borghaei, Paz-Ares et al. 2015). The efficacy of single agent PD-1/L1 inhibition in patients with highly advanced and treatment refractory MCRC seems to be limited to those with hypermutated tumors characterized by mismatch repair deficiency (Le, Uram et al. 2015).

	After 4-6 months of doublet chemotherapy a de-escalation to a less toxic regimen is needed for most of the patient with mCRC. The addition of Avelumab to a cytotoxic chemotherapy regimen with FOLFIRI plus cetuximab followed by Avelumab maintenance has not been investigated so far. It is known that FOLFIRI plus cetuximab leads to necrosis and therefore tumor antigens that usually are not presented to the host immune system become recognizable. This effect of a triggered immune response after induction treatment with chemotherapy is currently investigated in other trials. The ongoing IMPALA trial (Cunningham, Zurlo et al. 2015) is testing the toll-like receptor (TLR)-9 agonist MGN1703 as maintenance treatment in patients that have responded to an induction doublet chemotherapy. This effect may be enhanced by the fact that Cetuximab in Combination with 5-FU and Irinotecan triggers immunogenic cell death (Pozzi, Cuomo et al. 2016). The lately published data from the interim analysis of the PACIFIC trial using the anti-PD L1 antibody durvalumab after chemoradiation in stage II non-small cell lung cancer (NSCLC) proofed the concept of an anti-PD L1 antibody as a maintenance treatment after chemoradiation. Durvalumab prolonged PFS significantly (HR 0.52, $p<0.001$) (Antonia, Villegas et al. 2017). The study is not limited to MSI-h and should be able to demonstrate Avelumab efficacy in MSS tumors when used in combination with cetuximab plus FOLFIRI. The lately presented data on the use of atezolizumab plus cobimetinib (NCT01988896, IMblaze370) (Bendell, Bang et al. 2018) in in heavily pretreated MSS mCRC patients showed a 12-month OS rate of 43% which was higher than the 24% seen for Regorafenib in the pivotal CORRECT trial. But its primary endpoint, a benefit in median OS, was not met (Bendell, Ciardiello et al. 2018). As the IMblaze370 trial was conducted in heavily pretreated patients without the combination of chemotherapy, it is worthwhile to test this concept in MSS and MSI-h mCRC. Furthermore part of the cetuximab as of the avelumab effect can be attributed to ADCC (antibody derived cellular cyctotoxicity) with again leads to necrosis of tumor cells and the release of antigens. Both effects together may be able to present enough tumor-neo-antigens. To boost the effect, Avelumab is able to inhibit the PD-1 derived inhibition of cytolysis and other tumor cells within the body may be attacked by the immune system which leads to an anti-tumor effect represented by a prolonged PFS and finally OS of the patients. Patients will be included independent of microsatellite instability (MSI) status. It is expected that within the trial population the MSI rate will be as reported in stage IV MCRC with about 5% (Venderbosch, Nagtegaal et al. 2014).
Statistik	It is intended to study the progression-free survival within the context of the first-line treatment and maintenance trial. The goal of this phase-II study is to detect non-sufficient treatment timely. With regard to FOLFIRI plus cetuximab a median PFS of 10 months has been reported before (FIRE-3 study) Thereby a median PFS of at most 8 months will be rated as non-sufficient, in contrast a median PFS of 12.88 months as sufficient.. Hence the hypotheses to be tested are: H0: median PFS ≤ 8 months H1: median PFS ≥ 12.88 months PFS = period between start of treatment and progression or death. According to this hypothesis formulation, the tests of the objective (PFS) will be performed in line with a one-sided logrank test.

	Since a median PFS of ≥12.88 months is expected, 47 patients are required in order to reject the null hypothesis with a power of 80% at a one-tailed significance level of 0.025 (one sample testing using log-rank test) if an accrual period of 18 months and a minimum follow-up of 18 months is assumed. Due to possible drop-outs, a total of 55 patients (15% drop-out rate) are going to be included into this trial.

AIO-KRK/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:	in Vorbereitung		
Rekrutierungzeit:			
Anzahl Patienten:	geplant: 153	aktuell eingeschlossen:	
Anzahl Zentren:	geplant: 40	initiiert:	
Weitere Zentren:	sind erwünscht		
Letzte Aktualisierung	Okt. 2020		

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: o ECOG 0 vs. ECOG 1/ECOG 2 o 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

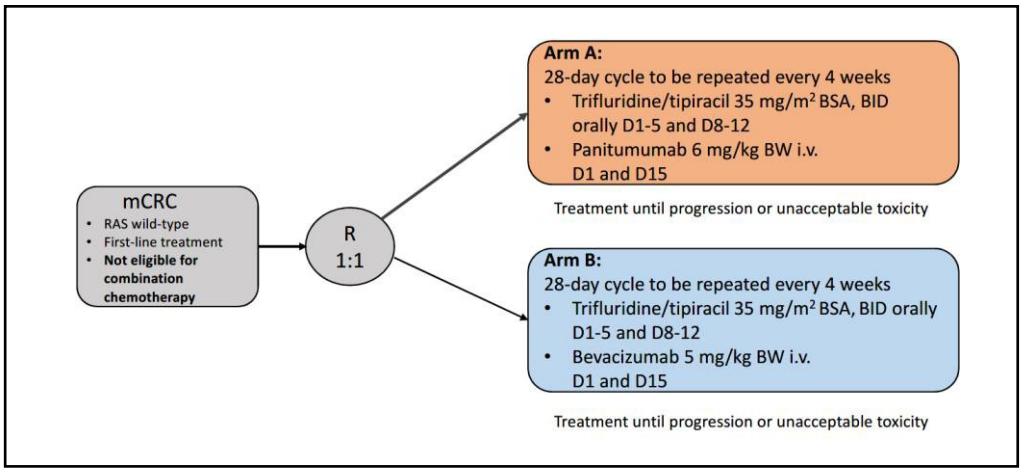
Inclusion criteria	1. Patient's signed informed consent 2. Patients ≥ 18 years at the time of signing the informed consent 3. Histologically confirmed adenocarcinoma of the colon or rectum 4. Metastatic colorectal cancer (mCRC) with at least one measurable lesion according to RECIST 1.1 in a computed 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 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. 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. Prophylactic anticoagulation is permitted if the patient receives the medication at a stable dose for at least 2 weeks before randomisation. 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: o during screening within 21 days before randomisation, o at the first restaging, o 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). 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). 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. An exact binomial 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%, 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: QIV 2020 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 QIV 2028
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:



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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:	in Vorbereitung
Rekrutierungszeit:	von: Q3/2020 bis: Q3/2022
Anzahl Zentren:	geplant: 40 aktuell initiiert: 0 aktiv rekrutierend: 0
Weitere Zentren:	sind sehr erwünscht
Anzahl Patienten:	geplant: 130 aktuell eingeschlossen: 0
Letzte Aktualisierung	13.10.2020

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

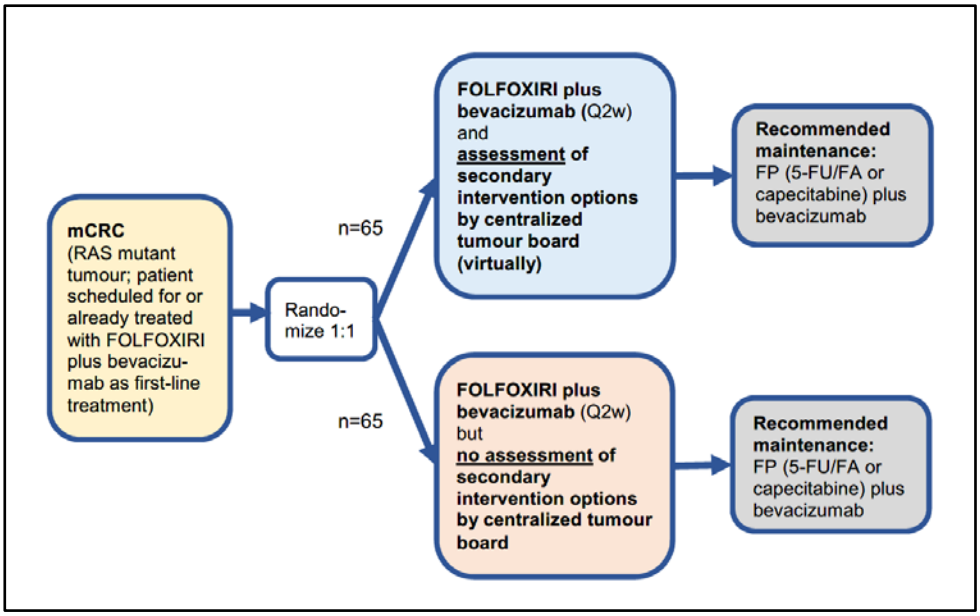
	deputy at the study center. The decision, whether or not any secondary intervention is performed as recommended by the centralized tumour board as well as the kind of interventional procedures is up to the discretion of the treating physicians and surgeons of each patient. Any secondary intervention 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	1. Written informed consent to participate in the study 2. Patients ≥ 18 years at the time of signing the informed consent 3. Histologically confirmed (in primary tumour or metastasis) UICC stage IV metastatic adenocarcinoma of the colon or rectum (mCRC) with primarily unresectable metastases 4. RAS mutant CRC (as determined by local pathology in tissue of primary tumour or metastasis) 5. At least one measurable lesion according to RECIST version 1.1 in a CT/MRI scan performed within 4 weeks prior to randomisation 6. ECOG performance status 0-1 7. 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. 8. Completion of adjuvant therapy for colorectal cancer > 3 months prior to study entry. 9. Patient's ability for treatment with FOLFOXIRI and bevacizumab according to participating physician's judgement.
OUTCOME(S)	**Primary endpoint** • Rate of patients in whom secondary interventions (e.g. resection, ablation treatment or combination of both) are performed in curative intent **Secondary endpoints** **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 Q3 2020 to Q3 2024 Planned first patient first visit: Q3 2020 Planned recruitment period: 24 months; estimated Q3 2020 to Q3 2022 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: Q3 2024
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 Vorbereitung Einreichung bei Ethik / Behörde geplant für Q4 2020		
Rekrutierungszeit:	von: 2021	bis: 2022	
Anzahl Zentren:	geplant: 25	aktuell initiiert: 0	aktiv rekrutierend: 0
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant: 55	aktuell eingeschlossen: 0	
Letzte Aktualisierung	16.09.2020		

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. 210, 1167 Kensington Crescent NW Calgary, Alberta Canada T2N 1X7
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 Q2/2020 geplant	
Zentren:	geplant: Phase I 3 / Phase II 10	initiiert:
Patienten:	geplant: Phase I 18 / Phase II 66	aktuell eingeschlossen:
Weitere Zentren:	sind erwünscht, Abfrage über AIO-Verteiler folgt in Kürze	
Letzte Aktualisierung	Oktober 2020	

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
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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	Evaluation of D-/L-methadone as a chemosensitizer for conventional mFOLFOX6 chemotherapy
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 Q4/2020		
Rekrutierungszeit:	von: Q4/2020		bis: Q2/2022
Anzahl Zentren:	geplant: 40	aktuell initiiert: 0	aktiv rekrutierend: 0
Weitere Zentren:	ja		
Anzahl Patienten:	geplant: 140	aktuell eingeschlossen: 0	
Letzte Aktualisierung	Oktober 2020		

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
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CONDITION	colorectal cancer
DESIGN	This is a 2-stage study: The main study is designed as an open-label, prospective, randomized study of atezolizumab with or without the multi-targeted immunomodulatory IMM-101 in patients with MSI high stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option and where atezolizumab will be administered post-operatively with or without IMM-101 The sub-study is designed as an open-label, prospective peri-operative therapy study of atezolizumab with IMM-101 in patients with MSI high clinical stage III colorectal cancer (as defined by the pre-operative CT/MRI-scans) for whom oxaliplatin regimens are not a viable treatment option. Atezolizumab and IMM-101 will be administered pre- and post- operatively.
INDICATION	patients with MSI high stage III colorectal cancer who are ineligible for oxaliplatin based chemotherapy
STUDY OBJECTIVES	Primary objective: In the Main study, the primary objectives are: • To assess the efficacy of adjuvant atezolizumab with or without IMM-101 in patients with MSI high stage III colorectal cancer who are ineligible for oxaliplatin based chemotherapy in terms of tumor specific disease free survival (DFS) rate at 3 years defined as the proportion of patients without relapse or tumor related death after enrollment by intention to treat analysis. Secondary objectives:

	• 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 assessed by the incidence of adverse events (AEs) and adverse events of special interests (AESI) overall and by severity, and serious adverse events (SAEs). Severity will be assessed using the National Cancer Institute-Common Toxicity Criteria (CTCAE) for Adverse Events, v. 5.0 (CTCAE v5.0). • To assess the efficacy of perioperative atezolizumab with IMM-101 in patients with MSI high clinical stage III colorectal cancer based on preoperative CT/MRI scan in terms of pathological complete (pCR) or subtotal (<10% vital tumor cells) regression after 6 weeks treatment in an explorative sub-study with 20 patients • To estimate the ctDNA free rate defined as the proportion of patients without detectable ctDNA after 12 months • To estimate 1,2 and 5 year tumor specific DFS rate • To estimate Overall Survival (OS) defined as time from inclusion into the trial to death • To estimate 1,3 and 5 year OS rate • Patient reported outcome (PRO), Health related Quality of life (HRQoL) assessed by the EORTC-QLQ-C30, Geriatric assessment by the G8 screening tool; additional assessment if G8 score ≤14: by Charlson Comorbidity score (CCI), Cumulative Illness Rating Scale Geriatric Version (CIRS-G) , Instrumental Activities of Daily Living (ADL / IADL), Mini Mental State Examination (MMSE), Geriatric depression scale (GDS), Timed-up-and-go-Test (TUG), Short Physical Performance Battery (SPPB), 2 question depression screen (Whooly) • Matched pair analyses with dMMR CRC patients registered in the COLOPREDICT registry, which were treated with a fluoropyrimidine or which did not received an adjuvant therapy • Translational projects
SCHEME OF THERAPY	**Arm A** ▪ atezolizumab 840mg i.v., q2w for 12 months; start of the therapy 3-10 weeks after the resection **Arm B** ▪ atezolizumab 840mg i.v., q2w for 12 months; start of the therapy 3-10 weeks after the resection ▪ IMM-101 1.0mg intradermally 7 days before the first atezolizumab dose, then 0.5mg q2w for a total of 2 doses and subsequently q4w for 12 months **Explorative perioperative sub-study (20 patients)** ▪ IMM-101 1.0mg intradermally day -35 before the planned resection (7 days before the first administration of atezolizumab) and subsequently 0.5mg q2w for two doses preoperatively, in the postoperative setting 1.0mg IMM-101 will be given 7 days before the first postoperative dose of atezolizumab, then 0.5mg q2w for a total of 2 doses and subsequently 0.5mg q4w for 12 months, start of the adjuvant therapy 3-10 weeks after the resection ▪ atezolizumab 1200mg i.v., q3w for two times preoperatively (start 7 days after die first IMM-101 dose) and subsequently 840mg i.v. q2w for up to 12 months after resection (start 7 days after the first postoperative administration of IMM-101)
STUDY RATIONALE	The median age of patients with newly diagnosed CRC is >70 years. Mismatch repair- deficient (dMMR) cancer with microsatellite instability (MSI) is more frequent in elderly patients due to a higher rate of methylated hMLH1 gene promoter. In the German COLOPREDICT registry the rate of dMMR tumors is up to 25% in stage II and 20% in stage III CRC. Median age of patients with dMMR CRC is 77 years in this registry (Reinacher-Schick et al., 2017). Oxaliplatin/fluoropyrimidin based adjuvant chemotherapy is the standard of care in stage III CRC. However, in patients >75 years oxaliplatin is not recommended

	by several guidelines and often not feasible due to underlying comorbidities in elderly patients (Schmiegel et al., 2017). The relapse rate in patients with stage III CRC not treated with oxaliplatin based adjuvant chemotherapy is relatively high with a 3 years DFS-rate and a 5 years OS rate of only 60% (Gill et al., 2014). In the COLOPREDICT register the 3 years DFS rate for patients >70 years with stage III dMMR tumors treated with adjuvant fluorpyrimidin therapy is 63% (95%CI: 53-75%) and the 5 year OS rate is 58% (95%CI: 47-71%) (Reinacher-Schick, unpublished data). Upon other checkpointinhibitors (CPI), the PD-L1 antibody atezolizumab demonstrated impressive activity and good tolerability in patients with metastatic dMMR CRC (Hochster HS et al., 2017). IMM-101 is a systemic immune modulator containing heat-killed *Mycobacterium obuense*. Results from *in vivo* and *ex vivo* non-clinical studies suggest that IMM-101 modulates the innate and adaptive immune systems. IMM-101 contains microbial-associated molecular patterns (MAMPs) that activate a defined selection of pathogen recognition receptors (PRRs) including toll like receptor (TLR) 1/2 on innate immune cells like dendritic cells (DCs) (Bazzi et al. 2017, Galdon et al. 2019). IMM-101 activation of immature DCs leads to the skewed maturation of activated cDC1, of which activation predominantly induces a type 1 immune response defined by the generation and maturation of IFN-γ, perforin and granzyme producing CTLs (Galdon et al., 2019), required for effective tumor cell killing. IMM-101 induced cDC1 activation also results in the generation of activated IFN-γ producing Th-1 cells NK, NKT and γδ-T cells (Fowler et al., 2014; Galdon et al., 2019), which can kill tumor cells by different mechanisms. Activated γδ-T cells are efficient antigen presenting cells (Moser et al., 2017), which may further boost anti-tumor responses. IMM-101 also activates other innate immune cells, including monocytes, which mature into M1 macrophages (Bazzi et al. 2015) that can enhance anti-tumour responses and prevent the formation of immune-suppressive M2 macrophages.. Previous clinical studies demonstrated the safety of IMM-101 as monotherapy and in combination with chemotherapy or CPIs (Stebbing et al., 2012, Dalgleish et al., 2016, Dalgleish et al., 2018). Therefore, atezolizumab with or without IMM-101 could be a promising therapeutic options to improve the unfavorable prognosis of patients with stage III dMMR CRC ineligible for oxaliplatin based adjuvant chemotherapy. In addition, preoperative short time administration of a combination of CPIs in MSI high colorectal cancers induce high rate 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 mismatched repair deficient colon cancer (Chalabi M et al., 2020). Therefore, the combination of atezolizumab and IMM-101 could be a promising strategy especially in MSI high CRC patients who are not candiates for extensive surgery
KEY EXCLUSION CRITERIA	1. Severe infection within 4 weeks prior to randomization, including, but not limited to, hospitalization for complications of infection, bacteremia, 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 2. Distant metastases or residual disease 3. Neoadjuvant radiotherapy or radio-chemotherapy (enrollment of rectal cancer patients without prior radio- or radio-chemotherapy is allowed); prior neoadjuvant radiochemotherapy (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. 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 randomization, 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 mineralocorticosteroids or low-dose corticosteroids for adrenalcortical insufficiency are allowed. 6. Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment 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 computed tomography (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. 7. Co-infection of HBV and HCV Patients with a history of HCV infection but who are negative for HCV RNA by polymerase chain reaction (PCR) will be considered non-infected with HCV. 8. Patient has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) 9. Treatment with a live, attenuated vaccine within 4 weeks prior to randomization, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab. 10. Active tuberculosis (as ruled out by clinical evaluation including medical history, physical examination, radiographic findings on baseline CT/ magnetic resonance imaging [MRI] of chest/abdomen/pelvis; if active tuberculosis is suspected, tuberculosis testing should be performed as per local standard of care). 11. 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 With the following exceptions: 12. Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study. 13. Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study. 14. 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: 15. Rash must cover < 10% of body surface area 16. Disease is well controlled at baseline and requires only low-potency topical corticosteroids 17. 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, which either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial urinary bladder tumor [Ta, Tis and T1]. 19. History of hypersensitivity to any of the study drugs or any excipient 20. Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy 21. Severe non-healing wounds, ulcers or bone fractions 22. Evidence of bleeding diathesis or coagulopathy 23. Major gastrointestinal bleeding within 4 weeks prior to randomization

KEY INCLUSION CRITERIA	Inclusion criteria for the main study: 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 Male or female ≥ 18 years of age 2. Histologically confirmed adenocarcinoma of the colon or rectum 3. R0 resected primary tumor, 4. Pathological Stage III disease 5. ECOG status 0 – 2 6. Ineligible for oxaliplatin based adjuvant chemotherapy or patient's refusal of oxaliplatin based adjuvant chemotherapy 7. Adequate blood count, liver-enzymes, and renal function: – White blood cell count ≥ 3.5 x 10^6/mL – Platelet count ≥ 100 x 109/L (>100,000 per mm^3) – AST (SGOT)/ALT (SGPT) ≤ 5 x institutional upper limit of normal – Serum Creatinine ≤ 1.5 x institutional ULN and a calculated glomerular filtration rate ≥ 30 mL per minute 8. Documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test. For patients with active hepatitis B virus (HBV): HBV DNA < 500 IU/mL obtained within 28 days prior to randomization, and Anti-HBV treatment (per local standard of care) for a minimum of 14 days prior to randomization and willingness to continue treatment for the length of the study 9. 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 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. 11. For females of childbearing potential (FCBP): negative pregnancy test within 14 days before randomization 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 5 months after the last dose of atezolizumab. 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. Inclusion criteria for the sub-study: 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 Male or female ≥ 18 years of age 2. Histologically confirmed adenocarcinoma of the colon or rectum 3. Resectable tumor based on the preoperative CT/MRI-scan for patients, 4. Clinical stage III disease based on a preoperative CT or MRI-scan. 5. ECOG status 0 – 2

	6. Ineligible for oxaliplatin based adjuvant chemotherapy or patient's refusal of oxaliplatin based adjuvant chemotherapy 7. Adequate blood count, liver-enzymes, and renal function: – White blood cell count ≥ 3.5 x 10^6/mL – Platelet count ≥ 100 x 109/L (>100,000 per mm^3) – AST (SGOT)/ALT (SGPT) ≤ 5 x institutional upper limit of normal – Serum Creatinine ≤ 1.5 x institutional ULN and a calculated glomerular filtration rate ≥ 30 mL per minute – Serum Creatinine ≤ 1.5 x institutional ULN and a calculated glomerular filtration rate ≥ 30 mL per minute 8. Documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test. For patients with active hepatitis B virus (HBV): HBV DNA < 500 IU/mL obtained within 28 days prior to randomization, and Anti-HBV treatment (per local standard of care) for a minimum of 14 days prior to randomization and willingness to continue treatment for the length of the study 9. 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 10. Negative HIV Test at screening 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 females of childbearing potential (FCBP): negative pregnancy test within 14 days before randomization 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 5 months after the last dose of atezolizumab. 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.
STATISTICAL ANALYSIS	Main study (randomized part) In the COLOPREDICT registry the 3 years DFS rate for patients >70 years with stage III dMMR tumors treated with adjuvant fluoropyrimidin 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 (A´Hern RP et al., 2001). A Fleming-Single-Stage Design will be used for this study. The anticipated 3 years DFS rate in the control (null hypothesis-H0) is 63% and will be tested against a one-sided alternative. The null hypothesis will be rejected if the true 3 years DFS rate with atezolizumab+/-IMM-101 is 80%. This design yields a type I error rate of 5% and power of 80%. Summary of the parameters:

Parameter	
H_0	3 years DFS rate = 0.63
H_1	3 years DFS rate = 0.80
α	5%
β	20%
power (1- β)	80%

	A study requires 46 subjects to decide whether the proportion surviving without disease relapse, H1, is less than or equal to 63% or greater than or equal to 80%. If the number of responses is 35 or more, the hypothesis that H1 ≤ 0.63 is rejected with a target error rate of alpha=0.05 and an actual error rate of 0.043. If the number of responses is 34 or less, the hypothesis that H1 ≥ 0.8 is rejected with a target error rate of beta=0.2 and an actual error rate of 0,195 [i.e. Power = 80.5%]. Analysis of primary endpoint: The primary endpoint 3year-DFS rate is defined as the proportion of patients being alive without recurrent disease 3 years after randomization. Each arm will be analyzed separately according to the ITT principle (i.e. include all patients randomized into the primary analysis, subjects lost –to-follow-up prior to the 3year landmark will be considered as progressive etc.). Additionally, the primary endpoint will be analyzed in a Per-Protocol-Population. The PP-Population is defined as all randomized ITT subjects who fulfill the following criteria: a) all of the inclusion criteria, none of the exclusion criteria are fulfilled; b)received at least 1 dose of study treatment; c) absence of other major protocol violations such as wrong treatment received. Analyses based on the PP population will serve as sensitivity analyses in order to assess the robustness of the results obtained from the ITT population. To facilitate a PP-analysis, the formal sample size is inflated by 8% to yield 50 patients per treatment arm as the accrual goal for the main study Beyond the formal ITT analysis, primary and secondary endpoints will be compared against real-world data from the COLOPREDICT registry available at the time of primary analysis. To assure the validity of such comparisons a matched pair (e.g. propensity score matching) analyses with dMMR CRC patients registered in the COLOPREDICT registry will be performed, Further statistical analyses are descriptive or explorative. The pathological complete or subtotal regression grade in the neoadjuvant sub-study will be evaluated exploratively. A complete or subtotal (<10% vital tumor cells) regression grade >30% will be considered as clinical meaningful to provide a rationale for further investigation of this strategy. The details of the statistical analysis will be defined in a Statistical Analysis Plan, which will be prepared before database closure.
TRIAL DURATION	Q4/2020-Q2/2022; 1.5 years enrollment, 1 year treatment FPFV Q4/2020 LPLV Q2/2025
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 T3N1 vs T4 or N2 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 BRAF mutated/pMMR localized colorectal cancer (NEOBRAF)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0420 - NEOBRAF	
Status:	In Planung	
Rekrutierungszeitraum:	24 Monate (geplant)	
Zentren:	geplant: 20	initiiert: 0
Patienten:	geplant: 48	aktuell eingeschlossen: 0
Weitere Zentren:	Auf Anfrage	
Letzte Aktualisierung	Oktober 2020	

Coordinating Investigator	Priv. Doz. Dr. med Alexander Stein Hämatologisch-Onkologische Praxis Eppendorf Eppendorfer Landstrasse 42/Orchideenstieg 12; 20249/22297 Hamburg Tel: +49 (0) 40 36035220, Fax: +49 (0) 40 473547 stein@hope-hamburg.de
Sponsor:	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 8145 344 31, Fax +49 30 3229 329 26 info@aio-studien-ggmbh.de
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	20 sites in Germany and 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	• Toxicity (according to NCI CTC AE v5) • Perioperative morbidity and mortality • Disease free survival (according to RECIST v1.1) • 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. • Evaluation of mechanism of relative resistance in patients with less response (about n=20) (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 (n=20)
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. Written informed consent. 31. 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. 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. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma).

	3. Pregnancy or lactation. 4. Known alcohol or drug abuse. 5. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrolment), myocardial infarction (< 6 months prior to enrolment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication. 6. All other significant diseases, which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment. 7. Any psychiatric condition that would prohibit the understanding or rendering of informed consent. 8. Any approved anticancer therapy, including chemotherapy, hormonal therapy or radiotherapy, within 4 weeks prior to initiation of study treatment.
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 (TRG2-4). In non-responding patients (TRG0-1) standard CAPOX will be applied postoperatively.
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), the triplet combination of encorafenib, binimetinib and cetuximab demonstrated superior efficacy in terms of response and survival compared to irinotecan-based chemotherapy and cetuximab (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) (Kopetz, Grothey et al. 2019); however, the study was not powered to compare triplet vs. doublet. Despite the similar OS (with no difference in median OS according to the updated analysis presented at ASCO-GI 2020), 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. Furthermore, in the curative and particular neoadjuvant setting response may have a closer correlation to survival compared to the metastatic setting. The evaluation of the highly efficacious treatment in this prognostically dismal patient subgroup of BRAF mutant (pMMR/MSS) patients is warranted. 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). The proposed study will give the exceptional chance for translation research to evaluate 1) the role of monitoring BRAF V600E in the blood during treatment by ddPCR, 2) the correlation between BRAF levels in the blood and response and 3) the possibility to evaluate mechanisms of resistance in patients with poor/less response.
Sample size estimation and statistical analysis considerations	With neoadjuvant chemotherapy a TRG of at least 2 (moderate regression or more) was achieved in 20% of pMMR/MSS patients treated with chemotherapy. The triplet combination of encorafenib, binimetinib and cetuximab should achieve a TRG of at least 2 in 35% of patients. Thus, by applying a two-sided test with 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 (Data on the TRG rate with BRAF mutants from FOxTROT are awaited within the next months; thus, the statistical assumptions may be adapted based on these data during study protocol generation).

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) Q1/Q2 2021	
Rekrutierungszeitraum:	geplant 2021 – 2022	
Zentren:	geplant:	initiiert:
Patienten:	geplant: 700 in total /200 in D/AT	aktuell eingeschlossen in D:
Weitere Zentren:	weitere Zentren auf Anfrage	
Letzte Aktualisierung	Oktober 2020	

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:
Zentren:	geplant:	initiiert:
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	Mai 2020	

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 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

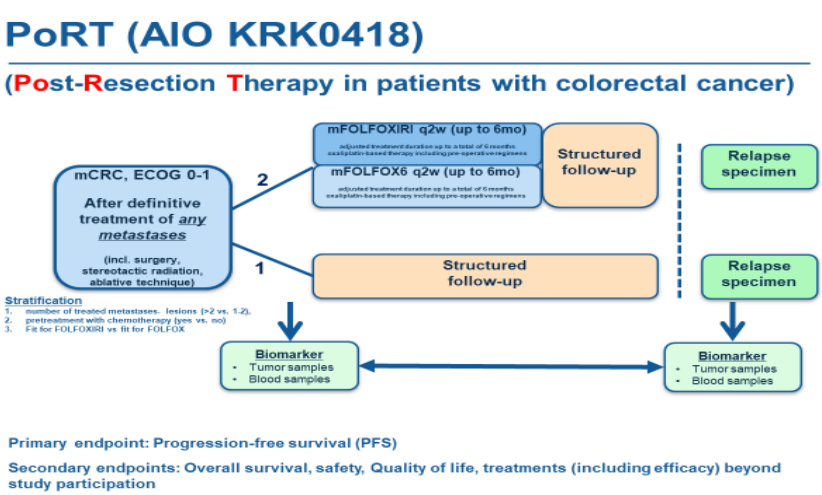
	- Entwicklung eines Value Sets für die Berechnung des qualitätsadjustierten Überlebens (parallele Kohorte)
Interventionen (Beoachtungsteil)	Die Behandlung erfolgt wie vom Prüfzentrum / dem Tumorboard besprochen. Der Behandlungsplan der Patienten wird erfasst, ferner die Daten der weiteren Therapie (Operation [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 therapy with mFOLFOXIRI in patients with colorectal cancer (PORT)

AIO-Studie	
Studiennummer/-Code:	**AIO-KRK-0418/xx - PORT**
Status:	in Vorbereitung, Finanzierung noch nicht gesichert
Rekrutierungszeitraum:	Studienstart noch offen - geplante Rekrutierungszeit: 48 Monate
Weitere Zentren:	sind sehr erwünscht
Letzte Aktualisierung	März 2020

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

DESIGN	
OBJECTIVE(S)	The study will pragmatically recruit all patients with definitely treated metastases from colorectal cancer, as the underlying question, what to do after treated metastases, applies to all sorts of disease spread in a variety of clinical settings. Furthermore, it is not realistic to recruit a trial limited to “after lung metastases” or “without prior treatment” or similar rarer constructs, as this will inevitably result in recruitment-failure. Besides this selection, the indicated criteria represent standard and take into account that patients were fit enough to undergo an intervention.
INTERVENTION(S)	**Experimental procedure**: 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 and a current 5-year mortality of appr. 50% (Robert-Koch-Institut: Krebsdaten 2015; www.krebsdaten.de). In Western Europe, the burden of colorectal cancer is reported to be 211 (female) and 298 (male) diability adjusted life years (DALYs) on a population of 100.000 [1]. Given the available screening-programs, no severe socioeconomic impact within the incidence appears present. Life-style attitudes however may effect individual risk. Patients with metastates from colorectal cancer (appr. 40-50% of all patients develop metastases) benefit from the resection or ablation of metastates, although relapse occurs in the majority (appr. 70-80%) of these patients [2-4]. Clearly, a reduction in relapse rates would improve the long term outcome of these patients. Unfortunately, additive/adjuvant therapy after local treatment of metastases is not established by phase III trials. Accordingly, no standard of care treatment to improve the relapse rates is available and the current S3-guidline for colorectal cancer does not recommend additive chemotherapy due to insufficient evidence on its benefit (http://www.awmf.org/leitlinien/detail/ll/021-007OL.html), explicitly.

	The present clinical trial aims to generate evidence that additive therapy after resection or ablation of metastases may improve DFS and OS in patients with colorectal cancer. This is of specific importance since both improvements in in localized, but also systemic therapies [5, 6] have resulted in increasing numbers of mCRC patients undergoing resection and/or ablation of metastases [7-9]. Optimal oncological management after removal of metastases is unclear. The result of this trial may be therefore be practice-changing. To support the purely clinical information a supporting translational study will help to identify subgroups (if present) of patients that benefit/ or not from systemic therapy after removal of metastases. The translational study-program consists of the following steps: 1. Characterization of the initial resected/ablated tumor (primary and/or metastases) for DNA mutations and RNA expressions (for example oncomine panel plus nanostring) 2. Sequential central assessment of tumor markers and circulating tumor DNA (according to initial tumor characteristics), two assessments during study (q2m). 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). Necessary platforms for DNA/RNA alterations are availaible at both universities. It is anticipated that tumor samples will be availaible for 400 patients and about 400 linear blood samles can be completed (3-4 samples per patient). With six samples from roughly 400 patients, ~2400 probes will be characterized for DNA/RNA.
KEY EXCLUSION CRITERIA	**Key exclusion criteria:** • 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 and/or ablated metastases (all techniques allowed) of colorectal cancer within 3-10 weeks before randomisation AND resected primary tumor (synchronous or metachronous) • No radiographic evidence of metastatic disease at study entry according to RECIST 1.1 scan no older than 4 weeks). • Signed written informed consent, • Adequate bone marrow, liver, kidney, organ and metabolic function, • ECOG performance status 0 – 2.

OUTCOME(S)	Progression-free survival (PFS) is defined as time from randomisation to prog (new metastases) or death from any cause. PFS is an established surrogate e in trials promoting adjuvant or additive therapy and correlates with overall s (randomisation to death from any cause). Quality of life is assessed by E QLQC30 and EDEQ5L. Treatments (including efficacy) beyond study participa analyzed descriptively. Blood samples are collected during follow-up to create a biobank of patients w without relapse. Moreover the relapses will be recorded as part of the study p including the collection of tumor tissue and blood samples, if possible at relap patterns of relapse will be correlated with the initially resected/ablated meta clinically and in terms of tumor characteristics (mutations, expressions).
STATISTICAL ANALYSIS	Dr. Ingrid Ricard, IBE, Marchioninistrasse 15, Ludwig-Maximilians-Universität, München **Statistical methods used to compare groups for primary and secondary outcomes:** Cumulative incidence of DSF will be estimated by Kaplan-Meier procedure, while comparison of treatment arms will be done by log-rank test, adjusted for stratification factors. Sensitivity analysis will be performed using Cox regression to adjust for relevant prognostic factors. Both analyses will be stratified according to respective criteria (see randomisation). The above analyses will be repeated for overall survival (OS). The influence of treatments received after the period of intervention on (DFS and) OS will be assessed. Specific post-study treatments will be included in a Cox model as time-dependent explanatory variables. **Methods for additional analyses, such as subgroup analyses and adjusted analyses:** Safety analyses will consist of comparisons of AEs, SAEs, event rates of grade 3 and 4 toxicities (NCI-CTCAE) and abnormal laboratory values/ increase/decrease between treatment arms during the 4 months of intervention. Descriptive tables will be created; Fisher exact tests will be performed to compare the number of patients with a specific characteristic between the 2 arms; longitudinal models will be fitted to examine the evolution over time of the 2 arms and to test potential differences between them. Biomarkers and quality of life/ patient reported outcomes will be evaluated exploratorily.
SAMPLE SIZE	To be assessed for eligibility: (n ~ 550) To be assigned to the trial: (n = 445) corresponding to 294/147 per arm To be analysed: (n = 445) 279 events needed
TRIAL DURATION	First patient in to last patient out (months): 52 Duration of the entire trial (months): 58 (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 Vorbereitung
Rekrutierungsdauer	geplant von/ bis: Q3/2020 - Q3/2025
Anzahl Patienten:	geplant: 702 eingeschlossen:
Anzahl Zentren:	geplant: 80 initiiert: rekrutierend:
Weitere Zentren:	Interessierte Zentren wenden sich bitte an: ralf.hofheinz@umm.de
Letzte Aktualisierung	Oktober 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
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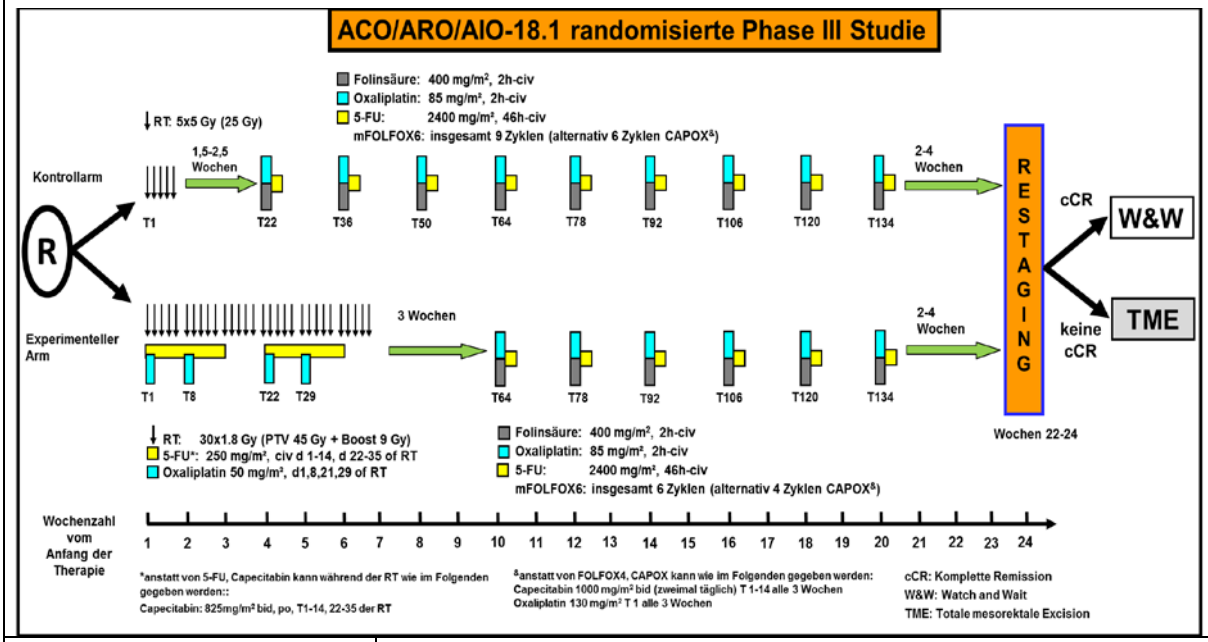
Protokollkomitee:	U. Attenberger, D. Arnold, T. Beissbarth, R. Fietkau, P. Wild, T. Friede, G. Folprecht, E. Fokas, C. Gani, M. Ghadimi, F. Greten, U. Graeven, R. Grützmann, A. Hartmann, R.-D. Hofheinz, P. Ströbel, C. Reißfelder, C. Rödel, J. Weitz, C. Wittekind, D. Zips
Monitoring:	Institut für Klinische 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:	die ersten Zentren sind initiiert
Rekrutierung:	geplant: ab Q3 2020 bis Q3 2025
Anzahl Patienten:	geplant: 818 randomisiert:
Anzahl Zentren:	geplant: 80-100 initiiert: rekrutierend:
Weitere Zentren:	Interessierte Zentren wenden sich bitte an: ralf.hofheinz@umm.de
Letzte Aktualisierung	Okt. 2020

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

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

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0214	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	Juli 2017 – Q3 2020	
Zentren:	geplant: 40	initiiert: 36
Patienten:	geplant: 119	aktuell 110 rand.
Weitere Zentren:	nicht möglich	
Letzte Aktualisierung:	Oktober 2020	

Study design	Randomized, open labeled, parallel group, multicenter phase II study with two arms. Patients with locally advanced rectal or rectosigmoid cancer staged cT3 CRM-negative with MRI will receive 6 cycles of neoadjuvant treatment with mFOLFOX6 (Arm A) vs. mFOLFOX6 + aflibercept (Arm B) followed by surgery.
Coordinating Investigator	Prof. Dr. Ralf-Dieter Hofheinz Tagestherapiezentrum am ITM & III. Med. Klinik Universitätsmedizin Mannheim Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany Phone: +49 - 621 – 38 32 855, Fax: +49 - 621 – 38 32 488
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin, Germany Phone: +49-30-8145 344 31, Fax: +49-30-3229 329 26
Anticipated start date	Q1/2017
Duration of study	5 years

Indication	Locally advanced cT3 rectal cancer
Countries Total number of sites	Germany, Austria 40 sites
Randomised patients	119
Primary objective	To investigate the ***pathological tumor response*** based on central pathologic review of the mFOLFOX6/aflibercept combination as compared to mFOLFOX6 alone in patients with locally advanced rectal cancer staged cT3 CRM-negative with MRI.
Secondary objectives	To compare the treatment Arms with respect to: **Safety** - Dose intensities of study medication - Type, incidence and severity of AEs and SAEs - Laboratory parameters **Efficacy** - Survival, disease-free survival, relapse-free survival - Downstaging and downsizing using a standardized regression grading (Dworak regression grading) **Surgical morbidity and mortality** - Perioperative in-hospital morbidity and mortality within 28 days after surgery **Others** - Vital signs, Physical examination, WHO/ECOG The following secondary objectives will be considered beyond the clinical study report: **Quality assurance of MRI (central read)** - Comparison of the local read of: • T, N, M Staging • Heigh localization • Distance to circumferential resection margin (CRM)
Planned sample size	119 patients total (40 Arm A, 79 Arm B)
Inclusion Criteria	1. Age ≥ 18 years 2. Signed and dated informed consent, and willing and able to comply with protocol requirements 3. WHO/ECOG Performance Status (PS) 0-1 4. Diagnosis of rectal adenocarcinoma 5. Candidate for sphincter-sparing surgical resection prior to neoadjuvant therapy according to the primary surgeon, i.e. no patient will be included for whom surgeon indicates need for abdomino-perineal resection (APR) at baseline. 6. Clinical staging is based on the combination of the following assessments: • Physical examination by the primary surgeon • CT scan of the chest/abdomen • Pelvic MRI • Rigid rectoscopy / endoscopic ultrasound (ERUS) • Both examinations (MRI + ERUS) are mandatory 7. The tumor has to fulfill the following criteria: • No symptomatic bowel obstruction • Locally advanced rectal and rectosigmoid cancer, i.e. lower border of tumor > 5 cm and < 16 cm from anal verge as determined by rigid rectoscopy • MRI criteria: a. Lower border of tumor below a line defined by promontorium and symphysis, regardless of the criterion "< 16 cm from anal verge as determined by rigid rectoscopy". b. No evidence that tumor is adjacent to (defined as within 2 mm of) the mesorectal fascia on MRI (i.e. CRM > 2 mm)

	c. Only T3-tumors are included, i.e infiltration into perirectal fat < 10 mm provided CRM > 2 mm d. ***Note:*** MRI criteria are used for the definition of T3 tumor (i.e. exclusion of T2 and T4 situation). 8. Hematological status: • Neutrophils (ANC) ≥ 2 x 10^9/L • Platelets ≥ 100 x 10^9/L • Hemoglobin ≥ 9 g/dL (previous transfusion of packed blood cells allowed) 9. Adequate renal function: • Serum creatinine level ≤ 1.5 x upper normal limit (ULN) or ≤ 1.5 mg/dl • Creatinine clearance ≥ 30 ml/min 10. Adequate liver function: • Serum bilirubin ≤ 1.5 x upper normal limit (ULN) • Alkaline phosphatase < 3 x ULN • AST and ALT < 3 x ULN 11. Proteinuria < 2+ (dipstick urinalysis) or ≤ 1 g/24hour or ≤ 500 mg/dl 12. Regular follow-up feasible 13. For female patients of childbearing potential, negative serum pregnancy test within 1 week (7 Days) prior of starting study treatment 14. Female patients of childbearing potential (i.e. did not undergo surgical sterilization – hysterectomy, bilateral tubal ligation, or bilateral oophorectomy - and is not post-menopausal for at least 24 consecutive months) must commit to using highly effective and appropriate methods of contraception until at least 6 months after the end of study treatment such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), vasectomized partner, bilateral tubal occlusion, sexual abstinence. If an oral contraception is used, a barrier method of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge) has to be applied additionally. 15. Fertile male patients with a partner of childbearing potential must commit to using highly effective and appropriate methods of contraception (details see above) until at least 9 months after the end of study treatment.
Exclusion Criteria	1. Distant metastases (CT scans of thorax and abdomen are mandatory) 2. cT2 and cT4 tumors (defined by MRI criteria) 3. Exclusion of potentially compromised CRM as defined by MRI criteria (i.e. > 2 mm distance from CRM) 4. Prior antineoplastic therapy for rectal cancer 5. History or evidence upon physical examination of CNS metastasis 6. Uncontrolled hypercalcemia 7. Pre-existing permanent neuropathy (NCI-CTCAE grade ≥ 2) 8. Uncontrolled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), or history of hypertensive crisis, or hypertensive encephalopathy 9. Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy, radiotherapy) 10. Treatment with any other investigational medicinal product within 28 Days prior to study entry 11. Known dihydropyrimidine dehydrogenase (DPD) deficiency 12. Treatment with CYP3A4 inducers unless discontinued > 7 Days prior to randomization 13. Any of the following in 3 months prior to inclusion: • Grade 3-4 gastrointestinal bleeding (unless due to resected tumor) • Treatment resistant peptic ulcer disease • Erosive esophagitis or gastritis • Infectious or inflammatory bowel disease • Diverticulitis 14. Any active infection within 2 weeks prior to study inclusion

	15. Vaccination with a live, attenuated vaccine within 4 weeks prior to the first administration of the study medication 16. 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 > 5 years 17. Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 Days 18. Pregnant or breastfeeding women 19. Patients with known allergy to any excipient to study drugs 20. History of myocardial infarction and/or stroke within 6 months prior to randomization, NYHA class III and IV congestive heart failure 21. Severe renal insufficiency (creatinine clearance < 30ml/min) 22. Bowel obstruction 23. Contra-indication to the assessment by MRI 24. Involvement in the planning and/or conduct of the study (applies to both Sanofi staff and/or staff of sponsor and study site) 25. Patient who might be dependent on the sponsor, site or the investigator 26. Patients who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 27. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
Investigational Product	Aflibercept (Zaltrap®) 4 mg/kg BW i.v.
Primary endpoint	Pathologic complete response (pCR) rate, defined by the number of patients with a pCR finding divided by the number of patients in the analysis set. The pCR will be assessed at the end of the treatment in a standardized manner independently by a central pathology.
Secondary endpoints	**Safety** • Dose intensities of study medication • Type, incidence and severity of AEs, SAEs and AESIs • Dose reduction or discontinuation of study drug due to adverse events • Rate of treatment discontinuation due to toxicity • Type, incidence and severity of laboratory abnormalities **Efficacy** • Rate of R0-wide, R0-narrow (according to CRM definitions in S3-guideline Version 1.1 August 2014), R1 and locoregional R2 resection • Disease-free survival (DFS) rate • Relapse-free survival (RFS) in resected patients • Overall survival (OS) • Downstaging and downsizing using a standardized regression grading (Dworak regression grading) **Surgical morbidity and mortality** • Type, incidence and severity of perioperativ medical events • Mortality within 28 days after surgery **Others** • Vital signs • Physical examination • WHO/ECOG

Treatment schedule after randomization	Arm A: Oxaliplatin 85 mg/m2, Leucovorin 350 mg/m2 i.v. as 2 h infusion on Day 1, 5-FU 400 mg/m2 i.v. as bolus on Day 1 and 2400 mg/m2 as 46 h infusion q2w Arm B: Oxaliplatin 85 mg/m2, Leucovorin 350 mg/m2 i.v. as 2 h infusion on Day 1, 5-FU 400 mg/m2 i.v. as bolus on Day 1 and 2400 mg/m2 as 46 h infusion q2w, Aflibercept 4 mg/kg BW i.v. on Day 1 q2w
Randomization procedure	After the initial screening procedure, eligible patients will be randomized in a ratio of 1:2 to receive either mFOLFOX6 or Aflibercept+mFOLFOX6. Permuted block randomization will be applied.
Scientific rationale	Patients with locally advanced rectal cancer are generally recommended to receive preoperative radiotherapy or radiochemotherapy. The advantage of combined-modality therapy in rectal cancer is that it has reduced local pelvic recurrence – a dreaded and morbid event – to rates of about 10%. There is good quality evidence that preoperative radiotherapy reduces local recurrence but there is little if any impact on overall survival. One strategy to reduce the distant recurrence rate, and thereby increase the cure rate, would be to introduce systemic treatment earlier to prevent dissemination of micrometastases. The present trial is designed to compare two neoadjuvant chemotherapy regimens in patients with non-metastatic T3 CRM-negative rectal cancers using quality-controlled MRI of the pelvis as a main inclusion criterion. This strategy is believed to reduce acute and long-term toxicity caused by preoperative radiotherapy and to administer effective systemic chemotherapy early in the course of disease as neoadjuvant chemotherapy.
Interim analysis	No interim analysis is planned for this study.
Statistical considerations and sample size calculation	**Sample Size Estimation:** The calculation of the sample size is based on a Fisher's exact test. It is assumed that the proportion for pCR in Arm A (mFOLFOX6) is 10%. The sample size is calculated such that a difference of absolute 17% (therefore, pCR in Arm B 27%) could be detected with a type I error rate of 20% and a power of 80%. Based on these assumptions and using a randomization ratio of 1:2, the resulting total sample size is given by 113 patients (Arm A: 38 pts; Arm B: 75 pts.). Accounting for a dropout rate of 5%, the study is planned to recruit a total of 119 patients (Arm A: 40; Arm B: 79). **Statistical Considerations:** An observed cases approach will be applied, and missing data will not be imputed.
Statistical analysis	STABIL – Statistische und Biometrische Lösungen Pistorstr. 7, 66482 Zweibrücken, Germany
Study plan	FPI: Q1/2017 LPI: Q3/2020 Duration of treatment: up to 5.5 months Follow-up: 3 years Follow-up for LPI: 12 months after EOT visit LPO: Q3/2021 Study report: Q3/2022

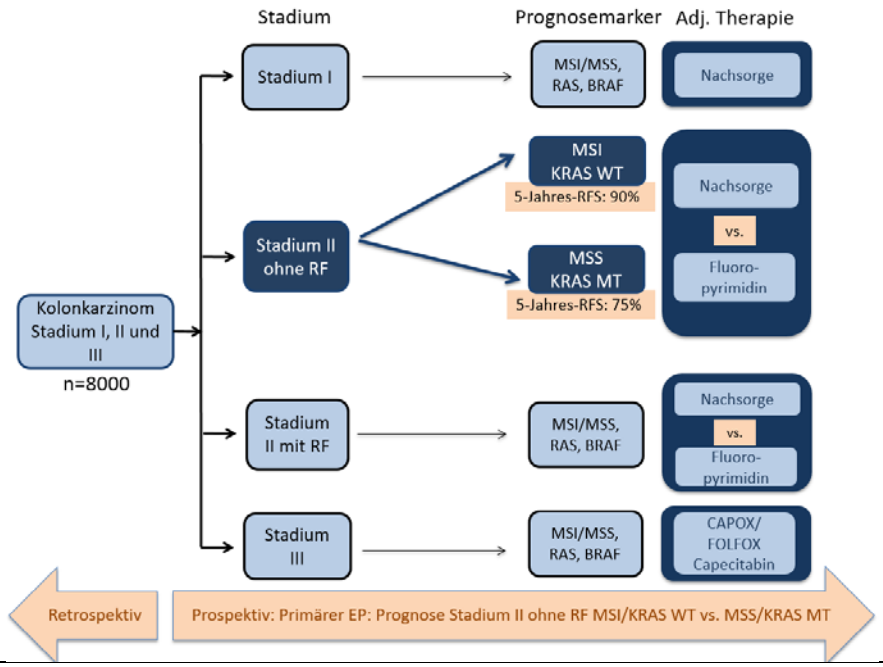
Registerstudien

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: 175
Patienten:	geplant: 8000	aktuell eingeschlossen: 5175
Letzte Aktualisierung	Oktober 2020	

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 SAKK 41/13-Aspirin (EudraCT 2015-001482-57, Prof. Güller, St. Gallen) • 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 5100, Rekrutierungsziel: 8800

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 • Temporäres Addendum	September 2013 August 2018 September 2020
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.

AIO-KRK-0520/ass: 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) (CancerCovid)

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

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-KRK-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 2020

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	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 Prof. Dr. med. Jochen Schmitt
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
Studienziele	<u>Primäres Studienziel des Konsortiums:</u> 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. <u>Studienziele Subprojekt Onkologie:</u> 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. Es werden drei Quellen verwendet: 1. Institut für Pathologie der Ruhr-Universität Bochum 2. Zentren aus der Colopredict Plus 2.0 Registerstudie und weitere Darmzentren 3. AIO-Zentren
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
Statistik	Alle dokumentierten Daten zur Beschreibung des Patientenkollektivs in Bezug auf Diagnostik, Therapie und Versorgung werden mittels statistischer Standardverfahren deskriptiv ausgewertet.

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

Fortgeschrittenes inoperables Kopf-Hals Plattenepithelkarzinom, 1st-line

AIO-KHT-0120/ass: 2 ARM RANDOMIZED PHASE II TRIAL TO ASSESS THE FEASIBILITY AND EFFICACY OF A TREATMENT WITH DURVALUMAB (MEDI4736) A PDL1-INHIBITOR PLUS TREMELIMUMAB A CTLA-4- INHIBITOR IN COMBINATION WITH RADIOTHERAPY AND A TREATMENT WITH DURVALUMAB IN COMBINATION WITH RADIOTHERAPY AS FIRST-LINE THERAPY FOR PATIENTS WITH NON-RESECTABLE LOCALLY ADVANCED HPV NEGATIVE HNSCC – A COMPARISON WITH A HISTORICAL CONTROL GROUP (DURTRERAD)

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-KHT-0120/ass - DURTRERAD**
Status:	in Rekrutierung
Rekrutierungszeit:	von:10/2018 bis: 10/2022
Anzahl Zentren:	geplant: 4 aktuell initiiert: 2 aktiv rekrutierend: 2
Weitere Zentren:	sind auf Anfrage an den LKP möglich
Anzahl Patienten:	geplant: 120 aktuell eingeschlossen: 16
Letzte Aktualisierung	06.11.2020

STUDY TYPE	interventionell
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TRIAL OFFICE	Clinical Trial Unit des CCCC Charité - Universitätsmedizin Berlin Charité Comprehensive Cancer Center Charitéplatz 1, 10117 Berlin 030 450 564648 susen.burock@charite.de
SPONSOR	Dr med. Susen Burock Charité - Universitätsmedizin Berlin Charité Comprehensive Cancer Center Charitéplatz 1, 10117 Berlin 030 450 564648 susen.burock@charite.de
CONDITION	Head and neck cancer
DESIGN	Phase II
INDICATION	Non-resectable locally advanced HPV negative HNSCC
OBJECTIVE(S)	The primary objective is to explore the feasibility and efficacy in terms of treatment discontinuation due to toxicity and in terms of 1-year progression free survival of a PDL1-Inhibitor plus a CTLA-4 Inhibitor in combination with radiotherapy vs a PDL1-Inhibitor in combination with radiotherapy as first-line therapy for patients with non-resectable locally advanced HNSCC in the poor prognostic subgroup.

INTERVENTION(S)	**Patients in arm 1** will receive a single dose of durvalumab of 1500 mg administered on day 1, 14 days prior to initiation of the radiotherapy. Radiotherapy with 35 fractions over 7 weeks (administered as daily fractions of 2 Gy given 5 days every week for 7 weeks) will start on day 14.. On week 5, 9, 13 and 17 patients will receive durvalumab (1500 mg) and tremelimumab (75 mg) for up to 4 doses/cycles and then continue 1500 mg durvalumab q4w starting on week 21 to complete a total of 12 months of therapy (overall 9 single doses durvalumab including the initial dose on day 1). **Patients in arm 2** will receive durvalumab (1500 mg) q4w up to a total of 12 months of therapy (up to 13 doses in total). Radiotherapy with35 fractions over 7 weeks (administered as daily fractions of 2 Gy given 5 days every week for 7 weeks) will start on day 14.
BACKROUND/RATIONALE	Despite aggressive initial treatment, the risk of recurrence in HNSCC is high and locoregional recurrence is the predominant pattern of failure. Patterns of failure are changing and distant metastases have been increasingly documented in recent times.
KEY EXCLUSION CRITERIA	Participation in another clinical study with an investigational product during the last 3 months Prior or current anticancer treatment to the head and neck area (e.g. radical attempted or tumor reductive surgery, neo-adjuvant chemotherapy, EGFR inhibitors or radiotherapy). Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA4, including tremelimumab Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, 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 (eg, 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 History of primary immunodeficiency History of allogeneic organ transplant 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 History of hypersensitivity to durvalumab and/or tremelimumab or any excipient 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 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

	Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control as described in the protocol from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period Distant metastasis Patients who are institutionalised by official order Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction Receipt of live attenuated vaccination within 30 days prior to study entry step 2 or within 30 days of receiving durvalumab or tremelimumab
KEY INCLUSION CRITERIA	Patients with locally advanced histopathologically confirmed HNSCC not candidate for primary surgical treatment Patients that are planned for radiotherapy No distant metastasis (M0) tumor tissue available for central testing Patients with HPV/p16 negative disease (≤70% positively stained cells) as determined by central testing Adequate normal organ and marrow function Measurable tumor according to RECIST Patients must be expected to complete the treatment. Age > 18 years at time of study entry Female patients must either be of non-reproductive potential or must have a negative serum pregnancy test upon study entry and be willing to use adequate contraceptive measurements as described in the protocol Non-sterilized males who are sexually active with a female partner of childbearing potential must be willing to use adequate contraceptive measurements as described in the protocol section 6.5.4
STATISTICAL ANALYSIS	The study is designed as an open-label randomized phase II trial with 2 experimental treatment arms. The primary endpoint is the 1-year progression free survival depicted as the 1-year in-field-progression-free survival and 1-year distant metastasis free survival. As raw data from the historical control are not available the value known from the literature for one year PFS (=30%) will be considered to be the true value in a 1-sample test. Assuming no censored cases the variance of the survival S(t) can be estimated by the binomial variance [S(t)*(1-S(t)]/n (Collet, Modelling survival data in Medical Research, page 25) where n is the sample size. A sample size estimation of the exact binomial test with H0 p = 0.3 and H1 p = 0.5 leads to n = 54 (type 1 error 0.025 one-sided, power 82%, software nquery). Assuming a 10% drop out rate, we include 60 subjects. The analysis will not be even driven but done when 54 subjects have reached one year follow up. This will be done separately in both experimental study arms. The Greenwood for the standard error of PFS(one year) will be used for analysis. If the lower bound of the 95% CI of S(t) is above 0.30, H0 (PFS(one year) = 0.30) will be rejected in favour of the alternative (PFS(one year) > 0.30).
PARTICIPATING CENTERS	Charité Berlin, Universität Essen, Vivantes Berlin

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: 15	rekrutierend: 8
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant: 350	aktuell eingeschlossen: 50	
Letzte Aktualisierung	22.10.2020		

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. 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. This also includes Catheter-related bloodstream infections (CRBSI), NOS, and Central line-associated bloodstream infections (CLABSI). 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. To test the hypotheses: H_{01}: "The CRI rate does not differ between the treatment Arms A and B (P11 = P21)." vs. H_{11}: "The CRI rate differs between the treatment Arms A and B (P11 ≠ P21)."

	and H_{02}: "The objective patient autonomy does not differ between the treatment Arms A and B (P12 = P22)." vs. H_{12}: "The objective patient autonomy differs between the treatment Arms A and B (P12 ≠ P22)." fisher's exact test is used with a type I error of 0.04 and 0.01, respectively.
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.

Registerstudie: Lebensqualität: Adenokarzinom des Pankreas

AIO-LQ-0214/ass: Platform for Outcome, Quality of Life, and Translational Research on Pancreatic Cancer (PARAGON)

Klinisches Register zu Prognose, Lebensqualität und Translationaler Forschung bei Patienten mit Pankreaskarzinom

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-LQ-0214/ass - PARAGON	
Status:	Rekrutierungsstart	
Rekrutierungszeitraum	ab QIV 2019	
Patienten:	geplant: offen	aktuell eingeschlossen: 170
Zentren:	geplant: offen	initiiert: 58
Weitere Zentren:	sind erwünscht	
Letzte Aktualisierung	Oktober 2020	

Art der Studie	Nicht-interventionelle Studie (NIS) / Register
Verantwortlicher Studienleiter nach AMG	Prof. Dr. Ralf Hofheinz Universitätsmedizin Mannheim III. Medizinische Klinik Theodor-Kutzer-Ufer 1-3 68167 Mannheim Tel. 0621/383-2855; Fax 0621/383-2488 ralf.hofheinz@umm.de Priv. Doz. Dr.med. Thorsten Oliver Götze Krankenhaus Nordwest gGmbH Institut für Klinisch-Onkologische Forschung (IKF) Steinbacher Hohl 2-26 60488 Frankfurt Tel: 069/76 01 – 4187; Fax: 069/76 01 – 3655 Goetze.Thorsten@khnw.de Institut für Klinisch-Onkologische Forschung (IKF) Ärztl. Direktor: Prof. Dr. Salah-Eddin Al-Batran Krankenhaus Nordwest GmbH UCT - Universitäres Centrum für Tumorerkrankungen Frankfurt Steinbacher Hohl 2-26 60488 Frankfurt E-Mail: albatran@aio-portal.de
Kontaktadresse/ Kontaktperson:	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Bianca Zäpf Tel: 069 7601 4636 E-Mail: zaepf.bianca@ikf-khnw.de
Studienziele/ Objectives	Primäres Studienziel: Das Studienregister sammelt in erster Linie Daten zu Verlauf und Behandlung von Patienten mit Adenokarzinom des Pankreas unter verschiedenen Therapielinien. Aus diesem Grund liegt dem Studienregister im Unterschied zu

	klinischen Prüfungen kein primärer Endpunkt zugrunde. Die Datenerfassung beinhaltet unter anderem die Erhebung der Lebensqualität, weiterer, sog. Patient-Reported Outcomes (PRO) und – soweit vorhanden – die Sammlung von Tumormaterial für translationale Begleitprojekte. <u>Sekundäre Studienziele:</u> Auch wie beim primären Endpunkt hat ein Register keine formalen sekundären Endpunkte. Einige Endpunkte sind aber für die Auswertungen unerlässlich. diese sind im Detail: - DFS/PFS, OS und Überlebensraten (z.B. aber nicht ausschließlich nach 2, 3 und 5 Jahren) für adjuvante und neoadjuvante Therapieverfahren - Mortalität und Morbidität für adjuvante und neoadjuvante Therapieverfahren - PFS und OS bei Patienten, die eine Erstlinientherapie erhalten - PFS und OS bei Patienten, die eine Zweit-, Dritt- oder weitere Behandlungslinien erhalten - Erfassung der verwendeten Therapieschemata und Therapiesequenzen über alle Behandlungslinien - Klinische und biologische Prädiktoren bzgl. Behandlungserfolg und Überleben <u>Translationale / Korrelative Begleitstudien</u> Assoziation vom Ansprechen und Überleben mit genetischen Alterationen mittels Next-Generation (NGS; Illumina HiSeq2000) und RNA Sequenzierungen
Patientenzahl	Offen (permanentes Studienregister)
Rekrutierungzeitraum	Offen (permanentes Studienregister)
Weitere Zentren?	möglich
Haupt-Einschlusskriterien /	• Vorliegen einer schriftlichen Einwilligungserklärung und anderer vorgeschriebener lokaler Einwilligungen (EU-Datenschutzrichtlinie in der EU) bevor jedwede studienspezifische Maßnahme, einschließlich Screening, durchgeführt wird. • Alter ≥ 18 Jahre • Histologisch oder zytologisch gesichertes Adenokarzinom des Pankreas • Eine systemische neoadjuvante, adjuvante oder Erstlinientherapie ist geplant oder wurde kürzlich (d.h. innerhalb der letzten 14 Tage) begonnen.
Haupt-Ausschlusskriterien	• Unfähigkeit, die Studie zu verstehen und Patienteneinwilligung zu geben • Unfähigkeit des Patienten, QoL-Fragebogen auszufüllen bzw. die Fragen zu beantworten • Zweit- oder weitere palliative Therapien, wenn die Erstlinientherapie des Patienten nicht innerhalb der Studie dokumentiert wurde
Therapieschema	Alle verfügbaren Therapielinien
Rationale	Das Pankreaskarzinom stellt die viert-häufigste Krebs-assoziierte Todesursache in Europa und den USA dar (American Cancer Society 2013; Malvezzi et al. 2013). Die Resektion stellt immer noch die einzige kurative Therapieoption dar. Jedoch führen unspezifische Symptome meist zu einer späten Diagnose des aggressiv wachsenden und früh metastasierenden Karzinoms, so dass nur 15-20% der Patienten resektabel sind. Seit 1997 ist die Gemcitabin-Monotherapie der Standard in der Erstlinienbehandlung von Patienten mit inoperabel fortgeschrittenen und metastasierten Erkrankungsstadien (Burris et al. 1997). Bei Patienten mit metastasierter Erkrankung beträgt die 5-Jahres-Überlebensrate lediglich 2%, die Einjahres-Überlebensrate unter Gemcitabin-Therapie ist mit 17-13% ebenfalls vergleichsweise gering (American Cancer Society 2013; Malvezzi et al. 2013). Zahlreiche Phase II-Studien zur Kombination von Gemcitabin mit anderen Substanzen zeigten vielversprechende Ergebnisse in Hinblick auf die Verbesserung des Gesamtüberlebens, die allerdings in nachfolgenden Phase

	III-Prüfungen nicht bestätigt werden konnten (Goncalves et al. 2012; Philip et al. 2011; Colucci et al. 2010; Kindler et al. 2010; Cunningham et al. 2009; Poplin et al. 2009; Chauffert et al. 2008; Abou-Alfa et al. 2006; Stathopoulos et al. 2006; Oettle et al. 2005; Rocha et al. 2004). Einzige Ausnahme bildete die Kombinationstherapie von Gemcitabin mit Erlotinib, die das Gesamtüberleben von Patienten mit metastasiertem Pankreaskarzinom signifikant, jedoch kaum klinisch relevant verbesserte (median 2 Wochen; Moore et al. 2007). In präklinischen Studien konnte gezeigt werden, dass Albumin-gebundenes NabPaclitaxel als Monosubstanz antitumorale Aktivität auf Pankreastumorzellen aufweist. Diese konnte durch die Kombination mit Gemcitabin aufgrund synergistischer Effekte noch gesteigert werden, insbesondere durch eine Erhöhung der intratumoralen Gemcitabin-Konzentration (Frese et al. 2012). Auf Grundlage dieser Daten wurde eine klinische Phase I/II-Studie bei Patienten mit metastasiertem Adenokarzinom des Pankreas durchgeführt, in welcher die maximale nab-Paclitaxel-Dosis bei akzeptabler Toxizität mit 125 mg/m2 in Kombination mit 1000 mg/m2 Gemcitabin ermittelt wurde. Die Effektivität dieser Kombinationstherapie war mit einem medianen Gesamtüberleben von 12,2 Monaten vielversprechend und wies ein tolerables Sicherheitsprofil auf (Von Hoff et al. 2011). Dieser positive Trend der Verbesserung des Gesamtüberlebens konnte im Rahmen der mit 861 Patienten größten randomisierten, jemals bei Patienten mit metastasiertem Adenokarzinom des Pankreas durchgeführten Phase III-Studie (MPACT) für die Kombinationstherapie von NabPaclitaxel/Gemcitabin bestätigt werden. Der Vorteil konnte in einen statistisch signifikanten Überlebensvorteil überführt werden. Das mediane Gesamtüberleben wurde signifikant um 1,8 Monate gegenüber Gemcitabin-mono erhöht und betrug 8,5 Monate im Kombinationsarm, versus 6,7 Monate im Gemcitabin-Monotherapiearm (Von Hoff et al. 2013). Eine weitere Therapieoption für Patienten mit metastasiertem oder lokal fortgeschrittenem Pankreaskarzinom stellt die Behandlung mit FOLFIRINOX dar. Diese Kombinationstherapie aus vier Komponenten (Fluorouracil [5-FU], Leucovorin, Irinotecan und Oxaliplatin) wird in einem zweiwöchentlichen Schema verabreicht. Aufgrund der Toxizität eignet sich FOLFIRINOX aber vornehmlich für Patienten mit gutem Performance Status. Häufige Nebenwirkungen stellen vor allem ein erhöhtes Risiko an Infektionen aufgrund von Leuko- und Neutropenien dar. Die Ergebnisse einer 2011 veröffentlichten randomisierten Phase III Studie zeigten für Patienten mit lokal fortgeschrittenem Pankreaskarzinom unter Therapie mit FOLFIRINOX ein Gesamtüberleben von 11,1 Monaten versus Patienten unter Gemcitabin Monotherapie mit einem Gesamtüberleben von 6,8 Monaten (Conroy et al., 2011). Nach dieser Studie folgten allerdings bislang keine randomisierten Phase III Studien, welche diese Ergebnisse bestätigen könnten. Eine Meta-Analyse (Thibodeau et al., 2018), welche die Populationen und Ergebnisse der Phase III (Conroy et al., 2011) mit zusammengefassten Daten von Phase II Studien und Berichten zu Datenreihen außerhalb klinischer Studien untersuchte, zeigte im Wesentlichen übereinstimmende Ergebnisse und bestätigte ein Gesamtüberleben von 10 bis 11 Monaten. Im Jahr 2014 wurde durch das Institut für Klinisch-Onkologische Forschung am Krankenhaus Nordwest eine nicht-interventionelle Studie zur Lebensqualität von Patienten mit metastasiertem Pankreaskarzinom unter NabPaclitaxel/Gemcitabin („QoliXane“) initiiert, an der sich bundesweit mehr als 90 Studienzentren beteiligten und bis Ende 2017 mehr als 600 Patienten eingeschlossen wurden. Die Studie wurde mehrfach in der Arbeitsgruppe Lebensqualität der AIO vorgestellt und besprochen. Aus diesem Studienprojekt entwickelte sich die Rationale für ein dauerhaftes, prospektives Studienregister zum Pankreaskarzinom in Deutschland, das neben der bislang erfassten Therapie mit NabPaclitaxel und Gemcitabin in der Erstlinie beim metastasierten Pankreaskarzinom auch andere Substanzen in weiteren Therapielinien berücksichtigt und auf diese Weise weitere Informationen über Lebensqualität und Versorgung von Patienten mit Pankreaskarzinom generiert.

Arbeitsgruppe Mammakarzinom und Gynäkologische Tumoren

Mammakarzinom – palliative Therapie – 1st-line

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

AIO-assoziierte Studie		
Studiennummer/-Code:	AIO-MAM-0117/ass - RIBBIT (*IOM-050371 CLEE011ADE04T)*	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2018 – 2021	
Weitere Zentren:	leider nicht möglich!	
Zentren:	geplant: 30	initiiert: 29
Patienten:	geplant: 158	aktuell eingeschlossen: 37
Letzte Aktualisierung:	20. Oktober 2020	

Leiter der klinischen Prüfung	*Prof. Dr. Thomas Decker* *Elisabethenstraße 19* *88212 Ravensburg*
Sponsor	*iOMEDICO*
Studiendesign	Dies ist eine prospektive, randomisierte, offene, zweiarmige, multizentrische interventionelle Phase III Studie in Deutschland. Die Studie wurde konzipiert, um die Wirksamkeit und Sicherheit der Erstlinientherapie mit einer Ribociclib-Aromataseinhibitor (AI) / Fulvestrant-Kombination im Vergleich zu Capecitabin mit Bevacizumab / Paclitaxel mit oder ohne Bevacizumab bei Patientinnen mit HR-positive, HER2-negativen Brustkrebs mit viszeralen Metastasen zu untersuchen. 158 Patientinnen werden eingeschlossen und 1:1 randomisiert (stratifiziert nach dem Vorhandensein von Lungen- und/oder Lebermetastasen) um Arm A: eine Kombination aus Ribociclib mit AI / Fulvestrant; ODER Arm B: Capecitabin + Bevacizumab oder Paclitaxel mit/ohne Bevacizumab zu erhalten. Die Verabreichung von Capecitabin mit Bevacizumab oder Paclitaxel als Monotherapie oder Kombinationstherapie mit Bevacizumab wird der Entscheidung des Arztes überlassen. Sollten Patienten eine adjuvante AI-Therapie erhalten haben, wird empfohlen, dass Ribociclib mit einem steroidalen AI kombiniert wird, wenn ein nicht-steroidaler AI in der Adjuvanz gegeben wurde und andersherum. Alternativ kann Ribociclib mit Fulvestrant kombiniert werden, wenn ein AI in der Adjuvanz gegeben wurde. Die Therapie wird bis zur Krankheitsprogression, nicht tolerierbarer Toxizität oder dem Tod fortgesetzt. Das progressionsfreie Überleben (PFS) wird basierend auf der Beurteilung des Tumors nach RECIST v1.1 durch den lokalen Radiologen/Prüfarzt bestimmt. Die Behandlung kann über einen nach RECIST definierten Progress hinaus weitergeführt werden, wenn dieser vernachlässigbar oder klinisch irrelevant ist und bis zur klinisch relevanten Krankheitsprogression oder bis zur symptomatischen Verschlechterung fortgesetzt werden. Die endokrine Therapie mit AI / Fulvestrant im Ribociclib + AI / Fulvestrant Arm kann nach Absetzen von Ribociclib fortgesetzt werden. Der Abbruch von Ribociclib und AI / Fulvestrant (oder AI / Fulvestrant, falls Ribociclib schon

	vorher beendet wurde) ist als Ende der Therapie (EOT) definiert. Die anti-VEGF Therapie im Capecitabin / Paclitaxel-Arm kann nach Absetzen von Capecitabin / Paclitaxel fortgesetzt werden. Wenn die Chemotherapie für mehr als einen Zyklus verzögert wird, muss die Chemotherapie beendet werden. Eine endokrine Erhaltungstherapie ist nicht erlaubt für Patienten in Arm B. Die Beendigung von Capecitabin und Bevacizumab (oder Bevacizumab, falls Capecitabin vorher abgebrochen wurde) oder Paclitaxel und Bevacizumab (oder Bevacizumab, falls Paclitaxel vorher abgebrochen wurde) ist als EOT definiert. Nach EOT nehmen die Patienten an der Nachbeobachtung teil, welche für alle Patienten eine 30-tägige Sicherheitsnachbeobachtung und eine Überlebensnachbeobachtung bis zum Tod bzw. maximal bis 48 Monate nach Randomisierung des letzten Patienten, einschließt. Bei Patienten, die bei EOT keine Krankheitsprogression haben, wird außerdem die Tumorevaluation bis zum Progress oder dem Start der nachfolgenden Therapie fortgesetzt, je nach dem was zuerst eintritt.
Indikation	Diese Studie schließt erwachsene weibliche Patientinnen mit HR-positivem, HER2-negativem Brustkrebs mit viszeralen Metastasen ein, die keine vorangegangene Therapie in der fortgeschrittenen Situation erhalten haben.
Prüfpräparat und Vergleichstherapie	Ribociclib (Kisqali®) oral (an den Tagen 1 bis 21 eines 28-tägigen Zyklus) in Kombination mit einem endokrinen Partner (entweder AI oral, einmal täglich eingenommenen oder Fulvestrant intramuskulär injiziert an Tag 1, Tag 15 und Tag 29 in Zyklus 1 gefolgt einer Injektion pro Zyklus in den Folgezyklen eines 28-tägigen Zyklus) oder Capecitabin (zwei mal täglich an den Tagen 1 bis 14 eines 21-tätgigen Zyklus) mit Bevacizumab (an Tag 1 eines 21-tägigen Zyklus) oder Paclitaxel (an den Tagen 1, 8 und 15 eines 28-tägigen Zyklus) mit oder ohne Bevacizumab (an den Tagen 1 und 15 eines 28-tägigen Zyklus). Arm A: Ribociclib (600 mg/day) plus AI / Fulvestrant (entweder Letrozol (2.5 mg/Tag) ODER Anastrozol (1 mg/Tag) ODER Exemestan (25 mg/Tag) ODER Fulvestrant (500 mg/Gabe)) Arm B: Capecitabin (1000 mg/m2 zwei mal täglich) + Bevacizumab (15 mg/kg) ODER Paclitaxel (90 mg/m2) ± Bevacizumab (10 mg/kg)
Anzahl von Patienten und Studienzentren	158 Patientinnen in 30 Zentren (niedergelassene Onkologen und Gynäkologen, onkologische Ambulanzen und Kliniken)
Studienrationale	Die endokrine Therapie stellt die wichtigste Therapiestrategie des HR-positiven, HER2-negativen Mammakarzinoms dar, da diese Zellen abhängig von Signalen des Östrogen-Rezeptors (ER) sind. Die Kombination aus endokriner Therapie mit zielgerichteter Therapie kann die Wirkung weiter verstärken. Ribociclib (Kisqali®) ist ein oral bioverfügbarer, selektiver Inhibitor der Cyclin-abhängigen Kinasen CDK4/6. Diese sind Proto-Onkogene, die, wenn sie an ihr Regulatorprotein Cyclin D1 gebunden sind, die Progression des Zellzyklus aus der G1- zur S-Phase regulieren. Dies stellt einen Schlüsselschritt in der zellulären Proliferation dar. Änderungen im CDK4/6 Signalweg werden als wichtige Antreiber der Brustkrebsentstehung und auch der endokrinen Resistenz angesehen. In klinischen Studien wurde die antitumorale Aktivität von Ribociclib gezeigt. Die Phase III Studie mit 668 Patientinnen (MONALEESA-2), welche die Kombinationstherapie aus Ribociclib mit Letrozol gegen Placebo mit Letrozol verglichen hat, zeigte, dass eine Zugabe von Ribociclib zu Letrozol das progressionsfreie Überleben (PFS) der HR-positiven, HER2-negativen Patientinnen mit fortgeschrittenem Brustkrebs inklusive derer mit Metastasen in der Lunge oder Leber verbessert (alle Patienten: HR 0,56; 95% CI 0,43-0,72; Patientinnen mit Leber-oder Lungenmetastasen: HR 0,57; 95% CI 0,41-0,79) (Gabriel N. Hortobagyi et al. 2016). Die häufigsten unerwünschten Ereignisse (UE) von Grad 3/4, die im Zusammenhang mit der Ribociclib-Gabe auftraten, waren Neutropenie (59,3% vs. 0,9% in der Placebo-Gruppe) und Leukopenie (21,0% vs. 0,6%). Die meisten unerwünschten Ereignisse waren durch Dosisreduktionen oder Therapieunterbrechungen

	reversibel. Zusammenfassend stellt die Zugabe des CDK4/6-Inhibitors Ribociclib zu Letrozol eine vielversprechende chemotherapiefreie Behandlungsoption für metastasierten Brustkrebs dar. Ähnliche Ergebnisse wurden in der Phase III Studie MONALEESA-3 beim Vergleich von Ribociclib oder Placebo in Kombination mit Fulvestrant beobachtet (HR 0.593; 95% CI 0.48-0.732) (Slamon et al. 2018). Die Phase III Studie MONALEESA-7 untersuchte die Kombination aus Ribociclib mit Tamoxifen oder AI in prämenopausalen Frauen und zeigte einen ähnlichen PFS-Vorteil (HR 0.55; 95% CI 0.44-0.69) (Tripathy et al. 2018) Daten aus dem deutschen TMK Register zeigen, dass mehr als die Hälfte der Patienten mit einem HR-positiven Karzinom eine Chemotherapie als erste palliative Therapie erhalten. Dies gilt insbesondere für Patienten mit viszeraler Metastasierung (Fietz et al. 2017). Die am häufigsten eingesetzten Chemotherapeutika waren Paclitaxel, welches eine der wirksamsten Substanzen bei Brustkrebs darstellt, und Capecitabin. Die Kombination von Paclitaxel mit dem anti-VEGF (vascular endothelial growth factor) Antikörper Bevacizumab verlängerte das mediane PFS im Vergleich zur Taxan-Monotherapie beim metastasierten Brustkrebs einschließlich der HR-positiven Subgruppe (Alle: 11,8 Monate vs. 5,9 Monate; ER-positive, PgR-positive: 14,4 Monate vs. 8,0 Monate) (K. Miller et al. 2007). In einer weiteren Phase III Studie (Alliance) resultierte die Kombination aus Paclitaxel mit Bevacizumab in einem medianen PFS von 11 Monaten in der Gesamtpopulation und 12,4 Monaten für die Subgruppe der Patienten mit HR-positiver Erkrankung (Rugo et al. 2015). Die Kombination aus Capecitabine und Bevacizumab wurde in verschiedenen Studien untersucht. Verglichen mit der Kombination aus Paclitaxel und Bevacizumab zeigte sich ein leicht verkürztes PFS im Capecitabin Arm ohne sich jedoch auf das Gesamtüberleben zu übertragen. Hinsichtlich Arzneimittelsicherheit/Verträglichkeit (inklusive Anzahl der unerwünschten Ereignisse (UE) sowie Therapieabbrüche aufgrund UE) zeigten sich Vorteile im Capecitabin Arm (Zielinski et al. 2016) Zusammenfassend stellen Capecitabin plus Bevacizumab sowie Paclitaxel als Monotherapie oder in Kombination mit Bevacizumab wirksame und dadurch auch häufig verwendete sowie empfohlene Therapieoptionen für Patienten mit metastasiertem Mammakarzinom dar. Das Ziel der RIBBIT Studie ist die Untersuchung der Wirksamkeit gemessen am PFS der Kombination von Ribociclib mit endokrinem Partner oder Capecitabin mit Bevacizumab oder Paclitaxel mit / ohne Bevacizumab bei Patientinnen mit einem HR-positiven, HER2-negativen metastasierten Mammakarzinom mit viszeraler Metastasierung. Zusätzlich werden weitere Wirksamkeitsparameter sowie die Sicherheit und die Lebensqualität (QoL) untersucht. Zudem wird das symptomatische PFS (sPFS) untersucht, welches als Zeitraum von der Randomisierung bis zur symptomatischen Verschlechterung oder dem Tod definiert ist. Dies stellt einen patientenrelevanten Wirksamkeitsparameter dar.
Zielparameter	**Primäres Studienziel:** Vergleich der Wirksamkeit gemessen am PFS der Kombination von Ribociclib mit AI / Fulvestrant gegen Capecitabin mit Bevacizumab oder Paclitaxel mit / ohne Bevacizumab als Erstlinientherapie des HR-positiven, HER2-negativen Mammakarzinom mit viszeraler Metastasierung bei erwachsenen Patientinnen. **Sekundäre Studienziele:** Vergleich der beiden Studienarme hinsichtlich der folgenden Wirksamkeitsparameter: Ansprechraten (ORR), klinische Benefitrate (CBR), Zeit bis zum Ansprechen (TTR) und Gesamtüberleben (OS). Bestimmung der Sicherheit und Verträglichkeit der beiden Behandlungsarme hinsichtlich der (S)UEs, ECOG Performance Status, Routinelaboruntersuchungen und Elektrokardiogramm.

	Einschätzung und Vergleich der beiden Behandlungsarme in Bezug auf die gesundheitsbezogene Lebensqualität (QoL) mittels Auswertung des EORTC QLQ-C30 Fragebogen sowie weiterer Einzelfragen zur Belastung durch Nebenwirkungen der Therapie und Zeitaufwand für die Therapie **Exploratives Studienziel:** Vergleich beider Therapiearme hinsichtlich des sPFS.
Studienendpunkte	**Primärer Endpunkt**: • PFS beurteilt durch den lokalen Untersucher mittels RECIST v1.1 Kriterien. PFS ist definiert als Zeit von der Randomisierung bis zur Krankheitsprogression oder Tod jeglicher Ursache, je nach dem, was zuerst auftritt. **Sekundäre Endpunkte:** *Wirksamkeit:* • ORR (komplettes oder partielles Ansprechen) erfasst durch den lokalen Untersucher mittels RECIST v1.1. • CBR (komplettes oder partielles Ansprechen oder stabile Erkrankung für mindestens 24 Wochen) erfasst durch den lokalen Untersucher mittels RECIST v1.1. • TTR (Zeit von der Randomisierung bis zum ersten Ansprechen (komplett oder partiell)) erfasst durch den lokalen Untersucher mittels RECIST v1.1. • Gesamtüberleben definiert als Zeit von der Randomisierung bis zum Tod jeglicher Ursache. *Sicherheit und Verträglichkeit:* • (Schwerwiegende) Unerwünschte Ereignisse ((S)UE): Häufigkeit und Schweregrad gemäß CTCAE v4.03 bis 30 Tage nach Ende der Therapie • Zeit bis zur Verschlechterung des ECOG Performance Status um mindestens einen Punkt • Routinelaboruntersuchungen bis zum Therapieende • Elektrokardiogramm (EKG) bis zum Therapieende *Vom Patienten berichtete Lebensqualität:* • Zeit bis zur Abnahme des Wertes der Skala „globaler Gesundheitsstatus“ des EORTC QLQ-C30 Fragebogens um mindestens 10 Punkte • Veränderung im Vergleich zur Baseline der Skala „globaler Gesundheitsstatus“ und aller funktionellen und Symptom –Skalen des EORTC QLQ-C30 • Fläche unter der Kurve der Skala „globaler Gesundheitsstatus“ und aller funktionellen und Symptom-Skalen des EORTC QLQ-C30 unter Studienmedikation von Baseline bis Woche 24 und von Baseline bis 1, 2 und 3 Jahre danach • Belastung durch Nebenwirkungen der Therapie zu allen Fragebogenzeitpunkten (Einzelfrage) • Zeitliche Belastung durch die Therapie zu allen Fragebogenzeitpunkten (vier Einzelfragen) ***Explorativer Endpunkt**:* • sPFS, definiert als Zeit von der Randomisierung bis zur symptomatischen Verschlechterung (neue oder Verschlechterung bestehender Symptome) gemäß Beurteilung des lokalen Untersuchers oder Tod jeder Ursache
Haupt-Einschlusskriterien	• Alter ≥ 18 Jahre. • Jeder Menopausenstatus. Bei Prä-/perimenopausalen Frauen Zustimmung zu einer Therapie mit einem LHRH-Agonisten (Goserelin oder Leuprorelin) oder einer Ovarektomie sofern sie in Arm A randomisiert werden.

	• Frauen im gebärfähigen Alter müssen zustimmen während der Behandlung mit Studientherapie und im Anschluss für den in der Fachinformation angegebenen Zeitraum nach der letzten Dosis eine wirksame Verhütungsmethode anzuwenden. • Frauen mit vor Ort bestätigter Diagnose eines metastasierten Adenokarzinom der Brust ohne vorangegangene systemische antineoplatische Therapie in der palliativen Situation. • Hormonrezeptor (HR)-positive Erkrankung, definiert als Östrogenrezeptor (ER)-positiv und / oder Progesteronrezeptor (PgR)-positiv. • Human epidermal growth factor receptor 2 (HER2)-negative Erkrankung, definiert als IHC-Status HER2 negativ/+ oder IHC HER2++ bei CISH/FISH negativem Befund. • Vorhandensein von viszeralen Metastasen (zusätzlich können weitere nicht-viszerale Metastasen vorhanden sein). • Vorliegen von Zielläsionen und / oder nicht-Zielläsionen gemäß RECIST v1.1. • Patienten müssen gemäß der entsprechenden Fachinformationen für eine palliative Therapie mit Ribociclib + AI /Fulvestrant und Capecitabin + Bevacizumab oder Paclitaxel +/- Bevacizumab qualifizieren. • Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1. • Ausreichende Organ- und Knochenmarksfunktion innerhalb 7 Tage vor Randomisierung. • Standard 12-Kanal EKG Werte: QTcF Intervall im Screening < 450 msec; durchschnittlicher Ruhepuls von 50-90 bpm • Unterschriebene, schriftliche Einwilligung nach erfolgter Aufklärung vor Beginn von protokollspezifischen Maßnahmen.
Haupt-Ausschlusskriterien	• Jegliche vorangegangene Palliativtherapie. • Vorangegangene Therapie mit irgendeinem CDK4/6 Inhibitor. • Vorangegangene adjuvante oder neoadjuvante Therapie mit einem Taxan, wenn die letzte Verabreichung innerhalb von 12 Monaten vor Studieneinschluss war. • Die Patientin erhält gleichzeitig eine andere anti-tumorale Therapie • Die Patientin hatte in den letzten 28 Tagen vor Randomisierung eine große Operation oder hat sich noch nicht von den bedeutenden Nebenwirkungen einer solchen erholt oder die Wunde ist noch nicht verheilt. • Die Patientin hat vor Randomisierung eine Bestrahlung erhalten (innerhalb von 4 Wochen eine extended-field Bestrahlung oder innerhalb von 2 Wochen eine limited-field Bestrahlung). • Bekannte Überempfindlichkeit gegen Ribociclib, AI, Fulvestrant, Capecitabin, Paclitaxel, Bevacizumab oder irgendeinen ihrer Inhaltsstoffe oder gegen Erdnuss, Soja, CHO-Zellprodukte oder Macrogolglycerolricinoleat. • Klinisch signifikante, unkontrollierte Herzerkrankung und / oder kardiale Repolarisationsanomalität (z.B. Vorgeschichte eines Myokardinfarktes innerhalb von 6 Monaten vor Studieneinschluss, verlängerte QT-Zeit, Long-QT-Syndrom, klinisch signifikante Herzrhythmusstörung oder systolischer Blutdruck von > 140 oder < 90 mmHg oder diastolischer Blutdruck von > 90 mmHg). • Die Patientin hatte eine arterielle Thrombose, die weniger als 12 Monate zurückliegt. • Die Patientin hat eine Proteinurie (≥ 2+ auf dem Protein Messstäbchen) • Die Patientin hat eine angeborene Blutungsneigung, eine erworbene Gerinnungsstörung oder nimmt die volle Dosis Anti-Koagulanzien ein • Die Patientin erhält gleichzeitig einen starken Induktor oder Inhibitor von CYP3A4/5 oder eine Medikation mit engem therapeutischen Fenster welches vorwiegend durch CYP3A4/5 metabolisiert wird und diese kann nicht innerhalb von 7 Tagen vor Beginn der Studienmedikation abgesetzt werden. • Bekanntes Vorhandensein zerebraler Metastasen mit Ausnahme, wenn der Abschluss der letzten Therapie (einschließlich Bestrahlung und / oder

	Operation) mindestens 4 Wochen vor Start der Studienbehandlung liegt und der ZNS Tumor zum Zeitpunkt des Screening klinisch stabil ist. • Patientin erhält gleichzeitig Warfarin oder ein anderes von Kumarin abgeleitetes Anti-Koagulanz in therapeutischer, prophylaktischer oder anderer Indikation. Eine Therapie mit Heparin, niedermolekularem Heparin oder Fondaparinx ist erlaubt. • Die Patientin erhält gleichzeitig oder innerhalb von 2 Wochen vor Begin der Studienmedikation systemische Kortikosteroide oder andere chronische Immunsuppressiva. • Patientin mit fortgeschrittener, symptomatischer viszeraler Tumorausbreitung unter Risiko kurzfristiger lebensgefährlicher Komplikationen (einschließlich Patientinnen mit massivem, unkontrolliertem Erguss [pleural, perikardial, peritoneal], pulmonale Lymphangiosis carcinomatosa, und mehr als 50% Leberbefall). • Patientin mit bekannter Anamnese einer HIV Infektion (Testung ist nicht vorgeschrieben). • Patientin mit aktiver unbehandelter oder unkontrollierter Infektion durch Pilze, Bakterien oder Viren. • Patientin hat gleichzeitig eine andere schwere und / oder unkontrollierte Krankheit, welche im Ermessen des Prüfers ein nicht akzeptables Sicherheitsrisiko darstellt, gegen eine Studienteilnahme der Patientin spricht oder die Einhaltung des Protokolls gefährdet (z.B. chronische Pankreatitis, chronische aktive Hepatitis, etc.). • Vorangegangene Teilnahme an einer klinischen Prüfung innerhalb von 30 Tagen oder 5 Halbwertszeiten des Prüfpräparats vor Randomisierung, je nach dem was länger ist.
Erfassung der Wirksamkeit	• Tumorbeurteilung (CT/MRT und klinische Beurteilung) zu Baseline und anschließend alle 12 Wochen bis zur Tumorprogression oder, falls dies früher erfolgt, dem Beginn der nachfolgenden Therapie. • Ganzkörper-Knochen-Scan zu Baseline und bei klinischer Indikation. • Überlebensstatus alle 6 Monate unabhängig von Therapieabbruchgrund bis zum Tod oder, fall dies früher eintritt, dem Studienende
Erfassung der Sicherheit	• Kontinuierliche Erfassung und Einstufung aller UEs einschließlich der SUEs bis 30 Tage nach Therapieabbruch • ECOG Performance Status zu Baseline und anschließend alle 12 Wochen bis zur Tumorprogression. • Überwachung von Routinelaborparametern zu Baseline und jedem nachfolgenden Zyklus bis Therapieabbruch. • EKG zur Bestimmung der QT-Zeit zu Baseline und zusätzlich an Tag 15 des ersten und Tag 1 des zweiten Zyklus für Patienten, die in Arm A behandelt werden, sowie klinisch indiziert.
Erfassung der Lebensqualität	*Die gesundheitsbezogene Lebensqualität (QoL) wird mittels des validierten European Organization for Research and Treatment of Cancer's core quality of life (EORTC QLQ-C30) Fragebogen erhoben. Zudem wird den Patientinnen eine Frage zur Belastung durch die Nebenwirkungen der Therapie und vier Fragen zur zeitlichen Belastung durch die Therapie gestellt.* *Alle Patientinnen werden zu Baseline vor Beginn der Studientherapie und anschließend alle 12 Wochen über einen Zeitraum von 36 Monaten befragt, sowie zum Zeitpunkt der Tumorprogression. Der Fragebogen zu Baseline und zum Zeitpunkt der Progression werden vom Zentrum ausgegeben, alle anderen werden 12-wöchentlich durch die iOMEDICO SMO GmbH bereitgestellt.*
Data Analysis	**Analyse Populationen:** Die Analysen zur Wirksamkeit werden basierend auf der Intention-to-Treat (ITT) Population durchgeführt, welche aus allen randomisierten Patienten besteht. Die Patienten werden in dem Arm analysiert, in den sie randomisiert

wurden unabhängig davon, ob sie die vorgesehene Therapie erhalten haben oder nicht.
Das Per-Protokoll Set (PPS) besteht aus der Untergruppe der Patienten der ITT, welche den Anforderungen des Studienprotokolls entsprechen, d.h. die Patienten ohne irgendwelche schwerwiegenden Protokollverletzungen.
Die Sicherheitspopulation (SAF) besteht aus allen Patienten, die Studienmedikation erhalten haben. Die Analyse wird stratifiziert nach der tatsächlich erhaltenen Therapie. Diese Population stellt die Analysepopulation für alle Sicherheitsanalysen dar.
Das QoL Set (QoLS) besteht aus der Untergruppe der Patienten aus der SAF, die den Fragebogen zu Baseline ausgefüllt und zurückgesendet haben (wobei mindestens eine Antwort gegeben worden sein muss). Alle Lebensqualitätsanalysen beruhen auf dieser Zusammenstellung.

Subgruppen:

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

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

- verabreichte Chemotherapie
  Die finale Analyse der Wirksamkeit, Sicherheit und Patientencharakteristika in Arm B wird stratifiziert nach der verabreichten Chemotherapie (Capecitabin + Bevacizumab ODER Paclitaxel + Bevacizumab ODER Paclitaxel Monotherapie).

Analysen:
Primäre Wirksamkeitsanalyse:

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

Sekundäre Wirksamkeitsanalysen:

- Absolute und relative Häufigkeiten der Gesamtansprechrate (ORR, komplettes oder partielles Ansprechen) nach 3 Monaten Therapie und gesamt werden für jeden Arm bestimmt.
- Absolute und relative Häufigkeiten der CBR (komplettes oder partielles Ansprechen oder stabile Erkrankung für mindestens 24 Wochen) werden für jeden Arm bestimmt.
- TTR wird mittels Kaplan-Meier-Methode berechnet. TTR ist definiert als Zeitraum von der Randomisierung bis zum ersten Auftreten eines Ansprechens jeder Art (komplettes oder partielles

	Ansprechen bestimmt durch den lokalen Untersucher). Wenn niemals ein Ansprechen erreicht wird, wird zensiert - mit der maximalen Beobachtungszeit (LPLV) für Patienten mit Krankheitsprogression oder die verstorben sind - mit dem Datum der letzten Tumorevaluation für Patienten, die zum Ende der Studie leben und deren Erkrankung nicht progredient ist. TTR wird dargestellt mit Quartilen inklusive Median, sowie den Raten nach 3 Monaten und 6 Monaten. Für all diese Parameter wird das 95% Konfidenzintervall mit angegeben. Zusätzlich wird die Häufigkeit der Ereignisse (Anzahl von Patienten mit komplettem oder partiellem Ansprechen) dargestellt. o Das OS wird mittels Kaplan-Meier Methode berechnet. Es ist definiert als Zeit von der Randomisierung bis zum Tod jeglicher Ursache. Patienten, die zum Ende der Studie noch leben, werden mit dem Datum des letzten Kontaktes zensiert. Die Häufigkeit der Ereignisse und die Quartilen unter Angabe des 95% Konfidenzintervall werden dargestellt. Zusätzlich wird die OS-Rate nach 2 Jahren, 3 Jahren und 4 Jahren mit dem entsprechenden 95% Konfidenzintervall dargestellt. Explorative Wirksamkeitsanalyse: o sPFS wird mittels Kaplan-Meier Methode berechnet. Das sPFS ist definiert als Zeitraum von der Randomisierung bis zur symptomatischen Verschlechterung (Auftreten neuer oder Verschlechterung bestehender Symptome) oder Tod (vor Beginn der nächsten Therapie), ja nach dem, was zuerst eintritt. Falls vor Beginn der nachfolgenden Therapie oder am Ende der individuellen Beobachtung (je nach dem, was zuerst eintritt) keine symptomatische Verschlechterung oder Tod eingetreten ist, wird mit dem Datum des Beginns der nachfolgenden Therapie oder des letzten Kontaktes (was immer zuerst ist) zensiert. Für jeden Arm wird die Anzahl an Ereignissen und alle Quartile des sPFS einschließlich der 95%-Konfidenzintervalle dargestellt. Sicherheitsanalyse: o Patienten- und Fall-bezogene Häufigkeiten und Anteile in jedem Therapiearm werden hinsichtlich des Auftretens der folgenden Ereignisse berechnet • UEs • SUEs • UEs mit Kausalzusammenhang zu Ribociclib, AI, Fulvestrant, Capecitabin, Paclitaxel, Bevacizumab • SUEs mit Kausalzusammenhang zu Ribociclib, AI, Fulvestrant, Capecitabin, Paclitaxel, Bevacizumab • UEs, die zum Abbruch von Ribociclib, AI, Fulvestrant, Capecitabin, Paclitaxel, Bevacizumab führen gesamt sowie nach CTCAE Schweregrad. o Auftretenshäufigkeit von UE (MedDRA-Preferred Term nach Systemorganklasse) in jeder Therapiegruppe wird berechnet für • UEs • SUEs • UEs mit Kausalzusammenhang zu Ribociclib, AI, Fulvestrant, Capecitabin, Paclitaxel, Bevacizumab • SUEs mit Kausalzusammenhang zu Ribociclib, AI, Fulvestrant, Capecitabin, Paclitaxel, Bevacizumab • UEs, die zum Abbruch von Ribociclib, AI, Fulvestrant, Capecitabin, Paclitaxel, Bevacizumab führen gesamt sowie nach CTCAE Schweregrad

	o Verschlechterung des ECOG Performance Status wird mittels Kaplan-Meier Methode berechnet. Eine Abnahme um mindestens einen Punkt verglichen mit der Baseline wird als Ereignis erachtet. Falls der ECOG Performance Status bis zum Ende der Beobachtung nicht abgefallen ist, dann wird mit dem Zeitpunkt der letzten ECOG Bestimmung zensiert. Die mediane Zeit bis zur Verschlechterung (einschließlich 95%-Konfidenzintervall), Häufigkeiten von Ereignissen und Rate zu 12 Monaten (mit 95%-Konfidenzintervall) werden für beide Therapiearme angegeben. o Ergebnisse aus Routinelaboruntersuchungen werden auf Patienten-Ebene in Listings dargestellt. QoL Analysen: o Die Zeit bis zur Abnahme des globalen Gesundheitsstatus Skalenwerts des EORTC QLQ-C30 um 10 Punkte wird mittels Kaplan-Meier Methode berechnet. Eine Abnahme von mindestens 10 Punkten im Vergleich zum Baseline Wert wird als Ereignis erachtet. Daten von Patienten, die keine Abnahme von mindestens 10 Punkten haben, werden mit Datum des letzten ausgefüllten Fragebogens zensiert. Die Analyse wird in der Subgruppe der Patienten ohne fehlende Fragebogen zwischen zwei ausgefüllten Fragebogen durchgeführt. Die mediane Zeit bis zur Verschlechterung (einschließlich 95% Konfidenzintervall), Häufigkeiten der Ereignisse und 12 Monatsrate (mit 95% Konfidenzintervall) wird für jede Behandlungsgruppe dargestellt. o Veränderung von der Baseline im globalen Gesundheitsstatus Skalenwert und den funktionellen und Symptomskalen des EORTC QLQ-C30 werden für jede Behandlungsgruppe mittels deskriptiver Statistik beschrieben. o Die Fläche unter der Kurve in den Skalenwerten des EORTC QLQ-C30 werden mittels deskriptiver Statistik für die Behandlungsgruppen zu den nachfolgenden Zeitpunkten dargestellt: • Baseline bis 24 Wochen nach Therapiebeginn • Baseline bis 1 Jahr nach Therapiebeginn • Baseline bis 2 Jahre nach Therapiebeginn • Baseline bis 3 Jahre nach Therapiebeginn Die Analysen werden für alle Patienten durchgeführt, für die die Baseline und der jeweilig letzte Fragebogen vorhanden ist und für die weniger als die Hälfte der Fragebogen / Skalen fehlt. Fehlende Werte werden mittels eines Regressionsmodels unter Berücksichtigung der Baseline Charakteristika ersetzt. Eine Sensitivitätsanalyse wird für die Fläche unter der Kurve in denjenigen Versuchspersonen durchgeführt, für die alle Fragebogen / Skalen bis zum jeweiligen Zeitpunkt vorhanden sind. Jede der genannten Analysen wird nur dann berechnet, falls mindestens 20 Patientinnen pro Behandlungsgruppe auswertbar sind. o Die Belastung durch Nebenwirkungen (Einzelfrage) wird pro Arm und Zeitpunkt mit Häufigkeiten und Anteil dargestellt Die zeitliche Belastung durch die Therapie (vier Einzelfragen) wird pro Behandlungsarm und Fragebogenzeitpunkt mit Häufigkeiten und Anteil dargestellt.
Geplante Studiendauer	Einschluss des ersten Patienten 24.05.2018 Einschluss des letzten Patienten Q2/2021 Letzte Visite des letzten Patienten Q2/2025 Finale Analyse / Studienbericht Q2/2026

Schlüsselworte	Metastasierter Brustkrebs; viszerale Metastasen; HR+; HER2-; ER+; PgR+; CDK4/6 Inhibitor; Ribociclib; Aromataseinhibitor; Erstlinie; PFS; Lebensqualität Zeitliche Belastung durch die Therapie (einzelner Punkt)

Registerstudie: Mammakarzinom, 1st-line

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

AIO-assoziiierte Studie

Studiennummer/-Code:	AIO-MAM-0218/ass // OPAL	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 – 2021	
Weitere Zentren:	erwünscht	
Zentren:	geplant: ca. 200	initiiert: 207
Patienten:	geplant: 2000	aktuell eingeschlossen: 1351
Letzte Aktualisierung	13.10.2020	

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	Advanced breast cancer (ABC)
DESIGN	National, observational, open, prospective, longitudinal, multicenter cohort study
INDICATION	Advanced breast cancer
OBJECTIVE(S)	To describe treatment reality (systemic treatments and sequential treatments) applied in German routine practice. To assess effectiveness of systemic treatment with cytotoxic, endocrine and signaling pathway inhibitors by various outcome parameters such as response rate, progression free survival, overall survival.
INTERVENTION(S)	Non-interventional
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Patients will be asked to give additional informed consent agreeing that their tumor samples taken during routine treatment can be used for further scientific testing. For the decentralized biobank, pathological material will remain with the local pathologist. Future research is possible.
BACKROUND/RATIONALE	The OPAL clinical research platform will continue the data collection from the Tumor Registry Breast Cancer, started in 2007, and provide data on treatment reality from all health care sectors in Germany. It will show if and how the choice of treatment changes over time and assess the effective-ness of different treatments for advanced breast cancer in routine care. Associated modules will set up a decentralized, biobank for future translational research and investigate patient-reported outcomes (PRO) in clinical routine.

KEY EXCLUSION CRITERIA	• Patients with prior systemic therapy for ABC • Patient who do not receive any systemic therapy for ABC

KEY INCLUSION CRITERIA	• Female and male patients with advanced breast cancer (synchrone or metachrone metastasized or locally advanced, inoperable)
	• 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
	  • Patients not participating in the PRO module: within six weeks after start of systemic first-line for ABC

OUTCOME(S)	Response rate, progression free survival, overall survival
STATISTICAL ANALYSIS	Descriptive
SAMPLE SIZE	2000 patients (1000 Hormonereceptor-positive, Her2-negative, 500 Her2-positive, 500 triple-negative)
TRIAL DURATION	9 years

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 Q4/2020	
Patienten:	geplant: 45	aktuell eingeschlossen: 11
Zentren:	geplant: 8	initiiert: 5
Weitere Zentren:	Interessierte Zentren wenden sich bitte an Prof. Michl	
Letzte Aktualisierung	Oktober 2020	

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-G2 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:	Q2 2017 bis Q1 2021	
Weitere Zentren:	ja, es sind weitere Zentren geplant	
Zentren:	geplant: 40-43	initiiert: 33
Patienten:	geplant: 300	aktuell randomisiert: 150
Letzte Aktualisierung	Oktober 2020	

APPLICANT/ COORDINATING INVESTIGATOR	ITM Solucin GmbH/ Prof. Dr. Richard Baum Zentralklinik Bad Berka GmbH
CONDITION	Well-differentiated neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET), with positive SSTR expression
OBJECTIVE(S)	**Primary objective** 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 **Secondary objectives** 1. To assess overall survival (OS) during study period, defined as the date from randomisation until death 2. To determine objective response rates (ORR), defined as the proportion of patients achieving partial (PR) or complete response (CR) as best outcome 3. To determine disease control rates (DCR), defined as the proportion of patients achieving stable disease (SD), PR or CR as best outcome 4. To determine the duration of disease control (DDC), measured from the time of initial diagnosis of response (SD, PR or CR), until diagnosis of progression 5. To determine functional response rates (FRR), considering Cg-A and specific hormones (where increased at baseline) 6. To assess the safety and tolerability of 177Lu-edotreotide in GEP-NET patients 7. To determine the health-related quality of life (HRQL) in GEP-NET patients during and after therapy (EORTC QLQ-C30 questionnaire) 8. To evaluate symptomatic tumour response (EORTC GI.NET21 questionnaire) 9. To evaluate the impact of patient characteristics (time from primary diagnosis, time from diagnosis of progression, number of prior therapies (1st vs 2nd line), type of prior therapies, KPS at randomisation) on tumour response 10. To evaluate the impact of tumour histology (histological entity, tumour grade, Ki-67 expression, SSTR expression, functional state) as determined in primary or current bioptic tumour specimen on tumour response **Tertiary objectives (in 177Lu-edotreotide patients)** 1. To assess differences in tumour and kidney radiation dose estimates,

	obtained with conventional 2D (planar), compared to hybrid (2D/3D), and 3D (SPECT) imaging 2. To evaluate the value of pre-therapeutic SSTR imaging (SRI) to predict tumour response (globally/at lesion level) 3. To evaluate the relationship between PRRT radiation dose (in Gy)
INTERVENTION(S)	- Slow intravenous infusion/injection (IV) of ^{177}Lu-edotreotide, an octreotide-derived somatostatin analogue containing the chelator DOTA, radiolabelled with n.c.a. lutetium-177, a radio-lanthanide, emitting β- and γ-radiation - 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. Known hypersensitivity to lysine, arginine, or any excipient of the nephroprotective amino acid solution 4. Prior exposure to any peptide receptor radionuclide therapy (PRRT), including ^{177}Lu-edotreotide, ^{90}Y-edotreotide or other SSTR-targeting agents (e.g. ^{177}Lu-octreotate or high-dose ^{111}In-pentetreotide) 5. Prior therapy with mTor inhibitors 6. Prior EFR (extended field radiation) to GEP-NET lesions or radioembolisation therapy (e.g. ^{90}Y microspheres, ^{131}I-lipiodol) with administration to the liver 7. Therapy with an investigational compound and/or medical device within 30 days or 5 half-life periods (whichever is longer) prior to randomisation 8. Subjects who have received a live vaccine up to 4 weeks prior to first dose 9. Current therapy with any prohibited medication 10. Ongoing toxicity grade 2 according to CTCAE version 4.03 from previous standard or investigational therapies 11. Indication for surgical lesion removal with curative potential 12. Planned (for the period of study participation): chemotherapy, immunotherapy, radiation therapy, chemo-embolisation, bland embolisation, radio-embolisation, treatment with cyclosporine-A 13. Neuroendocrine tumours, not meeting the inclusion criteria: • With known non-GEP-NET origin (e.g. pulmonary or gonadal primaries) • Functional GE-NET • NET with unknown primaries (CUP), manifesting as liver metastases • Poorly differentiated neuroendocrine carcinomas(G3) • NET for which no histological specimen for secondary histological analysis can be obtained 14. Total hepatic tumour burden > 70% 15. Brain metastases 16. Secondary malignoma within previous 5 years (except basalioma) 17. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator 18. Renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments, as follows: • Renal o Serum potassium > 5.0 mmol/L o Renal obstruction o Known nephropathy from any cause • Hepatic o Total bilirubin >1.5 x ULN o AST or ALT > 2.5 x ULN o Alkaline phosphatase > 5 x ULN o Albumin < 3 g/dL, unless prothrombin time is within normal range o Known cirrhosis or other distinctly restricted liver function • Cardiovascular

	o New York Heart Association classification III & IV o Uncontrolled hypertension • Haematopoietic o Platelets ≤ 80 * 10^9/L o Absolute neutrophil count (ANC) < 1 x 10^9 cells/L 19. Pregnant or breast-feeding women. Female patients of childbearing potential or male patients with female partners of childbearing potential, unless willing to practice full and true sexual abstinence or being surgically/permanently sterile or with a history of hysterectomy for women, not willing to practice effective contraception by using: a non-oral, injected or implanted non-oestrogen progesterone based hormonal method, male condom, vaginal diaphragm, cervical cap, intrauterine device, during the study period and for 56 days after treatment in the everolimus group and 66 days in the PRRT group (10 half-lives of ^{177}Lu) after the last treatment cycle. 20. Subjects not able to declare meaningful informed consent on their own (e.g. with legal guardian for mental disorders) or any other vulnerable population to that sense (e.g. persons institutionalised, incarcerated etc.).
KEY INCLUSION CRITERIA	All patients must meet all of the following criteria: 1. Written informed consent 2. Male or female ≥ 18 years of age 3. Histologically and clinically confirmed diagnosis of well-differentiated neuro-endocrine tumour of non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET), tumour grade G1 or G2 (Ki-67 < 20%), unresectable or metastatic 4. Availability of existing biopsy specimen from primary tumour or metastasis or, if unavailable, willingness to undergo current biopsy for secondary central analysis 5. Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥ 1 cm in longest diameter, and ≥ 2 radiological tumour lesions in total. A maximum of 5 target lesions visible on CT/MRI will be defined, thereof not more than 2 lesions per organ 6. Somatostatin receptor positive (SSTR$^+$) disease, as evidenced by SSTR imaging (SRI) within 4 months prior to randomisation, by: • ^{68}Ga-based SSTR PET imaging (e.g. using ^{68}Ga-edotreotide or ^{68}Ga-DOTATATE), or • ^{111}In-pentetreotide SSTR SPECT/planar imaging, or • ^{99m}Tc-octreotide SSTR SPECT/planar imaging All target lesions and ≥ 90% of non-target lesions need to be positive for SSTR, demonstrated by adequate tracer uptake, being defined as being "clearly differentiable from background" 7. Radiological disease progression, defined as: • Progressive disease per RECIST 1.1. criteria, eviden-ced by consecutive morphological imaging (CT or MRI) with ≥ 90 days interval during the 12 months prior to randomisation 8. Karnofsky performance status (KPS) scale ≥ 70 9. Life expectancy of at least 6 months 10. Glomerular filtration rate (GFR, MDRD) ≥ 60 mL/min/1.73 m^2 11. For patients included in France only, verification and confirmation of their affiliation with a social security
OUTCOME(S)	To demonstrate the efficacy of PRRT with 177Lu-edotreotide to prolong median progression-free survival (mPFS) in patients with inoperable, progressive, SSTR+ GEP-NET, compared to everolimus.
STUDY TYPE	This will be a confirmatory, prospective, randomised, controlled, parallel group, open-label, multi-centre phase III study to evaluate the efficacy and safety of 177Lu-edotreotide in comparison to molecular targeted therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).

STATISTICAL ANALYSIS	**Primary Variable:** **Progression-free survival** Median progression-free survival (mPFS) **Secondary variables:** **Efficacy** a) Percentage patients progression-free at 2 years (% 2y-PFS) b) Objective response rate (ORR), % patients achieving PR and CR c) Disease control rate (DCR), % patients achieving PR, CR and SD d) Median duration of disease control (mDDC) e) Median overall survival (mOS) f) Percentage overall survival at 2 years (% 2y-OS) g) Percentage patients experiencing functional tumour response (CgA, specific hormones), classified as functional SD, PR, CR h) Median duration of functional response i) Percentage of patients experiencing symptomatic tumour response (EORTC GI.NET21 questionnaire), classified as symptomatic SD, PR, CR j) Median duration of symptomatic response **Safety and tolerability** a) Calculated GFR, percentage depart from baseline value b) Measured TER, percentage depart from baseline value c) Renal volume (V_{kidney}), percentage depart from baseline value d) General safety parameters: Frequency of occurrence and severity of abnormal findings in safety investigations (physical examination, vital signs, 12-lead ECG, clinical laboratory, adverse events, concomitant medication) **Health-related quality of life (HRQL)** a) Maximum HRQL improvement (EORTC QLQ-C30 questionnaire) total scores, relative to baseline b) Median duration of maximum HRQL improvement **Tumour dosimetry measures** Cumulative absorbed dose (Gy) from ^{177}Lu-edotreotide to target tumour lesions, estimated from ^{177}Lu-edotreotide dosimetry after first dose. Stratified randomisation will be used to control for primary tumour origin (GE-NET vs. P-NET) and for prior medical therapy (1st line vs. 2nd line, as well as types of previous therapies). The primary variable progression-free survival (PFS) will be analysed using confirmatory statistics. All survival data will be analysed using the Kaplan-Meier method, which takes into account the impact of censored observations and the Log-rank test. Likewise, the secondary variable overall survival (OS) and progression-free survival in the treatment groups, adjusted for the co-variates primary tumour origin, prior medical treatment, tumour grade and baseline KPS, will be compared using exploratory statistics. All other secondary variables will be analysed descriptively by treatment group.
SAMPLE SIZE	In total, 300 GEP-NET patients will be randomised in 2:1 fashion to receive either • PRRT with ^{177}Lu-edotreotide consisting of a maximum of four cycles (7.5 ± 0.7 GBq ^{177}Lu-edotreotide each), administered as IV infusion at 3-monthly intervals for 9 months, or until diagnosis of progression (200 patients), or • 10 mg everolimus (Afinitor®) daily, administered orally as a tablet until diagnosis of progression (100 patients)
TRIAL DURATION	Study duration per patient will be 24 months. Collection of survival data and information on further antineoplastic treatments will be continued after EOS. • Screening period: 90 days (day -90 to day -1) • Study period: - Treatment period IMP: Four single doses administered on days 0, 90, 180 and 270, unless diagnosis of progression or EOS - Treatment period RP: Daily oral administration from day 0 until diagnosis of progression or EOS. - Follow-up period: day 0 – month 24 (or until diagnosis of progression, whichever is earlier). • Post-study period follow-up:

	- ^{177}Lu-edotreotide therapy for patients (having progressed under everolimus therapy): Administration and follow-up as for study patients, until secondary progression. - All patients: collection of overall survival (OS) data.

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 – 12/2023	
Zentren:	geplant:	initiiert: >30
Patienten:	geplant: 306	eingeschlossen: 184
Weitere Zentren:	Interessierte Zentren können sich melden	
Letzte Aktualisierung	Oktober 2020	

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 ≥ 150 mmHg or diastolic blood pressure (DBP) of ≥ 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): Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$ 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]

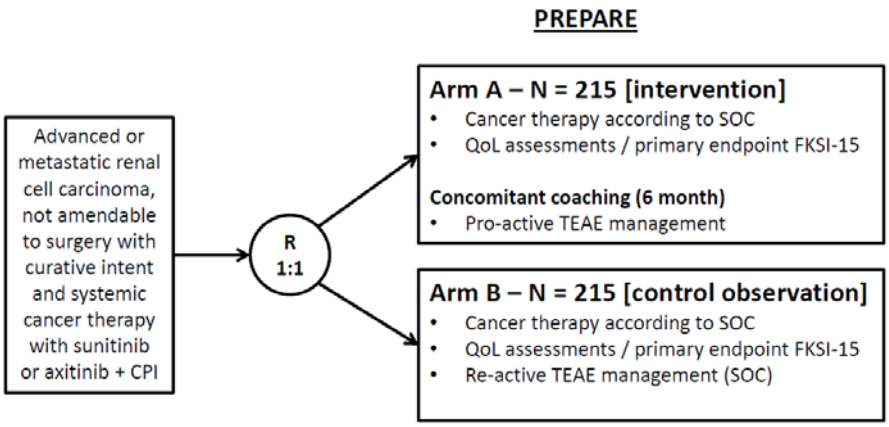
AIO-assoziierte Studie

Studiennummer/-Code:	AIO-NZK-0115/ass - PREPARE	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 - 2023	
Zentren:	geplant: 100	initiiert: 27
Patienten:	geplant: 430	aktuell eingeschlossen: 41
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	Oktober 2020	

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	Primary endpoint: QoL assessment during sunitinib treatment: Rate of responders to concomitant coaching assessed by the FKSI-15 questionnaire Secondary endpoints: • 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: 41
Start date	Q1/2017
More centres?	Target number: 100 / Yes (currently 27 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 o Information on nature and severity of treatment emergent AEs o Information about remedies for TEAEs o Propagation and explanation of tests and treatment decisions o Patient instruction on self-care and preventive measures • Preemptive AE treatment strategies o 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) 
Criteria for tumor evaluation	RECIST 1.1
Rationale	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. 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.

Fortgeschrittenes Nierenzellkarzinom

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

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-NZK-0118/ass - CaboCHECK	
Status:	rekrutierend	
Rekrutierungszeitraum:	Rekrutierungsstart: Q2 2019	
Weitere Zentren:	Keine weiteren Zentren in Planung	
Zentren:	geplant: 25	initiiert: 25
Patienten:	geplant: 200	aktuell eingeschlossen: 48
Letzte Aktualisierung	27.10.2020	

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Viktor Grünwald Universitätsklinikum Essen Innere Klinik (Tumorforschung) Hufelandstr. 55 45147 Essen
CONDITION	Advanced renal cell carcinoma (RCC)
OBJECTIVE(S)	Primary objective - To evaluate the safety of cabozantinib tablets in patients with advanced renal cell carcinoma (RCC) after pre-treatment with nivolumab or nivolumab plus ipilimumab Secondary objectives - To describe the efficency of cabozantinib tablets patients with advanced renal cell carcinoma (RCC) after pre-treatment with nivolumab or nivolumab plus ipilimumab.
INTERVENTION(S)	Cabozantinib after pre-treatment with nivolumab or nivolumab plus ipilimumab
KEY EXCLUSION CRITERIA	1. Patients who are unable to consent because they do not understand the nature, significance and implications of the observational trial

	2. Involvement in the planning and / or conduct of the study (applies to both Ipsen staff and/or staff of sponsor and study site)
KEY INCLUSION CRITERIA	1. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject, except for patients that already deceased at the time of inclusion and will be enrolled anonymously, except for patients that already deceased at the time of inclusion and will be enrolled anonymously 2. Patients with advanced or metastatic renal cell carcinoma, including all subtypes 3. Age ≥ 18 years 4. Completion of treatment with nivolumab or nivolumab / ipilimumab combination therapy (any line of therapy) directly followed by cabozantinib treatment
OUTCOME(S)	Endpoints • Incidence of serious adverse events at least possibly related to cabozantinib treatment during cabozantinib treatment • Secondary safety endpoints are the number of dose reductions, dose interruptions and terminations of cabozantinib treatment due to adverse events. Secondary effectiveness endpoints are objective response rate, clinical benefit rate, duration of response, duration of cabozantinib treatment, and time to next treatment.
STUDY TYPE	Retrospective non-interventional study
STATISTICAL ANALYSIS	The sample size has been set to 200 patients, treated with cabozantinib between June 2015 and today, based on feasibility considerations. This sample size will be sufficient to detect an adverse effect occurring with a true frequency of 2.3% at least once with a probability of 99%. On the other hand, the power to detect an adverse effect with a true incidence rate of 1% would be >80%. This implies that the proposed retrospective analysis will be able to provide important safety information, and a valuable addition to the global cabozantinib safety data base. Appropriate descriptive methods will be applied for all data analyses. If appropriate and unless otherwise specified, 2-sided 95% confidence interval (CIs) will be displayed and if p-values are presented, they will be for exploratory purposes only. Descriptive statistics will include number of available data, number of missing data and the following: - Mean, standard deviation (SD), minimum, interquartile range (0.25, 0.75), median, maximum when appropriate for continuous variables; - Frequency count and percentage for categorical nominal variables; - Both the above for categorical ordinal variables. - Missing data will not be replaced.
SAMPLE SIZE	N=200
TRIAL DURATION	18 months
PARTICIPATING CENTERS	25 sites planned
CONTACTS	Medical Scientific Lead Prof. Dr. Viktor Grünwald Universitätsklinikum Essen Mail: viktor.gruenwald@uk-essen.de Phone: Study Management IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest Dr. Caroline Schönherr Mail: Schoenherr.caroline@ikf-khnw.de Tel: 069 7601-4094

Arbeitsgruppe Ösophagus-/ Magen-Karzinom

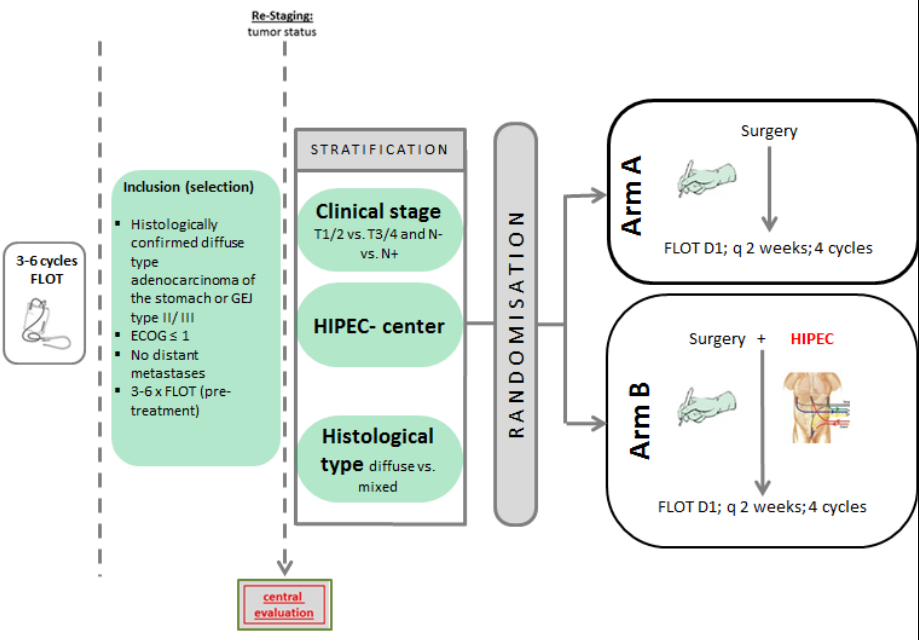
Lokal fortgeschrittenes Adenokarzinom des gastroösophagealen Übergangs oder Magens, perioperativ

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:	Förderantrag der Krebshilfe ist genehmigt, Voten erhalten, Initiierungen in Q4/2020 geplant	
Rekrutierungszeitraum:	Studienstart 2020, 3,5 Jahre Rekrutierung	
Weitere Zentren:	sind sehr erwünscht	
Zentren:	geplant: 20	initiiert:
Patienten:	geplant: 200	aktuell eingeschlossen:
Letzte Aktualisierung	09.10.2020	

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 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, including diagnostic laparoscopy 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 completed their therapy in Arm B, recruitment will be stopped, until a safety analysis is performed that shows feasibility, safety, and tolerability of Arm B
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 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 8.2After positioning of inflow catheter and drains intraabdominal cisplatin solution (50mg/m2 in NaCl 0.9%) will be administered at a temperature of 42°C for 90 minutes. Perfusion with cisplatin at a dose of 50 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 5 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. Peripheral polyneuropathy ≥ NCI Grade II 10. The patient has undergone major surgery within 28 days prior to enrollment except staging laparoscopy. 11. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or ascites. 12. On-treatment participation in another interventional clinical study in the period 30 days prior to inclusion and during the study 13. Subject pregnant or breast feeding, or planning to become pregnant 14. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) 15. Any other concurrent antineoplastic treatment including irradiation 16. Known intraabdominal adhesion situs
KEY INCLUSION CRITERIA	1. Histologically confirmed, medically operable, resectable diffuse or mixed type 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. Adequate hematological, hepatic and renal function parameters: a. Leukocytes ≥ 3000/mm³, platelets ≥ 100,000/mm³, neutrophil count (ANC) ≥1000/µL, hemoglobin ≥9 g/dL (5.58 mmol/L), b. Serum creatinine ≤ 1.5 x upper limit of normal c. Bilirubin ≤ 1.5 x upper limit of normal, AST and ALT ≤ 3.0 x upper limit of normal, alkaline phosphatase ≤ 6 x upper limit of normal 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. • R0 resection rate defined as the percentage of patients achieving a R0 resection referring to the total number of patients randomized into the respective treatment arm. • Pathological response rates • 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 • pCR/pSR, 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 • 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: 15
Patienten:	geplant: 340	aktuell eingeschlossen: 15
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	Oktober 2020	

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	IKF Klinische Krebsforschung 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, leucovorin 200 mg/m2 d1, oxaliplatin 85 mg/m2 d1, docetaxel 50

	mg/m2 d1) every two weeks (4 weeks of therapy) followed by radiochemo-therapy beginning at day 21 after day one of the last cycle of chemotherapy. Radiochemotherapy consists of oxaliplatin 45 mg/m2 weekly (d1, 8, 15, 22, 29) and continuous infusional 5-FU 225 mg/m2 plus concurrent radiotherapy given in 5/week fractions with 1.8 Gy to a dose of 45 Gy on 5 weeks. Resection is performed 4-8 weeks after the end of neoadjuvant treatment. Adjuvant treatment starts 6-12 weeks after surgery and consists of 4 cycles of FLOT (total treatment period of 26 – 33 weeks)
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, leucovorin, 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)

Lokal fortgeschrittenes 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)

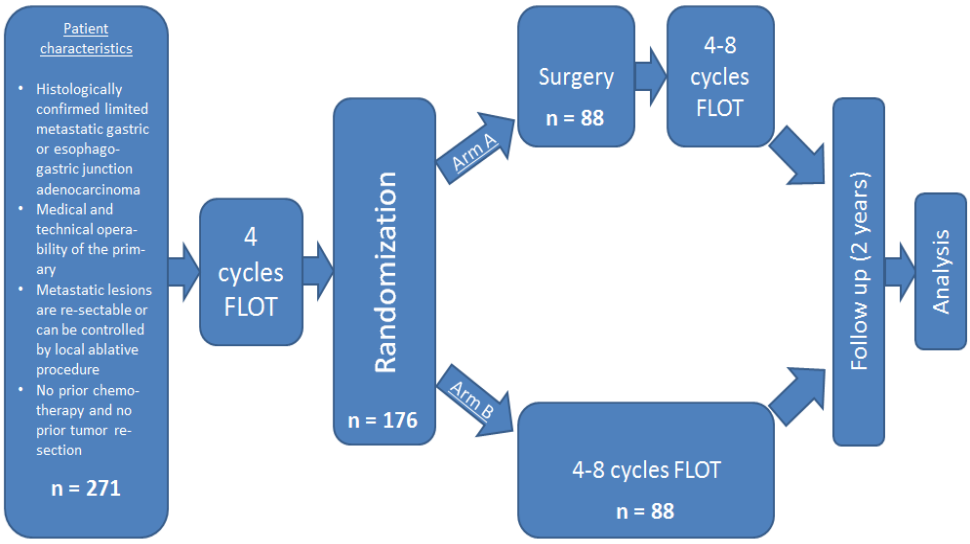
AIO-Studie

Studiennummer/-Code:	AIO-STO-0215 - RENAISSANCE / FLOT5	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2016 - 2021	
Zentren:	geplant:	initiiert:
Patienten:	geplant: 176 randomisierte Patienten aktuell eingeschlossen: 141 aktuell randomisiert: 108	
Weitere Zentren:	Weitere Zentren auf Anfrage	
Letzte Aktualisierung	23.10.2020	

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



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

AIO-Studie		
Studiennummer/-Code:	AIO-STO-0417 - MOONLIGHT	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2018 - 2022	
Weitere Zentren:	Nicht benötigt	
Zentren:	geplant: 30	initiiert: 27
Patienten:	geplant: 207	aktuell eingeschlossen: 160
Letzte Aktualisierung	Oktober 2020	

Study type	Randomized, open labelled, multicenter phase II trial
Lead Coordinating Investigator Deputy 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 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) Secondary endpoints: • Progression Free Survival acc. to RECIST v1.1 for Arms A1, A2 • Progression Free Survival rate at 6 months (PFS@6) • Overall Response Rate (ORR) according to RECIST v1.1 • Duration of response and disease stabilization • Overall survival (OS) • Safety (according to NCI-CTCAE V 4.03) and tolerability • Quality of life (EORTC QLQ-C30). The QoL analyses will include QoL mean values, QoL response and time to symptom deterioration (TTSD) • Translational research: correlation of biomarkers potentially associated with clinical efficacy (OS, PFS and ORR) from nivolumab plus ipilimumab by molecular quantitation of target gene expression and immune cell composition

Background / Rationale	Gastroesophageal (GE) cancers represent a major global healthcare problem. In 2002 approximately 1.4 million people worldwide developed GE cancers and 1.1 million died. When compared with best supportive care alone, chemotherapy yields a quite modest advantage of about 3 months until disease progression with Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (fluorouracil, capecitabine, and S1) being generally considered as the standard-of-care in 1L treatment. Cisplatin has been the most frequently administered platinum in gastroesophageal cancer treatment. Since the REAL-2 study demonstrated an oxaliplatin-based regimen to be non-inferior to cisplatin with a favorable safety profile (Cunningham et al 2008), oxaliplatin combinations with fluoropyrimidines have been studied in multiple Phase 2 and 3 trials, and showed similar efficacy trends across regions (Yamada et al 2015; Al-Batran et al 2008). A Phase 3 trial in esophageal/gastric/GEJ cancers comparing the FOLFOX regimen (5-fluorouracil plus leucovorin and oxaliplatin) vs FLP (5-fluorouracil plus leucovorin and cisplatin) showed no statistically significant differences between the 2 treatments, but favored the FOLFOX arm vs the FLP arm in terms of median PFS (the primary endpoint, 5.7 months vs. 3.9 months), response rate (35% versus 25%), and median survival (10.7 months vs 8.8 months) (Al-Batran et al 2008). As a result, oxaliplatin has become one of the major backbone platinum compounds in the 1L setting. Based on these observations, the oxaliplatin-based regimens FOLFOX is considered to be reasonable comparators in this Phase 2 study. The lack of a major benefit from the various newer-generation combination chemotherapy regimens has stimulated research to use targeted agents. Except trastuzumab, several monoclonal antibodies approved for other cancer indications including cetuximab and bevacizumab have failed to demonstrate efficacy as single agents and in combination with chemotherapeutics. Immunotherapeutic approaches have demonstrated clinical efficacy in several advanced cancer types. Anti PD-1 and PD-L1 inhibitors (eg, nivolumab, pembrolizumab, and avelumab) have been investigated in gastroesophageal cancer treatment and have demonstrated anti-tumor activity (Le et al 2016; Bang et al 2015; Chung et al 2015). Treatment with pembrolizumab achieved a 33% ORR by investigator assessment and 22% by central data review in gastric cancer subjects with PD-L1 expressing tumors (Bang et al 2015). The 6-month progression-free survival (PFS) rate was 26% and median PFS was 1.9 months. Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity (Curran et al 2010). The combined therapy of Nivolumab (BMS-936558), and ipilimumab (BMS-734016) has shown encouraging clinical activity with a confirmed ORR of 26% and a median OS of 6.9 months in patients with chemotherapy refractory gastric cancer disease (Janjigian et al 2016). Moreover, immunotherapy has been shown to improve the efficacy of chemotherapy (Kershaw et al 2013). In chemotherapy naïve non-small cell lung cancer, the phase II KEYNOTE 012 trial demonstrated an doubled response rate (55% vs 29%; p=0.0016) when pembrolizumab was added to a cisplatinum-doublet chemotherapy with a manageable safety profile (Langer et al 2016). It is anticipated that the combination of standard chemotherapy with combined Nivolumab/Ipilimumab immunotherapy will increase clinical activity, however, until now, no data exist for mGC. References: Cunningham et al 2008; N Engl J Med 2008; 358:36-46. Yamada et al; Annals of Oncology 2015;26:141-148. Al-Batran et al; J Clin Oncol 2008;26:1435 Le et al; ASCO GI 2016, abstract 6 Bang et al; ASCO 2015, abstract 4001 Chung et al; ESMO 2015, Abstract No. 2364 Curran et al; PNAS 2010;107: 4275-80. Janjigian et al; J Clin Oncol 34, 2016 (suppl; abstr 4010) Kershaw et al; OncoImmunology 2013 2:e25962. Langer et al; Lancet Oncol. 2016 Nov;17(11):1497-1508.

Population	Patients with advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction are eligible for this study.
Inclusion/exclusion criteria	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

Investigational and Control Arm, Dose, regimen, treatment cycle	Randomisation 1 (F+N+I) :2 (sequential therapy F+N+I) Each Cycle: either: - Treatment: Arm A1 (identical to Arm A in completed first part of the trial) 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 Or - Treatment: Arm A2 (“sequential”) 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. Duration of treatment Treatment with each of the components FOLFOX, nivolumab and/or ipilimumab will be administered until progression (according to RECIST v1.1), intolerable toxicity, patient’s request, or end of study treatment phase (24 months). The study treatment will be limited to a maximum of 24 months.
Statistical considerations	PFS analysed according to the ITT principle is the primary efficacy endpoint. The expected median PFS in the standard arm is 5.5 months; the expected median PFS in the experimental arm is 8.5 months. We hypothesize that the experimental therapy is associated with clinically relevant improvement according to a HR of 0.68. In the frame of a phase II testing, the use of a one-sided significance level of 10% is justified. Based on this, 118 randomized subjects (59 in the control and 59 in the experimental treatment group) will be enrolled to provide 80% power for detecting an average HR of 0.68 using the log rank test at a one-sided type I error of 10% and assuming a 5% drop out rate. The sample size calculation is based on 2 years recruitment time and 1 year follow up time after last patient-in. So the minimum follow-up time is 3 years.

	1:1 Randomization will be performed according to the following stratification criteria: • ECOG PS (0 vs 1) • Tumor status (prior resection vs. no prior resection) 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.
Key dates	FPFV: Q2 2018 Planned time for recruitment 2,0 years Follow-up after end of treatment (EOT): every 2 months for up to 1 year

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	2017 - 2021	
Weitere Zentren:	erwünscht	
Zentren:	geplant:	initiiert:
Patienten:	geplant: Phase II: 111/Ph III: 318	aktuell eingeschlossen: 111 Phase II, 30 Phase III
Letzte Aktualisierung	Oktober 2020	

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. 089/41409848; Fax 089/4140-3654822 sylvielorenzen@gmx.de
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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 during the study and for 3 months after the end of ramucirumab treatment (appropriate contraception is defined as surgical sterilization (e.g. bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier

	methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)). Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start. * 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 within 6 months of 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 <6 months after completion of the treatment. If progression occurred ≥ 6 months after completion of neoadjuvant/adjuvant therapy, the therapy is not counted as a treatment line. 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 10^9/L • Platelets ≥ 100 x 10^9/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 UNL • 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 institutional standard) 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	According to these parameters, and using a standard single-stage phase II design by FLEMING (1981), n = 67 patients evaluable for efficacy have to be recruited in the R-FOLFIRI arm. About n = 34 patients are to be allocated to the reference R-Pac arm, according to the 2:1 randomization. The final conclusion of the phase II trial will depend on the definite OS rate (and its confidence interval), the respective findings in the R-Pac reference arm, as well as the information on type, frequency and severity of toxicities. Thus, a total number of about 67 + 34 = 101 evaluable patients is required. Assuming a 10% drop out rate we are planning to include 111 pts
Key dates	FPFV: Q2 2017 Follow-up: every 2 months for up to 1 year
Number of patients and location	Phase II portion: Total number of patients: 111 (Arm A 67+ Arm B 34, recruitment completed) Phase III portion: Total number of patients: 318 (Arm A 159 + Arm B 159) Location of sites: Germany 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-0419/ass: A study of Ramucirumab beyond progression plus TAS- 102 in patients with advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction, after treatment failure on a ramucirumab based therapy – (RE- ExPEL)

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-STO-0419/ass - RE-ExPEL	
Status:	Rekrutierung startet voraussichtlich noch 10/2020	
Rekrutierungszeitraum:	Studienstart Q4 2020, 6 Monate Rekrutierung	
Zentren:	geplant: 7	initiiert: 2
Patienten:	geplant: 20	aktuell eingeschlossen: 0
Weitere Zentren:	eventuell noch möglich	
Letzte Aktualisierung	08.10.2020	

STUDY TYPE	Non-randomized, open-label, multicenter pilot 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	Institut für Klinische Krebsforschung IKF 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	advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction
DESIGN	This is an interventional, prospective, open label, multicenter single-arm pilot study in patients with advanced metastatic gastric or gastroesophageal junction adenocarcinoma, who progressed on ramucirumab containing pre-treatment in 2nd line. The scope of the trial is to evaluate tolerability and safety. Patients with advanced metastatic and inoperable, gastric or GEJ- cancer who have progressed on/after a 2nd line ramucirumab based pre- treatment • paclitaxel/ramucirumab • FOLFIRI/ramucirumab • ramucirumab monotherapy will be included in this trial (Ram beyond progression). Patients will receive ramucirumab/TAS- 102 and data will be compared to historical data of the TAGS- (TAS- 102 monotherapy) trial. Concurrent use of other chemotherapy is not allowed. Safety analyses will be conducted when 20 patients are fully documented after receiving 2 cycles (one 4-week cycle comprises ramucirumab 8mg/kg administered at d1 and d15 and TAS- 102 35mg/m2 p.o. twice daily administered on d1-5 and d8-12). The analysis will be reviewed by the lead coordinating investigator (PD Dr. T.O. Goetze) and members of the steering committee and then by the data safety monitoring board. Results of the safety analysis will be provided and discussed with Lilly for a possible continuation

of the trial in a randomized setting TAS- 102 monotherapy vs. TAS- 102 plus Ramucirumab beyond progression.

Patients will receive ramucirumab 8 mg/kg iv over 60 min on d1+15, q4w and TAS- 102 35mg/m2 p.o. twice daily (BID) d1-5 and 8-12, q4w until progression or intolerance or completion of 4 cycles in the trial.

Tumor assessments (CT or MRI) are performed before enrollment and then every 8 weeks (every 2nd cycle) during therapy and every 12 weeks during follow-up 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) will be performed prior to every treatment dose of ramucirumab or every two weeks if ramucirumab was discontinued. Safety of TAS- 102 +/- ramucirumab will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.

In this first part of the study only 20 patients will be treated with the combination therapy for tolerability and safety assessment of the combination of TAS- 102 plus ramucirumab beyond progression. If there are no safety issues based on the results of the current trial a randomized study is planned.

Figure 1: Study Scheme.

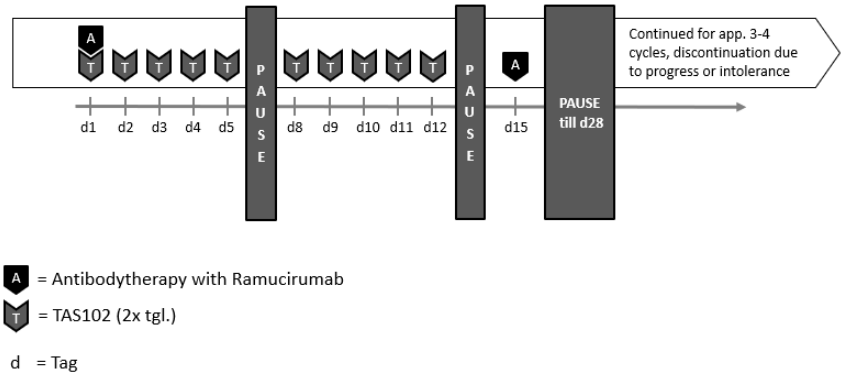


Figure 2: Scheme therapy time points

Study Drug	Dosage Strength	Formulation	Amount
Ramucirumab	8mg/kg KG every 2 weeks	i.v.	max. 8 applications/pts; 20 pts
TAS-102	15mg + 20mg tablets	p.o.	1x15mg + 1x20mg per application; app. 80 applications/pts; 20pts

INDICATION	advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction, after treatment failure on a ramucirumab based therapy
OBJECTIVE(S)	Primary endpoint The primary endpoint of the study is tolerability and toxicity, defined by the rate of serious adverse events (SAEs) of any cause according to CTCAE v5.0 Secondary endpoints • Rate of treatment-related AEs and SAEs according to CTCAE v5.0 • Rate of grade 3 or worse adverse events for neutropenia • Rate of grade 3 or worse adverse events for anemia • Rate of grade 3 or worse adverse events for leucopenia

	• Rate of grade 3 or worse adverse events for thrombocytopenia • Frequency of abnormal laboratory parameters • Progression Free Survival (PFS) according to RECIST 1.1 • Objective Response Rate (ORR) • Overall survival
INTERVENTION(S)	Patients will receive ramucirumab/TAS- 102 and data will be compared to historical data of the TAGS- (TAS- 102 monotherapy) trial. Patients will receive ramucirumab 8 mg/kg iv over 60 min on d1+15, q4w and TAS- 102 35mg/m^2 p.o. twice daily (BID) d1-5 and 8-12, q4w until progression or intolerance or completion of 4 cycles in the trial.
BACKROUND/RATIONALE	Ramucirumab is a proven and approved treatment option in patients with advanced gastric carcinoma, both as monotherapy and in combination with paclitaxel in 2nd line (Fuchs et al 2014, Wilke et al., 2014). In the Regard- trial ramucirumab showed and median PFS 2.1 months, OS 5.2 months, in Rainbow the combination of paclitaxel + ramucirumab showed a median PFS of 4.4 months and a median OS of 9.6 months. According to the TAGS phase III study, TAS- 102 showed a median overall survival (OS) of 5.7 months with TAS-102, compared to 3.6 months with placebo in heavily pre-treated patients with gastric carcinoma or adenocarcinoma of the gastroesophageal junction. Median PFS with TAS- 102 was 2.0 versus 1.8 months with placebo, representing a 43% reduction in the risk of progression or death (HR 0.57, 95% CI 0.47-0.70, P <0.0001). The 6-month PFS rates were 21% versus 13%. TAS- 102 leads to a significant improvement in overall survival compared to the best possible supportive care (BSC) treatment in the treatment of previously treated gastric carcinoma or adenocarcinoma of the gastroesophageal junction (Tabernero et al., Overall Survival Results from a Phase III Trial of Trifluridine / Tipracial vs Placebo in Patients with Metastatic Gastric Cancer Refractory to Standard Therapies (TAGS) (Shitara K, Lancet Oncol. 2018 Nov;19(11):1437-1448; Ann Oncol 2018; 29 (suppl 5; abstr LBA-002). Based on data showing that paclitaxel / ramucirumab and ramucirumab monotherapy are effective and used as standard therapy in the 2nd line of gastric carcinoma (Rainbow; Regard), it seems to be a logical consequence to combine it with TAS 102. Maintenance therapy with VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has shown clinical benefits in patients with metastatic colorectal cancer in the TML study. [Bennouna J Lancet Oncol. 2013 Jan; 14 (1): 29-37] Also in the RAISE study, survival in the same population for FOLFIRI in combination with ramucirumab was demonstrated by continuation of VEGF blockade beyond progression and was also well tolerated (Tabernero et al., Lancet Oncol 2015). The LSK-AM301 (EudraCT No.2016-003984-20) also tests VEGFR targeting with apatinib in the further line even after ramucirumab pretreatment in a global phase III study, as positive data from an Asian phase III provided a rationale for examination in a large trial (Li J. et al., JCO 2016). Recently, TAS102, an oral agent that combines the nucleoside analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil hydrochloride significantly improved overall survival in patients with refractory mCRC (Mayer et al., 2015), was approved in Germany in mCRC. In addition, the anti-angiogenic drugs bevacizumab, aflibercept, regorafenib, and ramucirumab are effective beyond progression on prior anti-angiogenic therapies in patients with mCRC (Bennouna et al., 2013; Grothey et al., 2013; Tabernero, Yoshino, et al., 2015; Van Cutsem et al., 2012) Ramucirumab is a human monoclonal antibody that specifically binds VEGF-R2. The binding of ramucirumab to VEGF-R2 prevents its interaction with the activating ligands VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGF-R2, thereby inhibiting ligand-induced proliferation, downstream signaling components including ERK1/2, and migration of human endothelial cells. Ramucirumab has been approved by the US FDA and European EMA in combination with FOLFIRI chemotherapy for the treatment of patients with

	metastatic CRC after prior oxaliplatin/fluoropyrimidine-containing chemotherapy in combination with the VEGF antibody bevacizumab. The approval of ramucirumab was based on clinical efficacy and safety demonstrated in the randomized phase III study, RAISE, which compared ramucirumab/FOLFIRI with placebo/FOLFIRI in patients with metastatic CRC whose disease had progressed after an oxaliplatin-based chemotherapy in combination with bevacizumab (n=1072) (Tabernero, Yoshino, et al., 2015). Median OS was 13.3 months in the ramucirumab/FOLFIRI arm versus 11.7 months in the placebo/FOLFIRI arm (HR: 0.844, 95% CI: 0.730-0.976; p=0.0219). Ramucirumab was well tolerated in this patient population, with similar rates for most adverse events (AEs) between the ramucirumab/FOLFIRI and placebo/FOLFIRI arms. Ramucirumab has also been approved by the US FDA and European EMA as a single agent and in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma after prior fluoropyrimidine-/platinum-containing chemotherapy based on the REGARD and the RAINBOW study (Fuchs et al., 2014; Wilke et al., 2014). In addition, ramucirumab has been approved in combination with docetaxel for the treatment of patients with advanced non-small cell lung cancer after failure of a platinum-based chemotherapy based on the results of the REVEL study (Garon et al., 2014). The combination of Ramucirumab and FOLFOX was safe and well tolerated in several phase II trials in patients with advanced CRC and gastric or GEJ adenocarcinoma (Garcia-Carbonero et al., 2014; Moore et al., 2016; Yoon et al., 2016). As ramucirumab was well tolerated without significantly increased toxicity in combination with different chemotherapy backbones. No unexpected toxicities will be anticipated in combination with the TAS-102. The studies mentioned above provide a strong rationale to conduct a study evaluating the tolerability, safety and efficacy of ramucirumab in combination with TAS- 102 in patients with refractory metastasized gastric or GEJ- cancer to improve efficacy and prevent resistance. It is therefore believed that a combination of TAS- 102 and ramucirumab can be safely administered in patients with gastric carcinoma, and ramucirumab is efficacious beyond progression, since VEGF- / R blockade appears to be effective and very well tolerated in the posterior lines, as well in the combination therapy as especially in monotherapy. The purpose of this clinical study is to investigate the tolerability, safety and benefit of ramucirumab beyond progression in combination with a change of backbone from paclitaxel/FOLFIRI to TAS 102 (Ram + TAS) over TAS-102 monotherapy (historical data from the TAGS trial) with respect to tolerability, safety and efficacy parameters (s. endpoints) in gastric adenocarcinoma and gastroesophageal junction patients for a possible continuation in a randomized study. In this first part of the study only 20 patients will be treated with the combination therapy for tolerability, safety assessment of the combination of TAS- 102 plus ramucirumab beyond progression. In the TAGS trial the most frequently reported grade 3 or worse adverse events of any cause were neutropenia in 34%, anaemia 19% and leucopenia 9% in the trifluridine/tipiracil group. Grade 3 or worse febrile neutropenia of any cause was reported in 2% patients in the trifluridine/tipiracil group. Serious adverse events of any cause were reported in 43% of patients in the trifluridine/tipiracil group. Any serious treatment-related adverse events were seen in 12% in trifluridine/tipiracil group and 4% in the placebo group.
KEY INCLUSION CRITERIA	Patients must meet all of the following Inclusion Criteria for trial participation: 1. Signed informed consent form. 2. Men or women* ≥ 18 years of age. Patients of reproductive age must be prepared to use a suitable contraceptive method during the study and up to 6 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 pregnancy test within the last 7 days prior to the start of study therapy. *There is no data that indicates a specific gender distribution. Therefore, patients are included regardless of their gender. 3. Histologically proven adenocarcinoma of the stomach, including adenocarcinoma of the gastroesophageal junction (note: previous histological assessment during disease history of patient sufficient, current biopsy during screening for this trial is not mandatory) 4. Documented, objective, radiological or clinical progression of the disease during or within 4-6 weeks after the last dose of a ramucirumab based second-line therapy (ramucirumab monotherapy or a combination of ramucirumab + paclitaxel, respectively ramucirumab + FOLFIRI). 5. Measurable or non-measurable but evaluable disease. 6. ECOG Performance status 0-2. 7. Life expectancy > 8 weeks. 8. Appropriate haematological, hepatic and renal function: a. Absolute number of neutrophils (ANC) ≥ 1.5 x 10^9/L b. Platelets ≥ 100 x 10^9/L c. Hemoglobin ≥ 9 g/dL (5.58 mmol/L) d. Total bilirubin ≤ 1.5 times the upper limit of normal (UNL) e. AST (SGOT) and ALT (SGPT) ≤ 2.5 x UNL without existing liver metastases, or ≤ 5 x UNL in the presence of liver metastases; AP ≤ 5 x UNL 9. 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 24h urine test must be performed to check the creatinine clearance to be determined). Protein level in urine ≤ 1+ by dipstick analysis or routine urine measurement (if the dipstick analysis or the routine test ≥ 2+, a subsequent 24h urine protein measurement must show a value of < 1000mg of protein within 24h of participation to ensure the study. 10. 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 must have a stable coagulation profile before starting study-specific therapy. 11. 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.
KEY EXCLUSION CRITERIA	Patients who meet at least one of the following **<u>Exclusion Criteria</u>** are not eligible for trial participation: 1. Presence of tumors other than adenocarcinomas (e.g., leiomyosarcoma, lymphoma) 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. The sponsor decides to include patients who have received curative treatment and have been disease-free for at least 5 years. 2. Squamous cell carcinoma of the stomach or gastroesophageal junction. 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 for symptom control). 5. 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 6. The patient has undergone major surgery within the last 28 days prior to the start of study-specific therapy or has undergone minor surgery within the last 7 days prior to the start of study therapy. The patient had

	subcutaneous venous access within the last 7 days prior to the start of the study-specific therapy. The patient plans to undergo major surgery while participating in the clinical trial. 7. Gastrointestinal bleeding grade 3-4 within the last 3 months prior to enrollment in the study. 8. History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other clinically important thromboembolic event during the last 3 months prior to the start of study-specific therapy (thrombosis caused by venous ports, catheters, or superficial venous thrombosis are not considered "clinically meaningful"). 9. 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. 10. Known brain or leptomeningeal metastases. 11. Known allergic / hypersensitive reactions to at least one of the treatment components. 12. Other serious illnesses or medical ailments within the last 12 months prior to the start of the study. 13. Any arterial thromboembolic event which includes, but is not limited to, the following: myocardial infarction, transient ischemic attack, cerebrovascular insult, unstable angina within the last 6 months prior to the initiation of study therapy. 14. Uncontrolled or under-adjusted hypertension (> 160 mmHg systolic or > 100 mmHg diastolic hypertension for more than 4 weeks) despite standard medical treatment. 15. Presence of an active, uncontrollable infection. 16. Chronic inflammatory bowel disease. 17. Active disseminated intravascular coagulation. 18. 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. 19. Known dihydropyrimidine dehydrogenase (DPD) deficiency. 20. History of gastrointestinal perforation / fistula (within the last 6 months prior to the start of study-specific therapy) or presence of risk factors favoring perforation. 21. Serious or non-healing wounds, ulcers, or broken bones within the last 28 days prior to the start of study-specific therapy. 22. The patient is pregnant or breast-feeding.
OUTCOME(S)	The objective of this study is to determine whether a combination of ramucirumab, beyond progression after a SOC 2nd line ramucirumab based pre- treatment (Ram beyond progression) in patients with locally advanced or metastatic adenocarcinoma plus TAS- 102 shows good tolerability without safety issues regarding the serious adverse event rate of any cause and shows positive signals regarding efficacy in the secondary endpoints (e.g. prolongation of progression-free survival of TAS-102 plus ramucirumab compared with TAS-102 monotherapy - historical data according to TAGS-trial). **Primary endpoint:** The primary endpoint of the study is tolerability and toxicity, defined by the rate of serious adverse events (SAEs) of any cause according to CTCAE v5.0 **Secondary endpoints:**

	• Rate of treatment-related AEs and SAEs according to CTCAE v5.0 • Rate of grade 3 or worse adverse events for neutropenia • Rate of grade 3 or worse adverse events for anemia • Rate of grade 3 or worse adverse events for leucopenia • Rate of grade 3 or worse adverse events for thrombocytopenia • Frequency of abnormal laboratory parameters • Progression Free Survival (PFS) according to RECIST 1.1 • Objective Response Rate (ORR) • Overall survival (OS) **Safety Measures:** Adverse events, laboratory tests, vital signs, physical examination, 12-lead ECG, and ECOG performance status.
SAMPLE SIZE	Total number of patients to be enrolled: 20 The present trial is designed as a single arm pilot study on safety and tolerability of the ramucirumab plus TAS-102 treatment regimen to prepare for a potential randomized study, which aims to estimate the therapeutic efficacy of the experimental regimen. The statistical concept will be mainly exploratory without formal sample size calculation, focusing on calculating the expected 95%-CI intervals for the primary endpoint. SAEs of any cause in the TAGS trial are reported in 43% in the TAS-102 treated group. Assuming that the SAE rate will increase up to 55% (corresponding to a clinically relevant increase of 30% compared to the SAE rate of the TAGS-102 treated group of the TAGS-trial) a sample size of 20 patients would result in an exact two-sided 95%-CI of 0.332 – 0.768 which is considered acceptable for an early phase exploratory trial.

Plattenepithelkarzinom Ösophagus, 2nd-line

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

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-STO-0216/ass - RAMOS-Study	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2018 - 2020 (geplant)	
Weitere Zentren:	sind sehr erwünscht	
Zentren:	geplant: 30	initiiert:25
Patienten:	geplant: 186	aktuell eingeschlossen: 14
Letzte Aktualisierung	Oktober 2020	

Trial type	A randomized, multicenter open label phase II trial
Coordinating investigator	Prof. Dr. Sylvie Lorenzen Klinikum rechts der Isar der Technischen Universität München, Abteilung für Hämatologie und Onkologie, Ismaningerstr. 22, 81675 München
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	squamous-cell carcinoma of the esophagus
Objective(s)	OS rate after 6 months, based on an ITT population. The experimental therapy (Paclitaxel + Ramucirumab) would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true OS rate amounted to 66%, corresponding to a median OS of 10 months, as this is considered to be a clinically highly relevant benefit compared to published results with taxane mono-chemotherapy (median of about 7 months).
Intervention(s)	**Arm A (investigational arm)** Paclitaxel 80 mg/m^2 on day 1, 8, 15 plus Ramucirumab 8 mg/kg i.v. infusion on day 1 and 15 Start of next cycle on day 29 (qd 28). **Arm B (control arm)** Paclitaxel 80 mg/m^2 on day 1, 8, 15 Start of next cycle on day 29 (qd 28).
Key inclusion and exclusion criteria	Key inclusion criteria: - Histologically proven squamous cell carcinoma of the esophagus - Metastatic or locally advanced disease, not amenable to potentially curative resection - Refractory or intolerant to a combination therapy of platinum and a fluoropyrimidine for esophageal cancer. An exception are patients with a contraindication for platinum or fluoropyrimidine or who refused therapy with one of the substances. Those patients are eligible after previous therapy with one of the substances The definition of refractory should be defined as follows:

	- Patients whose PD or recurrence was confirmed by imaging during their initial chemotherapy (including chemoradiation) or within 8 weeks after the last dose of chemotherapy will be assessed as “refractory”. - Patients after radical resection in conjunction with chemotherapy, including neoadjuvant/adjuvant therapy and chemoradiation, whose recurrence was confirmed by imaging within 24 weeks after the last dose of chemotherapy, will be determined “refractory”. - Measurable or non-measurable but evaluable disease determined using guidelines in RECIST 1.1 as confirmed within 28 days before randomization - Adequate blood and biochemistry parameters Key exclusion criteria: - Other tumor type than squamous carcinoma (e.g. leiomyosarcoma, lymphoma) or a second cancer except in patients with squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been effectively treated. Patients curatively treated and disease-free for at least 2 years will be discussed with the sponsor before inclusion - Patients with significant malnutrition who are fed exclusively by parenteral nutrition. Parenteral nutrition is no exclusion criterion if only given as supplemental care. - Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol - Previous therapy with paclitaxel in the metastatic setting or previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study
Outcome(s)	Primary endpoint: OS rate after 6 months Secondary endpoints: - Progression-free survival - Overall survival - Objective response rate (CR + PR) - Tumor control rate (CR, PR, SD) - Safety (according to NCI-CTCAE V 4) and tolerability - Quality of Life (EORTC QLQ C-30)
Sample size	186 (93 per Arm)
Trial duration	First patient in to last patient out (months): 48 Duration of the entire trial (months): 48 Recruitment period (months): 36
Number of enrolled pts.	14 (08.10.2020)
Participating centers	30 in total

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:	Initiated
Rekrutierungszeitraum:	28.10.2020-28.10.2021, **First patient in planned in October** 2020
Weitere Zentren:	Open for participation
Zentren:	planned: 40 initiated: 7
Patienten:	200 patients (approximately 40 patients per disease type) enrollments: 0
Letzte Aktualisierung	October 2020

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. med. Arndt Vogel Hannover Medical School (MHH) Department of Gastroenterology, Hepatology and Endocrinology Carl-Neuberg-Str. 1 30625 Hannover Tel.: +49 176 1 532 9590 Email: vogel.arndt@mh-hannover.de
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: 42	initiiert: 38
Patienten:	geplant: 270	aktuell eingeschlossen: 120
Weitere Zentren:	Maximale Zahl an Zentren erreicht.	
Letzte Aktualisierung	26.10.2020	

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≥ 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:	Förderantrag bei der DFG eingereicht	
Rekrutierungszeitraum:	geplanter Beginn: I Q 2021 – geplantes Ende IV Q 2026	
Anzahl Patienten:	geplant: 400	aktuell randomisiert: noch nicht gestartet
Anzahl Zentren:	geplant: 25	aktuell initiiert: noch nicht gestartet
Weitere Zentren:	sind leider nicht mehr möglich	
Letzte Aktualisierung	Nov. 2020	

Applicant(s) / coordinating investigator(s)	Michael Ghadimi, Prof. Dr. med.; Dept. of General and Visceral Surgery; University Medical Center Göttingen – Georg-August-University; Robert-Koch-Strasse 40, 37075 Göttingen, Germany; Tel: +49-551-39-8730, Fax: +49-551-39-91315, e-mail: mghadim@gwdg.de Jens Siveke, Prof. Dr. med.; Institute for Developmental Cancer Therapeutics and Division of Solid Tumor Translational Oncology (DKTK/DKFZ partner site Essen); West German Cancer Center, University Hospital Essen; Hufelandstr. 55, 45147 Essen, Germany; Tel: +49-201-723-3704, Fax: +49-201-723-6725, e-mail: jens.siveke@uk-essen.de
Statistician	Tim Friede, Prof. Dr.; Department of Medical Statistics; University Medical Center Göttingen; Humboldtallee 32; 37073 Göttingen, Germany; Tel: +49-551-39-4990; Fax:+49 -551-39-4995; Email: tim.friede@med.uni-goettingen.de
Co-applicant(s)	Uwe Pelzer, PD Dr. med.; Medizinische Klinik mit Schwerpunkt Onkologie und Hämatologie (CCM), Charité Universitätsmedizin Berlin; Charitéplatz 1, 10117 Berlin, Germany; Tel: +49-30-450-513002, Fax: +49-30-450-513952, email: uwe.pelzer@charite.de
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) and Norway No. of centres to be involved: approx. 25 high-volume centers in GER/NL/NOR Names of cities and centres: approx. 25/25

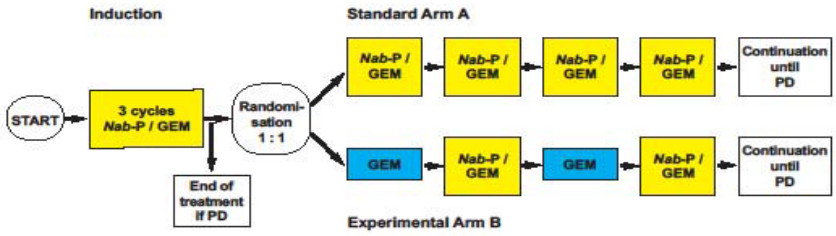
AIO-PAK-0114: Induction treatment with nab-paclitaxel/gemcitabine for first-line treatment of metastatic pancreatic cancer followed by either alternating application of gemcitabine monotherapy and nab-paclitaxel/gemcitabine or continuing application of nab-paclitaxel/gemcitabine: A randomized phase II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

AIO-Studie	
Studiennummer/-Code:	AIO-PAK-0114 - ALPACA
Status:	Aktiv rekrutierend
Rekrutierungszeitraum:	30 Monate (FPI 27.05.2016) Laufzeitverlängerung
Anzahl initiierter Zentren:	30
Weitere Zentren:	Momentan nur Warteliste
Patienten:	registriert: 308 von 325 randomisiert: 159 von 225
Letzte Aktualisierung:	Oktober 2020

Study Type	Multicenter, open-label, randomized active-controlled phase II trial
Coordinating Investigator	Prof. Dr. Frank Kullmann Kliniken Nordoberfalz AG Klinikum Weiden, Söllnerstraße 16, 92637 Weiden E-Mail: frank.kullmann@kliniken-nordoberpfalz.ag
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin, Germany Tel: +49 30-8145 344 31; Fax: +49 30-3229 329 26 E-Mail: info@aio-studien-ggmbh.de
Number of patients	A total of 325 patients will be enrolled to the trial. (228 randomized)
Study duration	**Accrual period:** The accrual period is estimated to last 30 months. **Estimated treatment duration of the individual patient:** Treatment duration in the individual patient will differ; estimated average treatment duration will be 6 - 8 months. **Duration of follow up after end of treatment:** Until death or the end of the study whichever is sooner and for at least 6 months or until death in each patient **Estimated study duration:** 3.5 years from the first patient enrolled until the end of study **Start of the study:** First patient First visit (FPFV): Date of the written informed consent by the first patient enrolled. **End of the study:** Last Visit Last Patient (LPLV) will be the last follow-up visit of the last patient having received study drug.

Planned number of sites	Up to 30 trial centers in Germany This study is not open for new sites.
Background and Rationale	In the MPACT trial nab-paclitaxel in combination with gemcitabine has been shown to significantly improve overall survival ([OS]; 8.5 vs. 6.6 months; median improvement of 2.1 months; p<0.001) compared to standard gemcitabine monotherapy in metastatic pancreatic adenocarcinoma. Progression-free survival ([PFS]; 5.5 vs. 3.7 months), objective response rate (23% compared to 7%), and time to treatment failure (5.1 vs. 3.6 months) evaluated as secondary endpoints likewise showed significant improvement. However, these results were less impressive than the results of the prior phase I/ II trial by Hoff and coworkers, in which a median OS of 12.2 months and a median PFS of 7.9 months had been observed for patients with the identical nab-paclitaxel dosage (125 mg/m^2). In the MPACT trial the median number of cycles applied was 3 (=3.9 months of treatment duration) in contrast to 6 cycles (= 6 months) in the phase I/II study, though for patients of all dosage levels (100, 125, or 150 mg/m^2). This shorter treatment duration could have contributed to reduced overall survival. It is the rationale of the study to investigate whether improved overall tolerability that would subsequently prolong treatment duration and increase efficacy can be achieved by alternating treatment cycles of gemcitabine monotherapy followed by nab-paclitaxel/gemcitabine compared to standard continuing nab-paclitaxel/gemcitabine treatment cycles in patients having received 3 cycles of induction therapy with standard nab-paclitaxel/gemcitabine and by means of an additional improved toxicity monitoring and quality of life monitoring. The considerations for the justification of alternating treatment cycles of gemcitabine monotherapy followed by nab-paclitaxel/gemcitabine are as follows: The proof of principle of an alternating gemcitabine-based regime in untreated metastatic pancreatic cancer is given. Trouilloud et coworkers had shown in the FIRGEM phase II trial that alternating cycles of FOLFIRI.3 (CPT-11 [nanoliposomal irinotecan] plus folinic acid plus 5-FU and gemcitabine monotherapy improved rate of PFS at 6 months compared to gemcitabine monotherapy (48% versus 30%). Von Hoff et coworkers had reported that in preclinical studies in mice with human pancreatic cancer xenografts nab-paclitaxel alone and in combination with gemcitabine decreased the peritumoral desmoplastic stroma. The intratumoral concentration of gemcitabine was increased by 2.8 fold in nab-paclitaxel plus gemcitabine treated mice versus those receiving only gemcitabine. Peritumoral desmoplastic stromal depletion allowing the chemotherapeutics to reach the tumor more efficiently has been postulated as one contributing mode of action of nab-paclitaxel. Other preclinical experiments in mouse models of pancreatic cancer suggest that nab-paclitaxel may increase the intratumoral gemcitabine levels by decreasing the enzyme cytidine desaminase, the main gemcitabine metabolizing enzyme, thus blocking the break-down of gemcitabine in pancreatic cancer, increasing intratumoral levels of gemcitabine and supporting synergism of nab-paclitaxel and gemcitabine. Thus it is assumed that induction therapy with the standard combination will be sufficiently long for all patients to allow for a continued increased tumoral accumulation of active gemcitabine– even in those patients subsequently treated with the alternating therapy.
Inclusion criteria	• Adult patients (≥ 18 years of age) • Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Patients with islet cell neoplasms are excluded • Karnofsky performance status (KPS) ≥ 70% • At least one unidimensionally measurable lesion as assessed by CT-scan or MRI according to RECIST 1.1 • 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. • Adequate renal, hepatic and bone marrow function, defined as - Calculated creatinine clearance ≥ 30 mL/min according to CKD-EPI formula

	- AST/GOT and/or ALT/GPT ≤ 2.5 x ULN and ≤ 5.0 x ULN in case of liver metastasis - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L - Haemoglobin ≥ 9 g/dL - Platelets ≥ 100 x 10^9/L • Females of childbearing potential (FCBP) must have a negative pregnancy test within 7 days of the first application of study treatment and they must agree to undergo further pregnancy tests before randomization and at the end of treatment visit **and** FCBP must either agree to use and be able to take effective contraceptive birth control measures (Pearl Index < 1) or agree to practice complete abstinence from heterosexual intercourse during the course of the study and for at least 1 month after last application of study treatment. A female subject is considered to be of childbearing potential unless she is age ≥ 50 years and naturally amenorrhoeic for ≥ 2 years, or unless she is surgically sterile. • Males must agree not to father a child during the course of the trial and for at least 6 months after last administration of study drugs. • Signed and dated informed consent before the start of any specific protocol procedures. Patient's legal capacity to consent to study participation.
Exlusion criteria	• Missing histological or cytological confirmation of metastatic adenocarcinoma of the pancreas • Locally advanced pancreatic adenocarcinoma without metastases • Any previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. (Prior adjuvant chemotherapy with gemcitabine or fluoropyrimidine in curative intent is allowed if terminated more than 6 months before first application of study treatment. Previous palliative radiotherapy of bone metastases for alleviation of pain is permitted provided that irradiated bone metastases are no target lesions.) • Known brain metastase/brain metastases. Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients. • Pre-existing polyneuropathy ≥ grade 2 according to CTCAE version 4 • Medical history of interstitial lung disease (ILD) or pulmonary fibrosis • Patients with high cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year • Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus) • Any other severe concomitant disease or disorder, which could influence patient's ability to participate in the study and his/her safety during the study or interfere with interpretation of study results e.g. severe hepatic, renal, pulmonary, metabolic, or psychiatric disorders • Previous or concurrent tumor other than underlying tumor disease (pancreatic cancer) with the exception of cervical cancer in situ, adequately treated basal cell carcinoma or squamous cell carcinoma of the skin, superficial bladder tumors (Ta,Tis, and T1) or any curatively treated tumors > 5 years prior to enrolment • Hypersensitivity against nab-paclitaxel, gemcitabine, or any excipients of these drugs • Continuing abuse of alcohol, drugs, or medical drugs • Pregnant females, breast feeding females or females of childbearing potential unable to either perform adequate contraceptive measures or practice complete abstinence from heterosexual intercourse • Participation in any other clinical trial or treatment with any experimental drug within 28 days before enrolment to the study or during study participation until the end of treatment visit.
Treatment regimen	**Induction treatment** All patients will be given: ***3 cycles nab-paclitaxel/gemcitabine; duration of each cycle 28 days***

	nab-paclitaxel 125 mg/m^2, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m^2 as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle Patient with progression or unacceptable toxicity have to discontinue study treatment. After three cycles nab-paclitaxel/gemcitabine tumor evaluation is performed. Randomization in Arm A and Arm B will take place for all patients with at least stable disease (SD). **<u>Continuous treatment after randomization</u>** ***Standard Arm A*** Patients randomized in Arm A will receive **continuing application of** nab-paclitaxel/gemcitabine **treatment cycles** until progression or unacceptable toxicity. Duration of each cycle is 28 days and comprises: nab-paclitaxel 125 mg/m^2, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m^2 as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle ***Experimental Arm B*** Patients randomized in Arm B will receive **alternating application of gemcitabine monotherapy and nab-paclitaxel/gemcitabine treatment cycles** until progression or unacceptable toxicity, starting with a treatment cycle of gemcitabine. Duration of each cycle irrespective of treatment cycle with GEM or with nab-paclitaxel/gemcitabine is 28 days. **Gemcitabine treatment cycle:** Gemcitabine 1000 mg/m^2 as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle **nab-paclitaxel/gemcitabine treatment cycle:** nab-paclitaxel 125 mg/m^2, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m^2 as a 30-minute IV infusion; D1, D8, D15 of each 28-day cycle At discontinuation of study treatment (standard or experimental arm) due to progression patients with a good performance status are encouraged to receive a non-neurotoxic combination of a fluoropyrimidine. In the presence of a reduced performance status treatment with a mono fluoropyrimidine may be recommended. However, this further second-line treatment is not part of the study protocol and at investigator's discretion.  • GEM = gemcitabine; Nab-P = nab-paclitaxel, PD = progession
Statistical and analytical plan and methodology	Standard statistical methods will be applied for analyzing this study. The primary goal is to derive a point estimate and an associated 80% confidence interval with a pre-specified precision for the overall survival treatment hazard ratio of alternating treatment cycles of gemcitabine monotherapy followed by nab-paclitaxel/gemcitabine relative to standard nab-paclitaxel/gemcitabine treatment cycles following induction treatment. A Cox-proportional hazards model will be applied.
Endpoints	<u>Primary endpoint:</u> Overall survival determined from time of randomization until date of death <u>Secondary endpoints:</u>

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

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:	in Vorbereitung	
Rekrutierungszeitraum:	2020 – 2022	
Zentren:	geplant: 8 -10	initiiert: 7
Patienten:	geplant: 75	eingeschlossen:17
Weitere Zentren:	sind leider nicht möglich	
Letzte Aktualisierung	12.10.2020	

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) 4) 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	→ <u>Descriptive analyses</u> → 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. → <u>Safety examinations</u> → 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

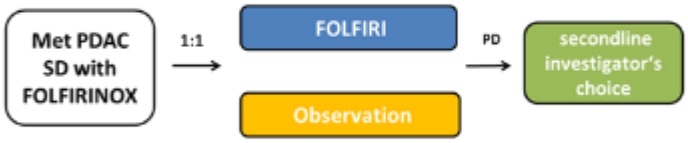
AIO-PAK-0120/xx: MAintenance ThErapy vs. Observation in FOLFIRINOX treated metastatic Pancreatic ductal adenocarcinoma patients - A prospective, randomized multi-center phase II AIO trial (MATEO-Panc)

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	MAintenance ThErapy vs. Observation in FOLFIRINOX treated metastatic Pancreatic ductal adenocarcinoma patients - A prospective, randomized multi-center phase II AIO trial  • Co-Primary Endpoints: 12 months Overall Survival, Quality of Life (EORTC QLQ-C30) • at least 8 cycles of initial chemotherapy, max 12 cycles • Secondary endpoints: PFS 1 und PFS 2, extended QoL/PROs

Pankreaskarzinom, palliative Therapie, 2nd-line

AIO-PAK-0216: Second line therapy with Nal-IRI after failure of gemcitabine/nab-paclitaxel in advanced pancreatic cancer - predictive role of 1st line therapy (PREDICT)

AIO-Studie		
Studiennummer/-Code:	AIO-PAK-0216 - PREDICT	
Status:	Aktiv rekrutierend	
Rekrutierungszeitraum:	FPI März 2018 // Rekrutierung geplant auf 24 Monate	
Weitere Zentren:	Momentan nur Warteliste	
Zentren:	geplant: 35	initiiert: 39
Patienten:	geplant: 270	aktuell eingeschlossen: 90
Letzte Aktualisierung:	Oktober 2019	

EudraCT No.	2016-005147-17
National Coordinating Investigator	Prof. Dr. med. Manfred P. Lutz Internal Medicine Caritasklinikum St. Theresia Rheinstrasse 2, 66113 Saarbrücken Phone +49 681 406 1001, Fax +49 681 406 1003 m.lutz@caritasklinikum.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, Fax +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Study design	Open label, single arm, multicenter phase IIIb trial
Duration of study	Enrollment: 24 month total study duration 34 month (incl. follow-up)
Indication	Second-line treatment for advanced or metastatic pancreatic cancer
Target population	Patients with locally advanced or metastatic pancreatic cancer after failure of a gemcitabine/nab-paclitaxel 1st-line treatment.
Total number of sites	35
Primary objective	Confirmation that longer Time-To-Treatment-Failure (TTF) during first-line treatment is predictive for the benefit of 2nd line treatment with Nal-IRI combination chemotherapy
Secondary objectives	Secondary objectives of this study are: • to generate additional efficacy and safety data for the 2nd-line treatment • to assess the Quality of Life and Patient Reported Outcomes during 2nd-line treatment • to assess the impact of the course of the 1st-line treatment on the outcome of the 2nd-line therapy • to explore the impact of physiological and molecular markers on the efficacy of the 2nd-line • to validate a prognostic second-line score accord. to Sinn et al., 2016
Planned sample size	N=270 total
Inclusion criteria	1. Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations 2. Clinical indication for a 2nd-line systemic therapy according to current standard-of-care. 3. Age ≥ 18 years at time of study entry

	4. Patients with histologically or cytologically confirmed pancreatic ductal adenocarcinoma 5. Imaging of evaluable lesions (either sonography, X-ray, CT scans, MRI): only in case of treatment failure because of progress 6. ECOG performance status 0-2 7. One line of systemic gemcitabine/Nab-paclitaxel therapy for advanced disease (irrespective of prior adjuvant therapy) OR Previous adjuvant gemcitabine/Nab-paclitaxel chemotherapy with documented progression less than 6 months after termination 8. Documentation of prior therapy (duration, maximum toxicity, reason for discontinuation) 9. Adequate blood count, liver-enzymes, and renal function: • neutrophil count > 1.5 x 10^6/mL • Platelet count ≥ 100 x 10^9/L (≥100,000 per mm3) • AST (SGOT)/ALT (SGPT) ≤ 5 x institutional upper limit of normal • bilirubin ≤1.5 ULN (<3 x ULN in patients with confirmed mechanical cholestasis) • Creatinine Clearance CLcr ≥ 30 mL/min 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.
Exclusion criteria	**Medical criteria:** 10. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to: (1) Active uncontrolled infection, chronic infectious diseases, immune deficiency syndromes (2) Premalignant hematologic disorders, e.g. myelodysplastic syndrome (3) Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment (4) Prior (<3 years) or concurrent malignancy (other than biliary-tract cancer) which either progresses or requires active treatment. ***Exceptions are:*** basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial urinary bladder tumor [Ta, Tis and T1]. (5) Pre-existing lung disease of clinical significance or with impact on performance status (6) History or clinical evidence of CNS metastases Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria: a) are asymptomatic and b) have no requirement for steroids 6 weeks prior to start of study treament. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases (7) Allogeneic transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy (8) Severe non-healing wounds, ulcers or bone fractions (9) Evidence of bleeding diathesis or coagulopathy (10) Major surgical procedures, except open biopsy, or significant traumatic injury within 28 days prior to start of study treatment, or anticipation of the need for major surgical procedure during the course of the study except for surgery of central intravenous line placement for chemotherapy administration. (11) Known Gilbert-Meulengracht syndrome

	(12) Known chronic hypoacusis, tinnitus or vertigo (13) Bone marrow depression (e.g., after radiation therapy) (14) Pernicious anemia and other megaloblastic anemias secondary to vitamin B12 deficiency (15) Severe impairment of hepatic function (16) Diarrhea **Drug related criteria:** 11. Medication that is known to interfere with any of the agents applied in the trial. 12. Known dihydropyrimidine dehydrogenase (DPD) deficiency 13. History of hypersensitivity to any of the study drugs or any of the constituents of the products. 14. Any other efficacious cancer treatment except protocol specified treatment at study start. **Safety criteria:** 15. Female subjects who are pregnant, breast-feeding or male/female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner]. Women of childbearing potential must have a negative pregnancy test (urine or serum β-HCG acc. to SOC) at screening. **Methodological criteria:** 16. Any experimental pretreatment for advanced disease 17. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lifes of previously used trial medication, whichever is longer, with the following exception: Any clinical study with the IMPs Nab-paclitaxel + gemcitabine and under the condition that the potential study subject was only exposed to Nab-paclitaxel + gemcitabine doublet chemotherapy during the course of the previous study is exempt. The previous Nab-paclitaxel + gemcitabine treatment must be consistent with current treatment approaches for first-line therapy with regard to dosing and scheduling. The following non-comprehensive list of clinical trials may serve as a guidance: ALPACA (EudraCT number: 2014-004086-24); GrantPax (EudraCT Number: 2015-002890-40), NEONAX (EudraCT number: 2013-005559-34), NEOLAP (EudraCT number: 2013-004796-12) 18. Previous enrollment in the present study (does not include screening failure). **Regulatory and ethical criteria:** 19. Patient who might be dependent on the sponsor, site or the investigator 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].
Investigational agents	• Nal-IRI (MM-398, IRINOTECAN LIPOSOME) • 5-Fluorouracil (5-FU) • folinic acid

	Study medications will not be provided by the Sponsor and must be prescribed locally. The investigator will ensure that the study medication is used only in accordance with the protocol.
Treatment schedule	• Nal-IRI 80 mg/m^2 as a 1.5 hour infusion • 5-FU 2400 mg/m^2 as 46 hour infusion • Leucovorin 400 mg/m^2 as 0.5 hour infusion • all on Day 1 of each cycle; cycle q2w Treatment until progressive disease or intolerable toxicity or withdrawal of consent. Key study procedures (and routine procedures): • Clinical and toxicity evaluations before each new cycle; Q2W • Disease evaluation (imaging if applicable) after 4 cycles of CTx (Q8W) • QoL assessments Q4W; Assessment tools: EORTC QLQ-PAN26, QLQ-C30; EQ-5D-5L • Tumor tissue analysis at reference pathology • Serum sample for cell-free DNA mutational analysis Q4W • CA19-9 measurement Q2W
Primary endpoint	Time to Treatment Failure of second-line treatment (TTF2) Expected increase of the TTF2 by 50% in the cohort of patients with favorable TTF1 (TTF1 high: upper third of the patient population) as compared to patients with short TTF1 (TTF low: lowest third of the patient population)
Secondary endpoints	• Overall survival • AEs / SAEs • QoL [EORTC QLQ-PAN26, QLQ-C30; EQ-5D-5L] • Evaluation of time to definitive deterioration of QoL (TDD) • Growth modulation index (GMI) • Second-line score accord. to Sinn et. al, 2016
Exploratory objectives and endpoints	• Time course of individual parameters of QoL during 2nd-line treatment • Correlation index of dose intensity of 1st-line treatment with TTF2 • Correlation of reasons for termination of 1st-line (progression or toxicity) with TTF2 • Correlation of BMI with TTF2 • Comparison of treatment effect on QLQ-C30/Pan26 parameters with PROM (patient-related outcome measures) • Correlation of CA19-9 response with TTF2 • Correlation of sequential cell-free DNA mutation levels with TTF2 • Correlation of CA19-9 to to TTF2 and OS Evaluate PROM as measure of treatment success • Comparison of QoL as measured by standard tools (i.e. EORTC QLQ-C30 or –PAN26 or EQ-5D-5L) with PROM • Compare variations and applicability of QLQ-C30/-PAN26 and PROM (Gerritsen et al. Europ J Cancer 57:68, 2016) in relation to treatment success • Sequential measure of cell-free DNA in correlation to imaging response at 6-8 weeks according to RECIST1.1 guidelines (if available) • Correlation of decrease in cell-free DNA to OS • Correlation of histology (collection of tumor blocks required) to cell-free DNA and TTF2/OS • Serum cell-free DNA analysis q4w and correlation with TTF2/OS/CA19-9
Rationale Hypothesis	Second-line nanoliposomal irinotecan (Nal-IRI) in combination with 5-FU/folinic acid increases median overall survival of patients with advanced pancreatic cancer from 4.2 months to 6.1 months as compared to 5-FU/folinic acid alone (Wang-Gillam et al., Lancet 387; 545-57: 2016), albeit with a considerable rate of grade 3/4 toxicities (e.g. 13% of grade 3/4 diarrhea and 14% fatigue).

	Exploratory subgroup analysis was unable to show a clear difference of treatment efficacy e.g. for sex, age, BMI, prior therapies or stage at diagnosis. However, the positive effect seemed to be more pronounced in patients with reduced performance status or with shorter time since diagnosis, a result which could not be easily explained and may be due to the limited patient number. In summary, it is currently unknown which patients profit most from 2nd-line treatment with Nal-IRI. It is also not known if 2nd-line treatment and its associated toxicities have an impact on symptom control or Quality of Life (QoL). Confounding factors for the efficacy of 2nd-line treatment have only rarely been examined in pancreatic cancer. In a subgroup analysis of the CONCO-003 trial (oxaliplatin/5-FU/FA compared to 5-FU/FA as second-line therapy after gemcitabine pretreatment), the hazard ratio for overall survival in favor of the investigational treatment barely reached significance for i) longer treatment duration during 1st-line (> 6 months, HR 0.58, 95% CI 0.35-0.98), for ii) patients in slightly reduced performance status (KI 70-80%, HR 0.67, 95% CI 0.38-0.95), and iii) for metastatic disease. Other factors are not reported (Oettle et al. J Clin Oncol 32; 2423-29: 2014). Additional hypothesis can be derived from other tumor types. In soft tissue sarcoma, a good performance status predicts success of 2nd-line therapy with trabectedin (Penel et al. Ann Oncol 24:537-42, 2013). In this group, the growth modulatory index (GMI) reaches 1.33 (PS 0, $p<0.04$), as compared to a GMI of 0.6 in the whole patient population. In addition, a high GMI was correlated with an increased response rate and with prolonged PFS. In advanced colorectal cancer, early progression during 1st-line treatment had a significantly negative effect on overall survival (Penichoux et al. Europ J Cancer 49; 1882-8, 2013), but this effect varied considerably between the type of treatment. It was more pronounced with an intensified regimen (FOLFOX, HR 18.0, 7.9-41.2) as compared to 5FU/FA (HR 7.7, 3.9-17.4) and was strongly dependent from the rate of severe toxicities. In summary, the success of first-line therapy seems to have a beneficial effect on the efficacy of 2nd-line treatment and on overall survival in soft tissue sarcoma as well as in advanced colorectal cancer. Relevant cofactors are toxicity and the performance status. There are no comparable analyses in pancreatic cancer. **Research hypothesis:** Patients profit from 2nd-line therapy with Nal-IRI if they also had a benefit from 1st-line treatment. Benefit from treatment (either 1st or 2nd-line) will be defined as a patient specific Time-To-Treatment Failure (TTF) which is in the upper third of the distribution of TTF values of the studied population.
Safety data	• AEs, SAEs and treatment emergent adverse events according to CTCAE Version 4.03 • Frequency of clinically significant abnormal laboratory parameters
Sample size estimation and Statistical considerations	• Confirm an increase of TTF2 by 50% in patients with favorable TTF1 ('highTTF1', i.e. the population with TTF1 in the upper third) as compared to the group with 'lowTTF1' (i.e. patients with TTF1 in the lowest third of the population) in patients pretreated with gemcitabine/Nab-Paclitaxel as 1st-line therapy for advanced disease. • Assumptions: The expected median TTF2 of the whole patient population is 2.3 months (95% CI 1.6-2.8), as derived from another 2nd-line trial with Nal-IRI/5-FU/FA (Napoli-1, Wang-Gillam et al. Lancet 387; 545-57: 2016). If the TTF2 in the 'lowTTF1' is assumed to reach 1.8 months, a calculated 50% increase would lead to a TTF2 of 2.7 months in the 'highTTF1' population. • Calculation – Log-Rank-Test: 156 events will be needed in 158 patients in the two compared groups to reach 80% power with a one-sided alpha of 0.05. Including 12% dropouts, this translates into 180 patients. Because only 2/3 of the patients are used for comparison (the ‘lowTTF1’ and

	'highTTF1' population), this translates into a total number of n=270 (180 x 1.5) patients to be included into the trial.
Study plan / time lines	First Patient In (FPI): Q4/2017 Last Patient In (LPI): after approx. 24 month Last Patient Last treatment (LPLT): after approx. 29 month End of follow-up period after LPI: after approx. 34 month Study report: after approx. 40 month Publication: after approx. 42 month

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

AIO-Studie

Studiennummer/-Code:	AIO-PAK-0116 - PANTHEON	
Status:	Rekrutierung	
Rekrutierungszeitraum:	2017 – 2020 (geplant)	
Zentren:	geplant: 30	initiiert: 29 (30 Standorte)
Patienten:	geplant: 204	aktuell eingeschlossen: 60
Weitere Zentren:	nicht mehr möglich	
Letzte Aktualisierung	Oktober 2020	

Study Type	Open label, randomized, sequential cross-over phase II study
Verantwortlicher Studienleiter nach AMG	Prof. Dr. med. Helmut Oettle, Praxis und Tagesklinik Friedrichstr. 53, 88045 Friedrichshafen Telefon: +49 7541 289956-0, FAX.: +49 7541 289950-10 E-Mail: helmut.oettle@charite.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 8145 344 31, Fax +49 30 3229 329 26 info@aio-studien-ggmbh.de
Studienziele/ Objectives	Primäres Studienziel: To assess efficacy of second and third-line therapies (OFF vs. FOLFIRI) in a sequential cross-over design in patients pretreated with *nab*-paclitaxel/gemcitabine first-line. The primary objective will be the demonstration of non-inferiority of FOLFIRI treatment regime compared to OFF with regard to progression-free-survival during 2nd-line therapy. Sekundäre Studienziele: Assessment of safety and feasibility of the sequential cross-over treatment approach for advanced treatment lines in PDAC
Rekrutierungzeitraum	Start Q1 2018 Last Patient In: approx. Q1 2020

Haupt-Einschlusskriterien 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. Irresectable adenocarcinoma of the pancreas previously treated in the palliative setting with gemcitabine and *nab*-paclitaxel (Abraxane®) 4. Adequatly documented recurrence and disease status after/under 1st line (Best response, duration of treatment, time to progression, preexisting PNP and other side effects) 5. Radiologically confirmed disease progression during 1st- line therapy and measurable reference cancer site(s) as defined by RECIST1.1 6. Randomization and start of 2nd-line treatment possible within 4 weeks after radiologically documented disease progression duiring 1st-line therapy 7. ECOG performance status 0-2 8. No prior radiotherapy 9. Adequate blood count, liver-enzymes, and renal function: • Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (> 1500 per mm^3) • Platelet count ≥ 100 x 10^9/L (>100,000 per mm^3) • AST (SGOT)/ALT (SGPT) < 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be < 5x ULN • Serum creatinine ≥ CL60 mL/min calcualtions according to local standard • Bilirubin < 3 ULN 10. 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. 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.
Haupt-Ausschlusskriterien / Key exlusion criteria	1. Serious cardiovascular disease (eg, unstable coronary artery disease or myocardial infarction within 3 months of study start) 2. Preexisting polyneuropathy (PNP) ≥ grade 3 [National Cancer Institute Common Toxicity Criteria grade 3 or 4 sensory or motor neuropathy] 3. Prior or concurrent malignancy (other than pancreatic cancer) which either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin 4. History of DPD deficiency 5. Morbus Gilbert 6. History of hypersensitivity to any of the study drugs or any of the constituents of the products 7. Medication that is known to interfere with any of the agents applied in the trial. 8. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year) 9. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results 10. Any medical condition that contraindicates dosing with any of the IMPs or constitutes a safety risk for the patient including but not limited to:

	a) chronic inflammatory bowel disease and/or bowel obstruction. b) active uncontrolled infection c) clinically significant bleeding or bleeding diathesis d) clinically significant stomatitis e) active ulceration of the gastrointestinal tract 11. Previous enrollment or randomization in the present study (does not include screening failure). 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].
Therapieschema Scheme of therapy	The OFF-regimen is an established second line treatment for adenocarcinoma of the pancreas. For the 5-FU/Irinotecan regimen, there is no formal comparison of the different regimen available. In order to ensure comparability, a schedule similar to the OFF regimen was chosen. OFF: • 5-FU 2000 mg/m^2 as 24 hour infusion + Na folinic acid 200 mg/m^2 on D1, 8, 15, 22 Oxaliplatin 85 mg/m^2 on D8, 22 • 3 weeks rest after D22; • Cycle q42d FOLFIRI (all on day 1) • Irinotecan 180 mg /m^2 • 5-FU 400 mg/m^2 (bolus) + 2400 mg/m^2 as 46 hour infusion • Na folinic acid 200 mg/m^2 • Cycle q2w Treatment until progressive disease or intolerable toxicity or withdrawal of consent. Treatment cross-over is only permitted after radiologically confirmed progression during 2nd-line treatment. Key study procedures (and routine procedures): • Tumor assessment according to standard of care q10w • Routine tumormarker asessments • Neurotoxicity assessments
Rationale	The prognosis of patients with locally advanced or metastatic pancreatic cancer after failure of first line treatment is dismal. In the era of gemcitabine monotherapy as standard of care, the OFF-regimen was the only approach with a proven overall survival benefit leading to an improvement in median OS of about two months. Nowadays, the combination of gemcitabine and *nab*-paclitaxel has been approved for first line treatment based on a similar improvement of OS. So far, no second line treatment has been formally evaluated following this regimen. Due to the neurotoxicity which is immanent to both *nab*-paclitaxel and oxaliplatin, concerns exist regarding the feasibility of the two regimen when given sequentially directly one after another.

	Irinotecan has been evaluated in combination with 5-FU in a number of phase II-trials. Furthermore, the intensive four drug combination of FOLFIRINOX has been shown to be superior to Gemcitabine in first line treatment. We assume, that both OFF and FOLFIRI are active regimen in pretreated pancreatic cancer, that both a non cross-resistant and can be given sequentially in a part of the patients as second and third line treatment to selected patients.
Statistik (optional)	Sample size estimation: It is hypothesized that OFF and FOLFIRI chemotherapy show similar efficacy with regard to PFS in 2^{nd}-line treatment of patients with metastatic PDAC. The test hypothesis is formulated to demonstrate non-inferiority of FOLFIRI treatment compared to OFF. Under the proportional hazards assumption, the hazard ratio $HR = h_{FOLFIRI} / h_{OFF}$ is constant across time. For a given non-inferiority margin $HR_0=1.5$ (the maximum ratio of clinical insignificance; PFS_{OFF} = 3 month, $PFS_{FOLFIRI}$ = 2 month), the statistical hypotheses tested are: $H_0 : HR \geq HR_0$ vs. $H_1 : HR < HR_0$ A non-inferiority Log-Rank test with an overall sample size of **N=204** subjects (102 in the OFF group and 102 in the FOLFIRI group) achieves 80.1% power at a one-sided $\alpha=0.025$ significance level to detect a non-inferiority hazard ratio of 1.5 when the actual hazard ratio is an equivalence hazard ratio of 1.0 and the OFF group hazard rate is $h_{OFF}=0.23$ (PFS_{OFF}=3 month). Total Follow-up is 40 month (second-line treatment) of which subject accrual (entry) occurs in the first 36 month. The accrual pattern across time is assumed to be uniform. The proportion dropping out of each study group is 0.004 subjects per month (equals a total study drop-out of 16%). In order to analyse the primary endpoint **191 events** need to be observed.

Pankreaskarzinom, local begrenzt, inoperabel

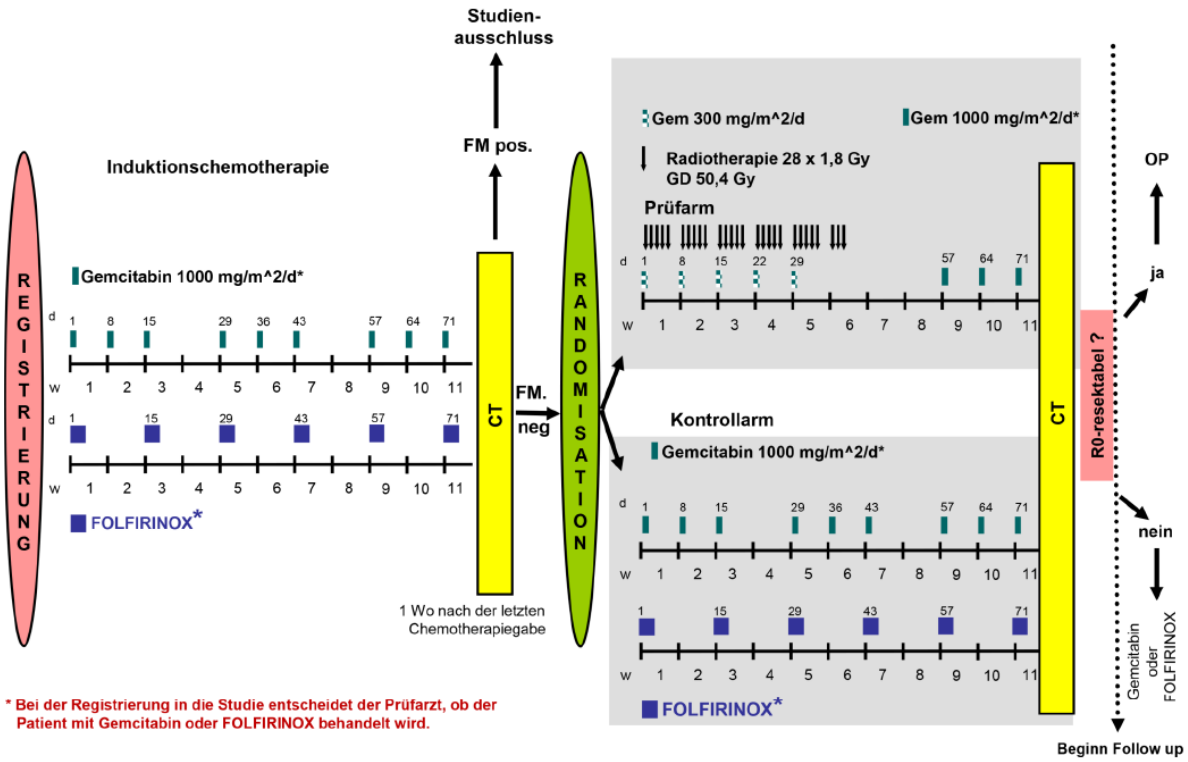
Randomisierte Phase-III-Studie zum Stellenwert einer Radiochemotherapie nach Induktionschemotherapie beim lokal begrenzten, inoperablen Pankreaskarzinom: Chemotherapie gefolgt von Radiochemotherapie im Vergleich zur alleinigen Chemotherapie (CONKO-007)

AIO-assoziierte Studie

Studiennummer/-Code:	CONKO-007	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2013 – 2020	
Weitere Zentren:	Keine Planung weiterer Zentren	
Zentren:	geplant: 24 (ursprünglich)	initiiert: 54 abgemeldet: 23 offen: 31
Patienten:	geplant: 830	aktuell eingeschlossen: 512
Letzte Aktualisierung	November 2020	

Kurztitel	CONKO-007, EudraCT-Nr.: 2009-014476-21
Art der Studie	Phase-III
Studienleiter nach AMG	Prof. Dr. Rainer Fietkau Universitätsklinikum Erlangen, Strahlenklinik
Kontaktadresse/ Kontaktperson:	Studiensekretariat Universitätsklinikum Erlangen, Strahlenklinik Universitätsstr. 27, 91054 Erlangen Tel.: 09131-85-33968 Fax: 09131/85-33996 E-Mail: st-studiensekretariat@uk-erlangen.de
Studienziele/ Objectives	Primäres Studienziel: • Gesamtüberlebenszeit Sekundäre Studienziele: • Tumorfreie Überlebenszeit • Rate an lokoregionären Rezidiven bzw. Progressionsrate • Rate an Fernmetastasen • Akute und chronische Toxizität der RCT • Lebensqualität • Remissionsraten • Häufigkeit des Erreichens einer Resektion nach Chemotherapie oder Radiochemotherapie • Häufigkeit des Erreichens einer R0-Resektion nach Chemotherapie oder Radiochemotherapie
Zielparameter/ Objectives	Geprüft wird die Fragestellung, ob beim inoperablen, nicht metastasierten Pankreaskarzinom nach einer Induktionschemotherapie mit drei Zyklen Gemcitabin bzw. 6 Zyklen FOLFIRINOX durch eine zusätzliche Radiochemotherapie im Vergleich zu einer alleinigen Chemotherapie eine Verbesserung der Prognose erreicht werden kann.
Patientenzahl	Geplant: 830 Patienten Bereits eingeschlossen: 512(Stand 12.10.2020)
Rekrutierungzeitraum	Q1 2013-Q4 2020 (verlängert)
Weitere teilnehmende Zentren erwünscht?	• keine weiteren Zentren geplant

	• 31 offene Zentren • 23 abgemeldete Zentren



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:	in Vorbereitung	
Rekrutierungszeitraum:	Q4/2020 – Q4/2022	
Zentren:	geplant: 6	initiiert:
Patienten:	geplant: 132 (Max 200)	aktuell eingeschlossen:
Weitere Zentren:	Aktuell leider nicht möglich	
Letzte Aktualisierung	26.10.20	

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

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)

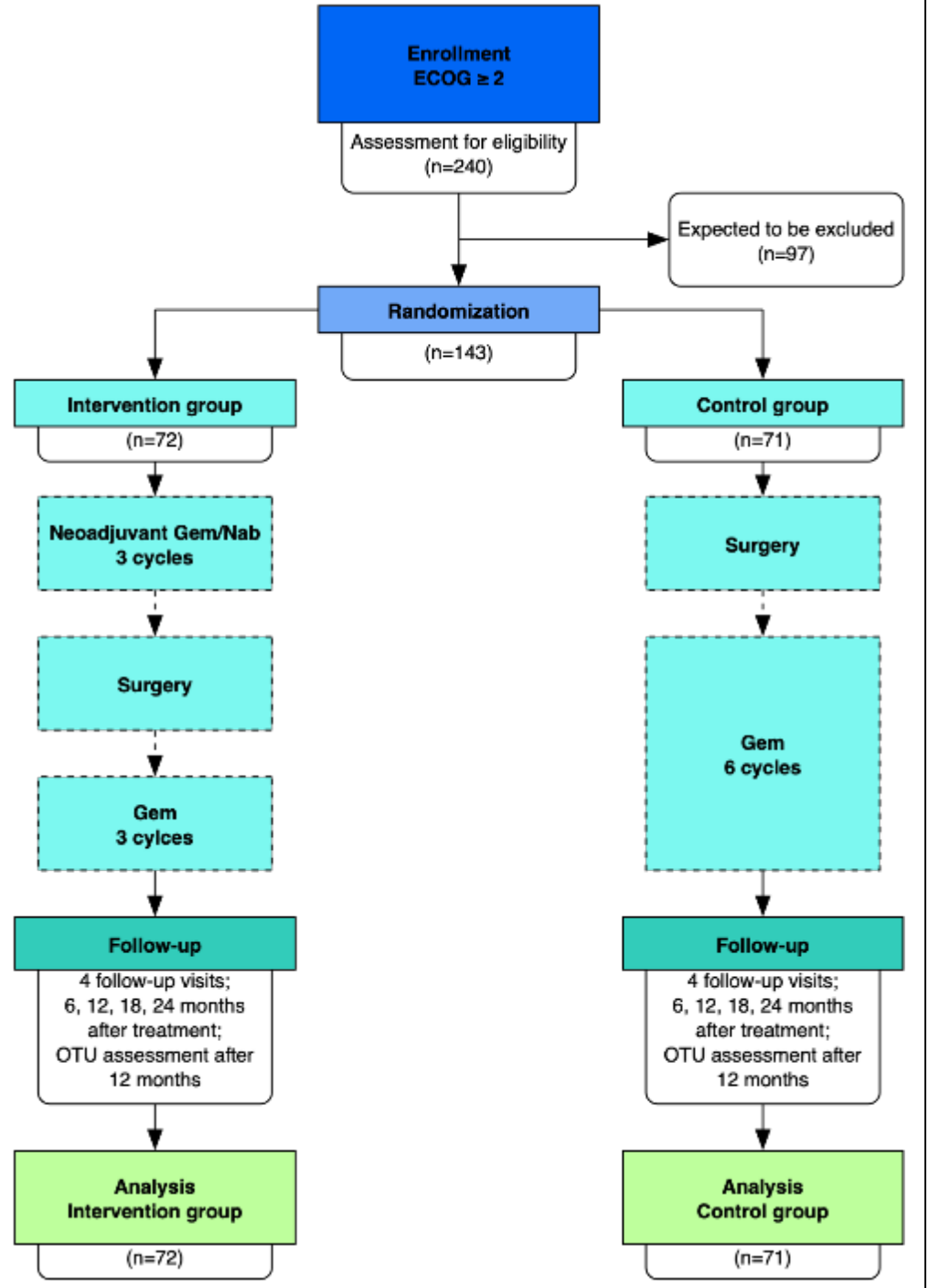
AIO-Studie

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

Derzeit sind leider keine Studien aktiv. Bitte wenden Sie sich an die Sprecher der Arbeitsgruppe.

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: 10	aktiv rekrutierend: 4
Weitere Zentren:	sind leider nicht möglich		
Anzahl Patienten:	geplant: 104	aktuell eingeschlossen: 7	
Letzte Aktualisierung	04.11.2020		

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 thoracic radiotherapy History of interstitial lung disease (ILD) History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan 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 or less 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 thorax Availability of pre-treatment tumor tissue specimen FEV1 ≥ 40% (Best) 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: 17
Patienten:	geplant: 70	aktuell eingeschlossen: 16
Weitere Zentren	sind leider nicht mehr möglich!	
Letzte Aktualisierung	Oktober 2020	

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=16
Inclusion criteria	1. 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. 2. Age ≥ 18 years 3. ECOG 2 4. At least one measurable tumor lesion (according to RECIST1.1) 5. Histologically confirmed small-cell lung cancer (SCLC) 6. Stage IV disease (according to UICC8) 7. No active autoimmune disease 8. 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): $$Female\ CrCl = \frac{(140 - age\ in\ years)\ x\ weight\ in\ kg\ x\ 0.85}{72\ x\ serum\ creatinine\ in\ mg/dL}$$ $$Male\ CrCl = \frac{(140 - age\ in\ years)\ x\ weight\ in\ kg\ x\ 1.00}{72\ x\ serum\ creatinine\ in\ mg/dL}$$ 9. Availability of tumor tissue/block 10. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the first dose of IMP. 11. 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.] 12. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving 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.

	13. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up.
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: o EORTC-QLQ-C30 o 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. 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.
Safety data	• AEs, SAEs and treatment emergent adverse events
Sample size estimation and statistical analysis considerations	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

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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>
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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.
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<td>Study plan / time lines</td>
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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>
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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 Dr. Antonio Pinto antonio.pinto@uk-koeln.de	
Anzahl Patienten:	geplant: 104	aktuell eingeschlossen: 61
Anzahl Zentren:	geplant: 20	aktuell initiiert:17
Letzte Aktualisierung	Okt 2020	

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 eine Zweitlinientherapie mit der Kombination aus Nivolumab und Ipilimumab über vier Zyklen und anschließend eine Nivolumab-Monotherapie bis zum Tumorprogress
Studienmedikation	(I) Nivolumab (II) Ipilimumab
Konzept der Studie	Der monoklonale IgG4-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 eine Kombinationstherapie mit Nivolumab und Ipilimumab profitieren können[4], aber dies gilt vermutlich eher nicht bei Patienten mit SCLC[5]. Daher wird der klinische Wert der PD-L1 IHC derzeit kontrovers diskutiert. 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 aktuelle 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, von peripherem Blut und des Mikrobioms. Die Gewinnung der Proben erfolgt vor Beginn der Studientherapie in beiden Kohorten, sowie zum Zeitpunkt des Tumorprogresses unter der Nivolumab-Monotherapie vor Einleitung der Kombinationstherapie aus Nivolumab und Ipilimumab in Kohorte 1, bzw. nach Komplettierung der vier Zyklen der Kombinationstherapie vor Fortführung mit Nivolumab als Monotherapie in Kohorte 2a/b. Die Durchführung der Rebiopsien ist obligat, eine optionale Rebiopsie ist im Falle eines Tumorprogresses bei Ende der Studientherapie vorgesehen. Die Charakterisierung der Tumorzellen und des Tumormikromilieus erfolgt histologisch und immunhistochemisch. Die Rolle von spezifischen somatischen Mutationen und der Mutationslast wird mittels DNA-Sequenzierung (whole genome oder whole exome sequencing), Transkriptom-Sequenzierung (RNAseq), der Prädiktion von Neoepitopen und der Erstellung eines Modells zur HLA-Prozessierung erfolgen. Zelluläre und lösliche Bestandteile des Blutes werden mittels FACS und ELISA untersucht. Die Zusammensetzung der Darmflora wird mittels Tiefensequenzierung analysiert. Diese Untersuchungen sollen zum Verständnis der zu Grunde liegenden immunologischen Mechanismen bei Wirksamkeit und Unwirksamkeit der Checkpointblockade beitragen, und dazu dienen, weiterführende prädiktive Biomarker zu identifizieren und Hypothesen für weitere Studien zu generieren.
Studientyp	Eine multizentrische, nicht-randomisierte Phase II-Studie zur Evaluierung der Sicherheit und Wirksamkeit der Kombinationstherapie aus Nivolumab und Ipilimumab bei Patienten mit rezidiviertem AD-NSCLC und SCLC mit daran

	angeschlossenem explorativem Biomarkerprogramm zur Analyse von mononukleären Zellen des peripheren Blutes, Tumorgewebe und dem Mikrobiom.
Studiendesign	BIOLUMA ist eine multizentrische, nicht-randomisierte Phase II-Studie bei erwachsenen Männern und Frauen mit rezidiviertem oder progredientem lokal fortgeschrittenem oder metastasiertem Adenokarzinom der Lunge (AD-NSCLC) zur Evaluierung der Ansprechrate der Kombinationstherapie mit Nivolumab und Ipilimumab bei Nivolumab-refraktären Patienten (Kohorte 1) und zur Evaluierung der Ansprechrate von Nivolumab in Kombination mit Ipilimumab bei Patienten mit rezidiviertem kleinzelligem Lungenkarzinom (SCLC) 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 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 und Stuhlproben zur Analyse des Mikrobioms 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 • Beschreibung der Zusammensetzung des Mikrobioms vor, während und nach der Studientherapie und Korrelation 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). Kohorte 2a: 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. Kohorte 2b: 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 $\beta = 0.1$. Demnach werden 51 evaluierbare Patienten benötigt. Die Nullhypothese $H_0: \pi \leq 0.075$ ist verworfen, wenn mindestens 47 von 51 Patienten ansprechen. Unter der Annahme einer Rate von etwa 10% nicht auswertbarer Patienten werden 59 ($\approx 51/0.9$) Patienten eingeschlossen. Unter der Annahme einer Prävalenz von 30% hoher Tumor-Mutationslast erwarten wir 197 Patienten zu screenen, um 59 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 563, um 59 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) • Der jeweilige Prüfarzt muss den Studienpatienten für fähig erachten, eine Tumorbiopsie durchführen zu lassen (Baseline) • 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. • 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 • Kohorte 2b: höhere Dosen von Corticosteroiden sind im Rahmen einer Bestrahlung erlaubt • Patienten mit interstitieller Lungenerkrankung, die symptomatisch ist, oder sich störend auf die Detektion oder das Management von Therapie-bezogenen pulmonalen Toxizitäten auswirken könnte • 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. • Kohorte 2b: SCLC Patienten, die mit einer Kombination aus platinbasierter Chemotherapie zusammen mit einem Anti-PD-1/PD_L1 behandelt wurden, dürfen eingeschlossen werden. • 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): 12/2022 Letzter Patient letzte Visite (LPLV): 12/2023

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: 17	initiiert: 10
Patienten:	geplant: 88	aktuell eingeschlossen: 5
Letzte Aktualisierung	16.10.2020	

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

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)	
Studiennummer/-Code:	AIO-YMO/TRK-0416 - DURATION	
Status:	In Rekrutierung	
Rekrutierungszeitraum:	2017 –2020	
Zentren:	geplant: 30	initiiert:
Patienten:	geplant: 200	aktuell eingeschlossen: 186
Weitere Zentren:	Leider nicht möglich	
Letzte Aktualisierung	Oktober 2020	

Study design	Open label, treatment stratified and randomized phase II study
National Coordinating Investigator	Dr. med. Jonas Kuon Internistische Onkologie der Thoraxtumoren Thoraxklinik – Universität Heidelberg Röntgenstrasse 1, 69126 Heidelberg jonas.kuon@med.uni-heidelberg.de
Die vollständige Synopse ist zu finden unter den Kurzprotokollen der Young-Medical Oncologists!	

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: 1.1.21 bis:1.9.23
Anzahl Zentren:	geplant: 10 aktuell initiiert:0 aktiv rekrutierend:0
Weitere Zentren:	sind aktuell leider nicht möglich
Anzahl Patienten:	geplant: 39 aktuell eingeschlossen: 0
Letzte Aktualisierung	31.07.2020

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 Thoraxklinik Heidelberg Universitätsklinik Mannheim LMU, Klinikum der Universität München Asklepios, Fachkliniken München-Gauting Universitätsklinikum Münster Oldenburg, Pius Hospital Klinikum Stuttgart

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

AIO-Studie

Studiennummer:	AIO-TRK-0117 - NintNivo	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2018 - 2020	
Zentren	geplant: 10	initiiert: 10
Patienten:	geplant: 56	aktuell eingeschlossen: 42
Weitere Zentren:	Aktuell keine weiteren Zentren erforderlich	
Letzte Aktualisierung:	29.10.2019	

Prüfplan Version	V 4.0
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	Fax: +49 4102 - 601 7101 E-mail: m.reck@lungenclinic.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Tel: +49 30 814534431 Fax: +49 30 322932926 E-Mail: info@aio-studien-ggmbh.de
Studiendesign	offene, einarmige Phase 1b Studie
Indikation	Patienten mit fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Versagen von bis zu zwei vorherigen systemischen Therapien.
Anzahl Prüfzentren	Ca. 10
Primäre Studienziele	Die primären Studienziele sind die Bestimmung einer sicheren Dosis für die Kombinationstherapie mit Nintedanib + Nivolumab und die Erzeugung von explorativen Wirksamkeitsdaten bei vorbehandelten Patienten mit fortgeschrittenem oder metastasiertem NSCLC mit einer Adenokarzinom-Histologie
Sekundäres Ziel	Untersuchung der Sicherheit und Verträglichkeit der Kombinations-therapie mit Nintedanib und Nivolumab
Exploratorische Ziele	Korrelation der PD-L1-Expression und anderer Immun-Biomarker mit Wirksamkeits-Ergebnissen.
Geplante Fallzahl	N = 56 Patienten • Safety run-in: N = 6 (Safety run-in Phase abgeschlossen) • Phase-1b-Erweiterung: N = 50
Einschlusskriterien	1. Vorliegen einer vom Patienten unterschriebenen und datierten Einwilligungserklärung einschließlich aller lokal benötigten Genehmigungen (z.B. EU-Datenschutzricht-linie) bevor jedwede studienspezifische Maßnahme, einschließlich Screening durchgeführt wird. 2. Patient erklärt seine Einwilligung und ist in der Lage an Visiten, Untersuchungen und der Behandlung inklusive der Nachbeobachtung gemäß Prüfplan samt aller damit verbundenen Anforderungen teilzunehmen 3. Alter ≥ 18 Jahre zum Zeitpunkt des Studieneinschlusses 4. Histologisch bestätigtes Adenokarzinom der Lunge des Stadiums IIIB/IV nach UICC8 5. Eine oder zwei vorangegangene systemische Therapien einschließlich einer Erhaltungstherapie für fortgeschrittenes und metastasiertes NSCLC. Den Patienten soll eine Standardtherapie, wie nach den aktuellen lokalen Leitlinien zur klinischen Praxis empfohlen, angeboten werden. Neoadjuvante und adjuvante Therapien sind zulässig, vorausgesetzt, dass eine Krankheitsprogression / ein Rückfall mehr als 6 Monate nach Beendigung der Therapie auftrat. 6. Allgemeinzustand nach ECOG 0-1 7. Angenommene Lebenserwartung von mindestens 3 Monaten 8. Patienten müssen eine nach RECIST-1.1-Kriterien messbare Erkrankung haben (mindestens eine eindimensional mittels CT oder MRT messbare Zielläsion). Wenn eine potenzielle Zielläsion zuvor bestrahlt wurde, muss ein deutlicher Nachweis der Progression am Zielort dokumentiert sein. 9. Ein Formalin-fixierter, Paraffin-eingebetteter (FFPE) Tumorgewebeblock (archiviert oder neu) oder ca. 10-15 ungefärbte Schnitte von Tumorproben (Schnitte müssen neu sein und auf Trägern aufgebracht werden, die vom Sponsor zur Verfügung gestellt werden) müssen für PD-L1 und andere Biomarker-Tests zur Verfügung stehen. Bei der Biopsie sollte es sich um eine excisionale, inzisionale oder eine Vakuumsbiopsie handeln. Eine Feinnadelpunktion ist unzureichend. 10. Vorangegangene Therapien und Operationen sind erlaubt, wenn diese 2 Wochen (für kleinere Eingriffe) oder 4 Wochen (palliative Strahlentherapie bei Knochenschmerzen; größere Eingriffe mit kompletter Wundheilung)

	jeweils vor Beginn der Behandlung abgeschlossen wurden und der Patient sich von den toxischen Wirkungen erholt hat. *11.* Adäquate Blut-, Leber- und Nierenwerte (bis spätestens 14 Tage vor Beginn der Behandlung erhalten): • Anzahl weißer Blutzellen ≥ 2000/µl • Anzahl Neutrophile ≥ 1500/µl • Anzahl Blutplättchen ≥ 100 x 10^3/µl • Haemoglobin > 9,0 g/dl • Serum-Kreatinin ≤ 1,5 x ULN oder Kreatinin- Clearance (CrCl) ≥ 40 ml/min (nach der Cockcroft-Gault Formel) • AST/ALT ≤ 1,5 x ULN (< 3 x ULN im Falle von Lebermetastasen) • Gesamt-Bilirubin ≤ 1,5 x ULN 12. Frauen im gebährfähigen Alter müssen geeignete Methode(n) zur Empfängnisverhütung anwenden. *Frauen im gebährfähigen Alter sollten eine geeignete Schwangerschaftsverhütungsmethode für 5 Monate (30 Tage plus die Zeit, die Nivolumab benötigt um 5 Halbwertzeiten zu durchlaufen) nach der letzten Gabe von Nivolumab. Da der Effekt von Nintedanib auf den Metabolismus und die Wirksamkeit von Verhütungsmitteln micht untersucht ist, sollen zur Vermeidung von Schwangerschaften Barrieremethoden als zusätzliche Form der Empfängnisverhütung angewendet werden.* 13. Frauen im gebährfähigen Alter müssen einen negativen Schwangerschaftstest (Serum oder Urin) innerhalb von 24 Stunden vor Studienbehandlung, monatlich während der Behandlung und bis 5 Monate nach der letzten Verabreichung der Prüfmedikation, vorweisen (minimale Sensitivität 25 IU/l oder äquivalente Einheiten des HCG) 14. Männliche Patienten, die mit einer gebährfähigen Frau sexuell aktiv sind, müssen eine geeignete Empfängnisverhütungsmethode anwenden (Fehlerrate < 1% pro Jahr). Sexuell aktive männliche Patienten, die Nivolumab erhalten, werden angewiesen, die Empfängnisverhütung für einen Zeitraum von 7 Monaten nach der letzten Gabe der Studienmedikation anzuwenden. Nichtgebährfähige Frauen (z.B. postmenopausal oder durch operative Sterilisation) und Männer mit Azoospermie benötigen keine Empfängnisverhütung.
Ausschlusskriterien	21. Mehr als zwei vorhergehende Behandlungslinie für fortgeschrittenes oder metastasiertes NSCLC 22. Patienten mit aktiven Hirn-Metastasen sind ausgeschlossen. Patienten sind einschlussfähig, wenn die Hirn-Metastasen adäquat behandelt werden und die Patienten neurologisch für mindestens 4 Wochen vor Studieneinschluss zum Niveau der Basiserhebung zurückgekehrt sind (mit Ausnahme von restlichen Anzeichen oder Symptomen im Zusammenhang mit der ZNS-Behandlung). Darüber hinaus müssen die Patienten entweder ohne Kortikosteroide auskommen, oder auf einer stabilen oder abnehmenden Dosis von ≤ 10 mg täglichem Prednison (oder gleichwertig) sein. 23. Leptomeningeale Erkrankung, karzinomatöse Meningitis, chronischer Diarrhö oder Kurzdarmsyndrom 24. Bekannte aktivierende EGFR-Mutation oder bekannte ALK-Translokation 25. Patienten mit symptomatischer interstitieller Lungenerkrankung 26. Jede vorherige Behandlung mit Nintedanib, Ramucirumab, oder immun-stimulatorischen Anti-Tumor-Wirkstoffen ausgenommen Checkpoint Inhibitoren. 27. Bestehende Toxizitäten infolge vorhergehender Anti-Tumor-Behandlung, ausgenommen Haarausfall und Fatigue, die nicht auf Grad 1 (NCI CTCAE Version 4.03) oder zum Wert der Basiserhebung vor Gabe der Studienmedikation abgeklungen ist. 28. Größere Verletzungen innerhalb von 4 Wochen vor Beginn der Studienbehandlung mit unvollständiger Wundheilung und/oder geplante Operation während der Studienbehandlungsphase. 29. Patienten mit aktiver, bekannter oder vermuteter Autoimmunerkrankung oder vorhergehender Transplantation von Gewebe/Oran sind nicht einschlussfähig. **HINWEIS**: Patienten mit Vitiligo, Diabetes Mellitus Typ 1, residuale Schilddrüsenüberfunktion (aufgrund einer Autoimmunerkrankung),

	die nur einen Hormonersatz erfordert, Psoriasis, die keine systemische Behandlung erfordert oder mit Bedingungen, die in der Abwesenheit eines externen Auslösers nicht erwartet werden, sind einschlussfähig. 30. Patienten, die aufgrund einer Erkrankung eine systemische Behandlung entweder mit Kortikosteroiden benötigen (> 10 mg pro Tag Prednisonäquivalente) oder andere immunsuppressive Medikamenten innerhalb von 14 Tagen vor der ersten Gabe der Studienmedikation. **HINWEIS:** inhalierte oder topikale Steroide oder Nebennierenersatz mit einer Dosis von > 10 mg / Tag Prednisonäquivalente, sind in Abwesenheit einer aktiven Autoimmunerkrankung erlaubt. 31. Positiver Test auf Hepatitis-B-Viurs Oberflächenantigen (HBV sAg) oder Hepatitis-C-Virus-RNA (HCV RNA), die Hinweis auf eine akute oder chronische Infektion geben, ODER positiver Test auf humanes Immundefizienz-Virus (HIV) 32. Vorgeschichte einer schweren Überempfindlichkeitsreaktion gegen andere monoklonale Antikörper oder jegliche Inhaltsstoffe. Bekannte Überempfindlichkeit gegen Nintedanib, Erdnüsse, Soja oder jegliche Inhaltsstoffe oder Kontrastmittel. 33. Strahlentherapie der Zielläsion innerhalb der letzten 3 Monate vor Baseline-Imaging (siehe auch Einschlusskriterium Nr. 8). 34. Radiographischer Nachweis von kavitären oder nekrotischen Tumoren 35. Zentral gelegene Tumore mit radiographischen Nachweis (CT oder MRT) einer lokalen Invasion der großen Blutgefäße 36. Therapeutische Antikoagulation mit Medikamenten, die eine INR-Überwachung erfordern (außer niedrig dosiertem Heparin und / oder Heparinspülung, wie es für die Aufrechterhaltung einer intravenösen Verweilkanüle erforderlich ist) oder Anti-Thrombozyten-Therapie (mit Ausnahme der Niedrigdosis-Therapie mit Acetylsalicylsäure < 325 mg pro Tag) 37. Vorgeschichte eines klinisch signifikanten hämorrhagischen oder thromboembolischen Ereignisses in den letzten 6 Monaten 38. Bekannte vererbte Prädisposition für Blutungen oder Thrombosen 39. Signifikante Herzerkrankung (d.h. unkontrollierter Bluthochdruck, instabile Angina pectoris, vorhergehender Infarkt innerhalb der letzten 12 Monate vor Beginn der Studienbehandlung, kongestive Herzinsuffizienz > NYHA II, schwere Herzrhythmusstörungen, perikardialer Erguss) 40. Aktiver Alkohol- oder Drogenmissbrauch 41. BMI < 20 kg/m^2 42. Vorgeschichte einer malignen Erkrankung (die sich vom NSCLC unterscheidet), die entweder fortschreitet, oder eine aktive Behandlung erfordert 43. Patienten mit vorhergehender maligner Erkrankung (Ausnahmen sind: Nicht-Melanom-Hauttumore, und die folgenden in-situ Krebserkrankungen: der Blase, des Magens, des Dickdarms, Zervix/Dysplasie, Endometrium, Melanom oder der Brust) werden nicht eingeschlossen, es sei denn, es wurde eine vollständige Remission mindestens 2 Jahre vor dem Studieneinschluss erreicht UND es ist keine zusätzliche Therapie erforderlich oder voraussichtlich während des Studienzeitraums erforderlich. 44. Schwangere, stillende, gebährfähige Patientinnen oder gebährfähige Patienten, die keine hocheffektive Empfängnisverhütungsmethode anwenden (Fehlerrate von weniger als 1% pro Jahr) 45. Erhalt der letzten Gabe einer Anti-Krebs-Therapie (Chemotherapie, Immuntherapie, endokrine Therapie, gezielte Therapie, biologische Therapie, Tumor-Embolisation, monoklonale Antikörper, andere zu prüfende Wirkstoffe) ≤ 28 Tage vor der ersten Gabe der Studienmedikation 46. Jede andere schwerwiegende oder unkontrollierte Erkrankung (z.B. aktive Geschwüre), aktive Infektion, körperliche Untersuchungsbefunde, Laborbefunde, veränderter geistiger Status oder psychiatrischer Zustand, der, im Ermessen des Prüfarztes, die Fähigkeit des Patienten beeinflussen würde, die Anforderungen der klinischen Studie zu erfüllen, das Risiko für den Patienten erheblich erhöhen oder die Interpretierbarkeit der Studienergebnisse beeinflussen würde. 47. Vom Sponsor, Prüfzentrum oder Prüfarzt abhängige Personen

	48. Patienten, die auf gerichtliche oder behördliche Anordnung in einer Anstalt untergebracht sind (§ 40 Abs. 1 S. 3 Nr. 4 AMG).
Prüfmedikation	• Nintedanib • Nivolumab
Behandlungsablauf	**Safety run-in – Dosisfindung (abgeschlossen)** Die safety run-in Phase wurde nach einem Standard-3+3-Design zur Dosiseskalation/-deeskalation durchgeführt, in das, je nach Auftreten von dosisbegrenzenden Toxizitäten, 3 bis 6 Patienten in jeder Kohorte nacheinander eingeschlossen wurden. Die folgenden Dosisstufen wurden untersucht: Dosislevel A: • Nintedanib 150 mg bid • Nivolumab 240 mg Q2W Dosislevel B: • Nintedanib 200 mg bid • Nivolumab 240 mg Q2W Dosislevel C: • Nintedanib 100 mg bid • Nivolumab 240 mg Q2W Die empfohlene Phase-2-Dosis (RP2D) ist die höchste Dosis, bei welcher die DLT-Häufigkeit unter 33% lag, wenn keine anderen Sicherheits- oder Durchführbarkeitsüberlegungen bestanden. **Erweiterungsphase** • Nintedanib RP2D (200mg bid) + Nivolumab 240 mg Q2W • Wenn die Behandlung aufgrund von Toxizitäten dauerhaft unterbrochen wird und die Toxizitäten eindeutig eines der Studienmedikamente zugeordnet werden können, kann die Studienbehandlung als Monotherapie fortgesetzt werden.
Endpunkte	Primäre Endpunkte: • Sicherheit und Verträglichkeit, bestimmt durch die Häufigkeit und Schwere von unerwünschten Ereignissen • progressionsfreie Überlebensrate bei 6 und 9 Monaten Sekundäre Endpunkte: • Ziel-Ansprechrate (ORR) • Progressionsfreies Überleben (PFS) • Zeit bis zur Tumor-Progression (time to progression, TTP) • Gesamtüberleben (OS) • AEs/SAEs und therapiebedingte Nebenwirkungen nach CTC 4.03 • Dauer des Ansprechens (duration of response, DoR) und Zeit des Ansprechens (time to response, TTR) Exploratorische Endpunkte: • PD-L1 Expressionsstatus • Korrelation der Wirksamkeit und PD-L1 Expression und andere Biomarker • Korrelation von Wirksamkeit und Zeit seit Beginn der Erstlinien-Therapie
Rationale	Zwei verschiedene Behandlungskonzepte haben zu einem verbessertem Überleben in der Zweitlinien-Behandlung des NSCLC beigetragen: im Vergleich zu Docetaxel allein hat die anti-angiogene Behandlung mit Nintedanib in Kombination mit Docetaxel eine signifikante Verlängerung des Gesamtüberlebens in der LUME Lung 1-Studie für Patienten mit Adenokarzinom gezeigt (Medianes OS: 12,6 vs 10,3 Monate; HR=0,83; 95% CI; 0,70-0,99; P=0,0359) [Reck et al. (2014), *Lancet Oncol.*]. In der Checkmate 057 Studie konnte eine Immun-Checkpoint-Inhibition mit Nivolumab im Vergleich zu Docetaxel eine OS-Verlängerung in Patienten mit Nicht-Plattenepithel-NSCLC erzielen (12,2 vs 9,4 Monate; HR=0,73; 96% CI; 0,59-0,89; P=0,002). Kombinationsstrategien haben das Potential das Ansprechen auf Immuntherapien zu erhöhen, indem sie die endogene Antitumor-reaktion auf verschiedenen Ebenen stimulieren. Es gibt zunehmendes Verständnis dafür, dass vaskuläre Endothelzellen und VEGFR-Signalisierung nicht nur für die Tumorangiogenese wichtig sind, sondern auch eine wichtige Rolle bei der Regulation von Immunantworten innerhalb der

	Tumor-Mikroumgebung spielen. Daher sind synergistische Effekte zwischen antiangiogenen Behandlungen und Immun-Checkpoint-Blockaden zu erwarten. Es wurde gezeigt, dass • VEGFR 1 und 2 eine Rolle bei der dendritischen Zellreifung spielen (VEGF hemmt die Reifung von DCs) [Dikov et al. (2005), *Journal of Immunol*.] • eine Inhibition der VEGFR1-Signalisierung unter Verwendung eines neutralisierenden VEGFR1-spezifischen monoklonalen Antikörpers die DC-Funktion wiederherstellt [Tartour et al. (2011), *Cancer Metastasis Rev*.; Bruno et al. (2014), *Front Oncol.*] • unreife DCs die Immuntoleranz fördern und regulatorische T-Zellen induzieren • die Inhibition von VEGFR verhindert, dass Lungenendothelzellen induziert werden, um T-Zell-Funktionen zu unterdrücken [Mulligan (2010), *J Immunother*.] • eine Blockade von VEGFR2 die Akkumulation von MDSCs reduziert [Finke et al. (2011), *Int Immunopharmacol*.] • MDSCs und regulatorische T-Zellen eine wichtige Rolle bei der Unterdrückung der Entwicklung einer Antitumor-Immunität bei Krebspatienten spielen • die anti-angiogene Behandlung die Verfügbarkeit von Glukose und Sauerstoff erhöht (durch die vaskuläre Normalisierung, wie für Nintedanib gezeigt [Kutluk et al. (2013), *Mol Cancer Ther*.; Mross et al. (2014), *BMC Cancer*] gezeigt) und den Verlust von ICAM-1 und VCAM-1 auf Endothelzellen verhindert, wodurch die T-Zell-Migration und Infiltration erhöht werden [Kamrava et al. (2009), *Molecular bioSystems*; Voron et al. (2014), *Front Oncol*.; Dirkx et al. (2006), *The FASEB Journal*] Somit wird vermutet, dass eine kombinierte Behandlung mit Nintedanib und Nivolumab zu einer verbesserten Sensitivität für die PD1-Blockade führen kann, indem eine Verschiebung von einer immunsuppressiven zu einer immunsupportiven Tumor-Mikroumgebung durch Nintedanib-vermittelte Effekte induziert wird. In dieser Phase Ib-Studie soll die Sicherheit der Kombinationsbehandlung mit Nintedanib und Nivolumab bei Patienten mit NSCLC untersucht und erste explorative Wirksamkeitssignale generiert werden.
Sicherheitsdaten	• Sichere Dosis und Dosis-limitierende Toxizitäten • AEs / SAEs / therapiebedingte Nebenwirkungen nach CTC 4.03 • Häufigkeit abnormer Laborparameter
Rationale für die Fallzahl und Statistik	Nach der Festlegung einer sicheren Dosis in N = 6-12 Patienten und einer explorativen Analyse ist geplant, 50 weitere Patienten mit vorbehandelten fortgeschrittenen Adenokarzinom der Lunge zu registrieren. Deskriptive statistische Instrumente werden verwendet, um die Wirksamkeit und Verträglichkeit zu beschreiben. Die 6-monatige PFS-Rate sowie die 9-monatige PFS-Rate werden mit den Ergebnissen der LUME 1 und der Checkmate 057-Studie verglichen und verwendet, um eine weitere Untersuchung dieser Kombination in einer randomisierten Studie zu fördern. Die zu rekrutierende Anzahl von Patienten beträgt N = 56
Zeitplan	Einschluss erster Patient (FPI) — Q2 /2018 Einschluss letzter Patient (LPI) — nach ca. 29 Monaten Letzter Patient letzte Behandlung (LPLT) — nach ca. 35 Monaten Studienende (Ende der Nachbeo- — nach ca. 47 Monaten

	bachtungsphase nach LPLT) Studienreport Publikation
	<u>Q2-Q3 2022</u> nach ca. 57 Monaten nach ca. 60 Monaten

<u>NSCLC mit EGFR-Mutation, metastasiert</u>

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:	von: 2020 bis: Mrz. 2022
Anzahl Zentren:	geplant: 8 aktuell initiiert: 0 aktiv rekrutierend: 0
Weitere Zentren:	erwünscht
Anzahl Patienten:	geplant: 60 aktuell eingeschlossen: 0
Letzte Aktualisierung	Oktober 2020

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 Quality of Life during and after irradiation therapy and concomitant osimertinib. To investigate types of irradiation (conventional vs. stereotactic) and target volumes used.
Primary endpoint	Safety and tolerability, including pneumonitis and necrosis 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 1st- or later line treatment of tumor positive for a common or uncommon *EGFR* 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. 6. ECOG performance status 0-2. 7. At least one measurable site of disease as defined by RECISTv1.1 criteria that is not planned to be irradiated. 8. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. [WOCBP should use an adequate method to avoid pregnancy for 6 weeks after the last dose of osimertinib.] 9. 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 4 months after the last dose of osimertinib. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) and 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.
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. Previous enrolment in the present study. 3. Any chemotherapy, biologic or hormonal cancer therapy other than EGFR-TKIs used concurrently or within 4 weeks prior to study enrolment. Hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable. 4. 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. 5. History of another primary malignancy. Exceptions are:

	• Malignancy treated with curative intent and with no known active disease ≥6 months before the first dose of IMP and of low potential risk for recurrence. Any previous radiation therapy must not affect locations of planned irradiation under osimertinib. • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease • Adequately treated carcinoma in situ without evidence of disease • Malignancy with no indication for concomitant systemic treatment/last systemic treatment more than 6 months previous to study enrolment 6. Congenital long QT syndrome 7. Women who are pregnant or breast-feeding 8. Male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 4 months after the last dose of osimertinib 9. 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	24 months of follow up for documentation of PFS, OS and possible late-toxicity
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
FURTHER CENTERS DESIRED?	yes
NUMBER of PATIENTS	60 (at least 10 per cohort)

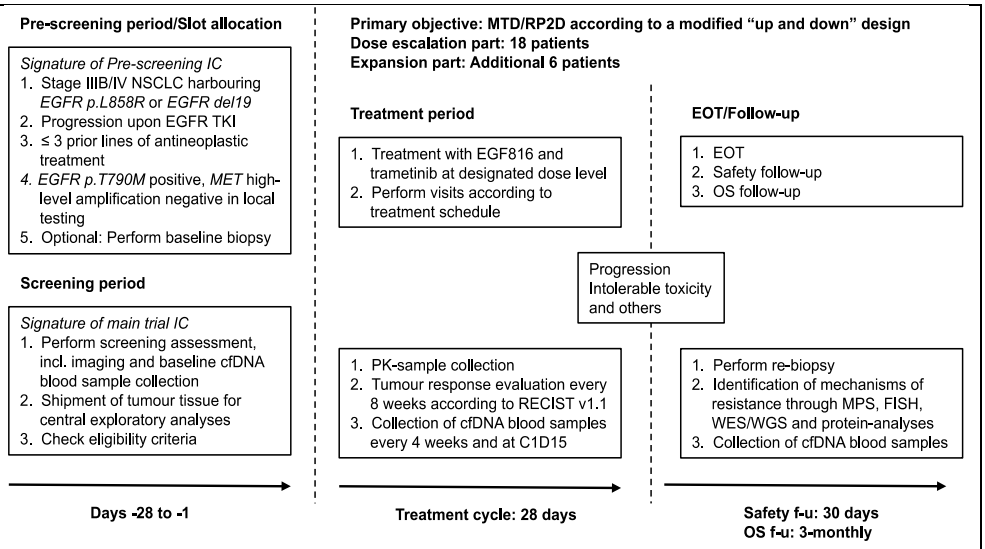
AIO-TRK-0216: An open-label, multicenter, phase I dose-escalation trial of EGF816 and trametinib in patients with non-small cell lung cancer and acquired EGFR p.T790M positive resistance to 1st or 2nd generation EGFR TKI therapy (EATON)

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, Las Palmas de Gran Canaria	
Patienten:	geplant: 24	aktuell eingeschlossen: 8
Zentren:	geplant:8	aktuell initiiert: 8
Letzte Aktualisierung	Okt 2019	

Principal Investigator	Prof. Dr. Jürgen Wolf, University Hospital of Cologne, Kerpener Str. 62, 50937 Cologne, Germany
Study sponsor	University Hospital of Cologne, Kerpener Str. 62, 50937 Cologne, Germany
Primary indication	Patients with advanced non-small cell lung cancer harbouring sensitizing EGFR mutations (EGFRdel19 or EGFR p.L858R) with progression upon treatment with 1st or 2nd generation EGFR TKI and acquired resistance mutation EGFR p.T790M 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
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 have not received any EGFR TKI treatment or 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): 04/2018 Inclusion last patient: 01/2020 Last patient last visit (LPLV): 01/2021

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: 17
Patienten:	geplant: 116 aktuell eingeschlossen: 10
Weitere Zentren:	Ggf. nach Rücksprache weitere Zentren möglich
Letzte Aktualisierung	Oktober 2020

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	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 o intracranial ORR (iORR) o intracranial DOR (iDOR) o 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: 12	aktuell initiiert: 10 aktiv rekrutierend: 6
Weitere Zentren:	Evtl. möglich	
Anzahl Patienten:	geplant: 92	aktuell eingeschlossen: 13
Letzte Aktualisierung	09.10.2020	

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)
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. Stage I-III (TNM 8th Edition; pT1-pT4, pN0-pN2, cM0). Patients are only included with a completeness of cytoreduction score (CC score) <3 (i.e., residual tumor nodules ≤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. 11. 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 is approximately 25 days. 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.
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)	<u>Primary efficacy endpoint:</u> • 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) <u>Safety endpoints:</u> Safety (according to NCI-CTCAE v 5.0) and tolerability <u>Secondary endpoints:</u> • 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: 150	initiiert: 175
Patients included:	5951	
Weitere Zentren:	auf Anfrage	
Letzte Aktualisierung	01.Oktober 2020	

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 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) Lisa Spring, lisa.spring@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: **5951** (01.October 2020) 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: **800** (01.October 2020) 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: **547** (01.October 2020)
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: 150, 175 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

Colorectal Cancer - translationale Studie – Organoidmodell

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

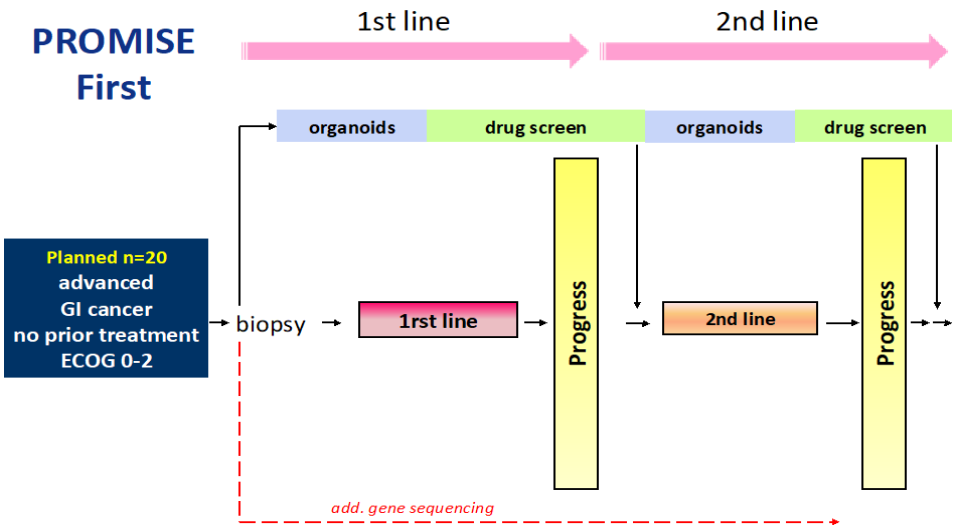
AIO-Studie

Studiennummer/-Code:	AIO-TF-0217 – PROMISE-First	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2017 – 2020	
Weitere Zentren:	leider keine weiteren möglich	
Anzahl Patienten:	geplant: 20	aktuell eingeschlossen: 17
Anzahl Zentren:	geplant: 1	aktuell initiiert: 1
Letzte Aktualisierung	3.11.2019	

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

	- To establish individual patient derived organoids of tumor and normal tissue - To treat the individual tumor organoid with the same substances as the patient - To characterize molecular alterations of the tumor organoid emerging under treatment - To analyze gene-drug-response associations as potential predictive biomarkers - To assess the efficacy of systemic chemotherapy in regards to response rate and progression-free survival - To compare systemic chemotherapy in the patient with treatment results of the corresponding organoid
Population, number of patients	20 patients with metastatic or locally non-resectable gastrointestinal cancer before the last established line of therapy. Patients will be recruited at University Hospital Mannheim and at additional centers throughout Germany. Drug screens and sequencing will be performed at DKFZ

Inclusion criteria	- Patients ≥ 18 years of age.
	- Performance status ECOG 0-2
	- Histologically confirmed advanced stage* gastrointestinal cancer prior last line therapy
	- Tumor accessible to biopsy and patient willing to undergo biopsy
	- Absence of HIV, HBV and HCV infection
	- At least one measurable lesion of disease according to RECIST criteria.
	- Adequate end organ function:
	  - renal function: serum creatinine ≤ 1.5 x ULN or GFR ≥ 30mL/min.
	  - hematopoietic function: white blood cell (WBC) count ≥3000/µL, absolute neutrophil count (ANC) ≥1500/µL, platelets ≥100000/µL, hemoglobin level >9.0 g/dL
	  - Liver function: total bilirubin ≤1.5 x ULN, AST / ALT ≤3.0 x ULN
	- Signed informed consent prior to any screening procedures

Study design	 Fig. 1. Scheme of the PROMISE-First study. A biopsy of tumor/metastasis will be obtained – if possible together with normal tissue from the site of the tumor origin - prior to start of chemotherapy. With the help of this material, individual organoid cultures will be established. Patients will undergo standard-of care first line treatment according to established treatment guidelines. Organoids will be used to model the patient's cancer biology ex-vivo (Avatar). While the patient undergoes standard first line treatment for the cancer, the avatar will be treated with the same active drug combination, using concentrations published for ex-vivo or in-vitro assays. Thereby, emerging resistance mechanisms will be explored by molecular analysis. Furthermore, sensitivity of other drugs and drug combinations will be assessed in the avatar by drug screening. Through this approach, cancer biology and treatment can be modeled for each patient, resistance mechanisms can be revealed well in advance and based on these resistance mechanisms and drug screens in organoids, treatment strategies for each patient can be tested before the cancer in the patient reaches the stage of non-responsiveness.

Clinical part	The choice of first-line therapy will be the sole discretion of the treating physician. First-line therapy must be an established Standard-of-Care treatment recommended by current guidelines. No pharmaceutical intervention will be prescribed in the protocol. From a regulatory perspective this trial is purely observational. An appropriate ethical approval will be obtained by the coordinating investigator. The clinical part will commence as a monocenter trial. After informed consent patients will be followed-up for the full course of first-line therapy until disease progression, discontinuation of treatment or death. Clinical data will be acquired according to a pre-defined schedule and will include: Efficacy data: • tumor response evaluation according to RECIST 1.1 • Best overall response • Time-to-response (TTR) • Duration of response (DOR) • Time-to-failure of treatment strategy (TTFS) • PFS, OS Safety data: • AEs / SAEs • dose density administered • dose modifications due to toxicity Follow-up after discontinuation of first-line therapy: Patients will be followed-up for subsequent cancer therapies and overall survival. The choice of second-line therapy will be the sole discretion of the treating physician. However, the results of the Avatar will be disclosed to the treating physician and may shape the decision-making process for the most suitable second-line treatment.
Clinical Data assessment, study visits and re-stagings	1. Inclusion: - Patients with metastasized CRC or GEC before the start of palliative chemotherapy are identified by screening inpatients and endoscopy-patients - Patients undergo endoscopic biopsy of their CRC and organoid lines are established before start of Treatment 2. First study visit: Chemotherapy informed consent / chemotherapy initiation - Obligatory assessments: ECOG-Status, weight, clinical examination - Obligatory Lab tests: Diff-BB, CEA, CA-19-9, CRP, LDH, (Na, K, Krea, Billi-Gesamt, AP, yGT, ALAT, ASAT, Quick) - A CT-Scan of thorax, abdomen and pelvis is obligatory before start of treatment, this must have been performed within 3 weeks before the start of chemotherapy. If the CT-scan is older, a new CT scan has to be performed before start of treatment - Other obligatory documentation: Primary tumor location, Metastatic sites, number and size of metastatic lesions in each organ, Chemotherapy regimen, dose-reduction, relevant co-morbidities, medication 3. Follow-up visits - The patient receives 6 cycles (bi-weekly) of chemotherapy (12 weeks) followed by re-staging CT (thorax, abdomen, pelvis) in week 13-14. After this, another 6 cycles of chemotherapy are applied, followed by CT-scan, and so on. - after week 3, study nurses are informed if organoid culture was successful and if patient remains “on-study” - Obligatory assessment and documentation every visit (bi-weekly): -- Therapy protocol (including regimen, dose reductions) -- ECOG status, weight, clinical examination (as above) -- Lab (as above) -- Chemotherapy side-effects (according to CDC) 4. Re-Staging Re-staging CT (thorax, abdomen, pelvis) is performed every 3 months (week 13-14). - CT-results are assessed according to RECIST-criteria - Both CT images and CT report have to be saved in the clinical documentation system

	- all CT-scans should be performed “in-house” at the UMM, if external CTs are inevitable, all documents and CDs have to be obtained and saved - obligatory documentation after re-staging (in addition to basic documentation in every visit): -- Response according to RECIST, size and number of metastases in affected organs, primary tumor size -- relevant new co-morbidities
Sample size	The clinical part of this research project targets to enroll n=20 patient. Due to the exploratory nature of this trial no clinical hypothesis will be formulated and no formal sample size calculation will be performed. A sample size of n=20 shall suffice to generate informative pilot data on the feasibility and utility of the Avatar approach.
Data analysis	Multivariable analysis will be used to identify gene-drug associations and potential biomarkers, as well as associations between drug effects in organoids and in patients. Half-yearly interim analyses will be performed concerning patient characteristics, response evaluation, organoid drug response, molecular analysis, toxicity and outcome.
Planned timelines	First Patient In: Q2 2017 Last Patient In: Q2 2020 Last Patient Out: 2022 Individual observation time: 24 months Interim-analysis: every 6 months Final Analysis: 2022
Contact details	Prof. Dr. M. Ebert, Universitätsklinik Mannheim, Universität Heidelberg, matthias.ebert@medma.uni-heidelberg.de Prof. Dr. M. Boutros, DKFZ Heidelberg, m.boutros@dkfz.de Dr. J. Betge, johannes.betge@medma.uni-heidelberg.de

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

AIO-Studie

Studiennummer/-Code:	AIO-TF-0317 - PROMISE-Last	
Status:	in Vorbereitung	
Rekrutierungszeitraum:	Studienstart noch offen	
Weitere Zentren:	sind sehr erwünscht	
Anzahl Patienten:	geplant: 30	aktuell eingeschlossen:
Anzahl Zentren:	geplant: 3	initiiert:
Letzte Aktualisierung	November 2019	

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 – 2021
Weitere Zentren:	Not planned
Letzte Aktualisierung	November 2019

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 o 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) o o Radiation-induced oophorectomy with last menses >1 year ago o Chemotherapy-induced menopause with >1 year interval since last menses o 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: o Hemoglobin ≥ 10 g/dl o Neutrophil count ≥ 1,500/mm^3 o Platelet count ≥ 100,000/µl o Bilirubin ≤ 1.0 x upper limit of normal (ULN) o ALT and AST ≤ 2.5 x ULN o Alkaline phosphatase ≤ 2.5 x ULN o PT-INR/PTT ≤ 1.5 x ULN o Albumin ≥ 25 g/l o Creatine kinase ≤ 2.5 x ULN

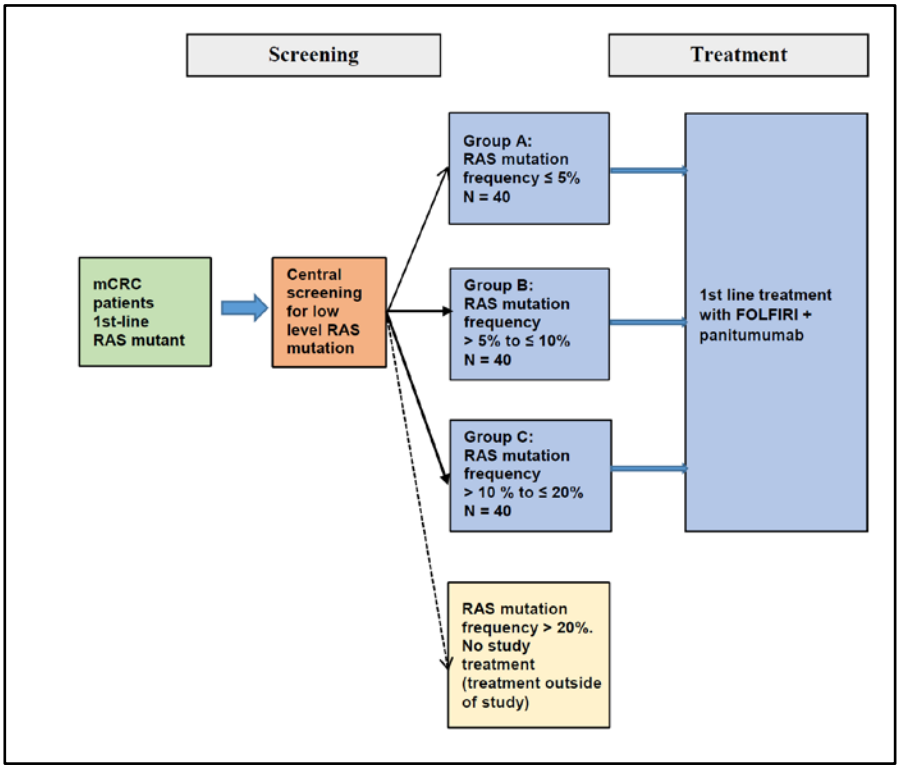
	o Serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 51 ml/min calculation according to Crockroft-Gault)
OUTCOME(S)	Clinical efficacy, determined by disease control rate (DCR) at week 16 after five 21-days cycles of treatment
STUDY TYPE	Multicenter randomized, open-label, phase II study designed 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. 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. Klaus Metzeler (initiated)
current number of patients included	57

Metastasiertes kolorektales Karzinom, Erstlinientherapie von RAS mutierten Tumoren

AIO-TF-0118: Optimal anti-EGFR Treatment of mCRC Patients with Low-Frequency RAS Mutation – The Phase II FIRE-5 LowRAS Study (FIRE-5)

AIO-Studie		
Studiennummer/-Code:	AIO-TF-0118 – FIRE-5 LowRAS	
Status:	On hold	
Rekrutierungszeitraum:	2019 - 2022	
Zentren:	geplant: 55	initiiert: 35
Patienten:	geplant: 120	aktuell eingeschlossen: 3
Weitere Zentren:	Keine gesucht	
Letzte Aktualisierung	Oktober 2020	

STUDY TYPE	An open, non-randomized multicentre phase II trial with three groups according to the frequency of RAS mutant cells within the tumorous tissue in first-line treatment of patients suffering from mCRC with low-frequency RAS mutation
PRINCIPAL INVESTIGATOR	Klinikum der Universität München Marchioninistraße 15, 81377 München Vertreten durch: Prof. Dr. med. Volker Heinemann
TRIAL OFFICE	Matthias Wolff Medizinische Klinik III, Campus Großhadern Klinikum der Ludwig-Maximilians-Universität 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 (represented by the managing medical director) Ludwig-Maximilians-Universität München Marchioninistr. 15, 81377 München, Germany
CONDITION	RAS-mutant colorectal cancer
DESIGN	An open, non-randomized multicentre phase II trial with three groups according to the frequency of RAS mutant cells within the tumorous tissue in first-line treatment of patients suffering from mCRC with low-frequency RAS mutation. The study will screen patients with known RAS mutation as determined decentrally by the local pathologist. Tumor probes of participating patients will be submitted to a central NGS-based analysis of RAS mutation status including RAS mutation frequency (=screening phase). **Three groups of patients with low-frequency RAS mutation will be defined:** 1. **Group A**: patients with low-frequency RAS mutation ≤ 5% 2. **Group B**: patients with low-frequency RAS mutation > 5% to ≤ 10% 3. **Group C**: patients with low-frequency RAS mutation > 10% to ≤ 20%) Patients with **high-frequency RAS mutation** are defined as those with a RAS mutation frequency >20% and will not be enrolled for treatment. The study design is displayed in the following figure:

<table>
<tr><td></td><td>


Only patients with low-frequency RAS mutation (Group A, B or C) will be treated within the study and will receive 1st-line therapy with FOLFIRI plus panitumumab. FOLFOX is avoided as a treatment option, since we cannot exclude a negative interaction of anti-EGFR agents and oxaliplatin-based chemotherapy in RAS mutant tumors. Patients with high-frequency RAS mutation (>20%) are considered as screening failures and thus will not receive study treatment. They will be treated according to their treating physician's decision outside of study.
Treatment will be performed until progression or when toxicity requires termination. Toxicity-related de-escalation from FOLFIRI plus panitumumab to FUFA plus panitumumab or panitumumab will be allowed within the trial. Re-escalation is allowed. Treatment within the study will be ended, once a new agent, not contained in the study regimen, will be used.</td></tr>
<tr><td>INDICATION</td><td>RAS mutant mCRC</td></tr>
<tr><td>OBJECTIVE(S)</td><td>The primary objective of the study is to define an optimal cut-off for anti-EGFR treatment with panitumumab of patients with low-frequency RAS mutation.
Secondary objectives include.
• To analyze efficacy parameters other than ORR
• To analyze early tumor shrinkage (ETS) and depth of response (DpR)
• To analyze safety and tolerance of the first-line treatment</td></tr>
<tr><td>INTERVENTION(S)</td><td>All patients will receive panitumumab in addition to background chemotherapy with FOLFIRI in 14-day cycles until progression or unacceptable toxicity.
Each 14-day-cycles consists of:
Panitumumab 6 mg/kg BW as 60-min i.v. infusion* D1

*If the 1st infusion is well tolerated, all subsequent infusions can be applied over 30-60 minutes.
Followed by
FOLFIRI regimen
• Irinotecan 180 mg/m² i.v., 30 - 90 min D1
• Folinic acid (racemic) 400 mg/m² i.v., 120 min D1
• 5-FU 400 mg/m² bolus, D1
5-FU 2400 mg/m² i.v. infusion over a period of 46 h
D1-2</td></tr>
</table>

<table>
<tr><td>OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH</td><td>

Investigation of EGFR pathways related biomarkers for prediction of sensitivity and secondary resistance to an anti-EGFR treatment (including tumor biopsies and liquid biopsies from blood samples)
Analysis of gene expression parameters allowing classification according CMS subtypes

</td></tr>
<tr><td>BACKROUND/RATIONALE</td><td>
1. RAS mutation in colorectal cancer

RAS mutations (KRAS and NRAS, exons 2-4) are expected to occur at a rate of 50% in mCRC. Typically, RAS mutation is associated with a more unfavorable outcome compared to RAS wild-type. The present notion is that tumors with RAS mutation are resistant to anti-EGFR agents (van Cutsem 2015).

2. Limited treatment options in patients with RAS mutant tumors

Since treatment options are limited in patients with RAS mutant tumors, all treatment options should be exploited even if remissions are of limited duration. The addition of a further treatment option including anti-EGFR treatment in patients with low-level RAS mutation may therefore prove to add to the continuum of treatment and may accordingly contribute to prolonged overall survival.

3. Longer survival of patients with RAS mutant tumors treated with anti-EGFR agents compared to anti VEGF agents

Three studies (FIRE-3, PEAK, CALGB) are presently available to compare the 1st-line use of targeted therapy with either anti-EGFR- or anti-VEGF directed agents. In an analysis of patients with KRAS exon-2 wild-type other RAS mutant mCRC, two of these studies predominantly using an oxaliplatin-based chemotherapy showed a superior survival in patients receiving 1st-line therapy with an anti-EGFR agent. A subsequent meta-analysis of the available studies showed an OS related HR of 0.70 (p=0.0426) favoring the anti-EGFR arm (Heinemann EJC 2016)

This finding is surprising since it was expected that anti-EGFR agents should not be effective in RAS mutant tumors. While multiple considerations may explain this observation, an important hypothesis is that the group of RAS mutant mCRC may in fact be heterogeneous.

4. Low-frequency RAS mutation

Using technologies such as Sanger sequencing, the cut-off for RAS wild-type versus mutant tumors was in the range of 20%. With the advent of modern techniques such as NGS and the availability of increasing depth and coverage, the sensitivity of detection has been improved markedly (Jiang 2013).

While low-frequency RAS mutation is assumed to be present in a clinically relevant number of patients, a clear definition of this subgroup of tumors has not been performed so far. Hikosaka and coworkers used a cut-off of 10%. Among 358 mCRC patients, the rate of low-frequency KRAS mutation was 26% (93/358) (Hikosaka 2013).
<table>
<tr><th></th><th>RR</th><th>DCR</th><th>PFS</th></tr>
<tr><td>no KRAS mutation
(n=65)</td><td>26%</td><td>72%</td><td>168 days</td></tr>
<tr><td>low level KRAS mutation
(n=59)</td><td>36%</td><td>68%</td><td>132 days</td></tr>
</table>
5. Detection of low-frequency RAS mutation

Presently, reports on RAS mutation are dichotomic and simply differentiating RAS wild-type from RAS mutant tumors. Accordingly, the treating physician does not receive quantitative information on the extent of RAS mutation. Depending on the cut-off level of sensitivity (typically ≤ 5%) RAS mutation may range from very low levels such as ≤ 5% to 100% in the evaluated tumors.
</td></tr>
</table>

	Detection of low-frequency RAS mutation requires first the definition of the percentage of tumor / normal tissue subjected to the RAS analysis. As a next step, the analysis of RAS mutation needs to provide a quantitative readout. For each single specimen, an exact percentage of mutant versus wildtype tumor cells needs to be indicated. To generate optimal results, screening for low-level RAS mutation should be performed in an experienced central pathology laboratory. At present time, the true incidence of low-level RAS mutation in the population of mCRC patients is unclear. Since 1st-line anti-EGFR treatment is well established and unquestioned in patients with RAS-wildtype tumors, the present study will focus on mCRC patients with previously determined RAS mutation. In this subpopulation, the study aims to define the incidence of low-level RAS mutation.
KEY EXCLUSION CRITERIA	• Previous chemotherapy for metastatic disease with the exception of one cycle of FOLFIRI (e.g. while waiting for the result of RAS mutation frequency). • Primarily resectable metastases and the patient agrees to resection • Grade III or IV heart failure (NYHA classification) • Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study • Additional cancer treatment (chemotherapy, radiation, immunotherapy or hormone treatment) during the study treatment (treatments that are conducted as part of an anthroposophic or homeopathic treatment approach, e.g. mistletoe therapy do not represent an exclusion criterion) • Previous chemotherapy for the colorectal cancer with the exception of adjuvant treatment, completed at least 6 months before entering the study • Participation in a clinical study or experimental drug treatment within 30 days prior to study inclusion or within a period of 5 half-lives of the substances administered in a clinical study or during an experimental drug treatment prior to inclusion in the study, depending on which period is longest or simultaneous participation in another study while taking part in the study • Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, panitumumab, irinotecan, and chemically related substances and/or hypersensitivity to any of the excipients of any of the aforementioned substances including known hypersensitivity reactions to monoclonal antibodies NCI CTCAE Grade ≥ 3. • Known hypersensitivity to Chinese hamster ovary cell (CHO) – cellular products or other recombinant human or humanised monoclonal antibodies • History of uncontrolled bronchial asthma • Patients with interstitial pneumonitis or pulmonary fibrosis • Patients with uncontrolled brain metastasis • History of acute or subacute intestinal occlusion or chronic inflammatory bowel disease or chronic diarrhoea • Symptomatic peritoneal carcinomatosis • Severe, non-healing wounds, ulcers or bone fractures • Patients with acute or chronic infection requiring systemic therapy • Known history of positive testing for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) • Active or chronic Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive; serologic tests required). • Known DPD deficiency (specific screening not required)

	• Known glucuronidation deficiency (Gilbert's syndrome);(specific screening not required • History of a second primary malignancy during the past 5 years before inclusion in the study or during participation in the study, with the exception of a basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ, if these were treated curatively. • Known alcohol or drug abuse • Pregnant or breast-feeding patients • Any other severe concomitant disease or disorder which, in the investigator's opinion, could influence the patient's ability to participate in the study or influence his/her safety during the study or interfere with interpretation of study results • Absent or restricted legal capacity.
KEY INCLUSION CRITERIA	• Histologically confirmed, UICC stage IV metastatic adenocarcinoma of the colon or rectum • Primarily non-resectable metastases or surgical resection refused by the patient • RAS mutation determined by the local pathology • Low level RAS mutation in the tumor (KRAS and NRAS exon 2, 3, 4) with frequency of RAS mutation ≤ 20 % according to the central molecular pathology report • Age ≥18 • ECOG performance status 0-2 • Patients suitable for chemotherapy administration • Patient's written declaration of consent obtained • Estimated life expectancy > 3 months • Presence of at least one measurable reference lesion according to the RECIST 1.1 criteria • Primary tumor tissue available and patient consents to storage and molecular and genetic profiling of tumor material. Molecular profiling of blood samples is optionally performed. • Females of childbearing potential (FCBPs) and men must agree to use two highly effective contraceptive measures simultaneously (Pearl index <1) or practice true abstinence from any heterosexual intercourse for the duration of the study treatment and for at least 6 months after last administration of study medication. Complete sexual abstinence is acceptable only if the subject is refraining from heterosexual intercourse during the entire study treatment and up to 6 months after the discontinuation of all study drugs and the reliability of sexual abstinence is in line with the preferred and usual lifestyle of the subject. A woman will be considered as being of childbearing potential unless she is at least 50 years old and moreover has gone through menopause for at least 2 years or has been surgically sterilised. • Adequate bone marrow function: ▫ Leukocytes ≥ 3.0 x 10^9/L with neutrophils ≥ 1.5 x 10^9/L ▫ Thrombocytes ≥ 100 x 10^9/L ▫ Haemoglobin ≥ 5.6 mmol/L (equivalent to 9 g/dL) • Adequate hepatic function: ▫ Serum bilirubin ≤ 1.5 x upper limit of normal (ULN) ▫ ALAT and ASAT ≤ 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT ≤ 5 x ULN) • Adequate renal function: ▫ Creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50 mL/min No previous chemotherapy for metastatic disease. Patient with need of immediate treatment (high tumor load, symptoms) may have received one application of FOLFIRI prior to study treatment.

PLANNED INTERIMS ANALYSIS	In each group, an interim analysis will be performed, when ORR is evaluable in 20 patients. Treatment within the respective study arm will be continued as long as ORR is ≥ 45%.
STATISTICAL ANALYSIS	The study will be performed in three subgroups (RAS mutation frequency ≤ 5%, > 5 to ≤ 10%, >10% to ≤ 20%). Each group will contain 40 patients (at least 35 evaluable patients) and will be analysed within an independent exploratory evaluation. The data will be compared to historical data obtained in patients with RAS wild-type tumors. In this patient group, an objective response rate of 59% and a PFS of 10 months were induced by a chemotherapy doublet plus panitumumab. Patients with RAS mutant tumors treated with chemotherapy alone achieved an ORR of 46% and a PFS of 7.6 months in the PRIME study (FOLFOX) (Douillard NEJM) and an ORR of 36% and a PFS of 7.6 months in the CRYSTAL study (FOLFIRI) (van Cutsem JCO 2015). The study results may also be evaluated in relation to 188 patients with RAS mutant tumors that were treated in FIRE-3. In 97 patients who received FOLFIRI plus cetuximab, ORR was 38.1% and PFS was 7.5 months. By contrast, in 91 patients treated with FOLFIRI plus bevacizumab, ORR was 50.5% and PFS was 9.6 months (Stintzing, European Journal of Cancer 2017).
SAMPLE SIZE	No formal sample size calculation will be done. The sample size of 35 evaluable patients for the final analysis and 20 patients in the interim analysis approximately corresponds to the following two-stage design by Simon: since an ORR of ≥59% is expected, 38 patients are required in order to reject the null hypothesis (ORR ≤ 45%) with a power of 80% at a significance level of 0.2.

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: 175
Patienten:	geplant: 8000	aktuell eingeschlossen: 5175
Letzte Aktualisierung	Oktober 2020	

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 2020

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

Arbeitsgruppe Weichteilsarkome

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: 171 davon 18 in Deutschland
Anzahl Zentren:	geplant: 9	initiiert: 9
Letzte Aktualisierung	12.10.2020	

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– 2021
Weitere Zentren:	auf Anfrage
Letzte Aktualisierung	November 2019

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 refractory to treatment with tyrosine kinase inhibitors. The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of at least one confirmed complete response (CR) or confirmed partial response (PR) or stable disease (SD) according to RECIST version 1.1. Secondary Objectives include: • Tumor Response (TR) • Progression-free Survival (PFS) • Overall Survival (OS) • Safety/tolerability • 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). • 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 or 30 mg hydrocortisone. • 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

	• Uncontrolled infection • 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).
KEY INCLUSION CRITERIA	• Patients with locally advanced or metastatic chordoma with confirmed diagnosis in a reference pathology (with immunohistology for epithelial membrane antigen, S100, Brachyury, INI-1) who have no response or have lost response to treatment with a tyrosine kinase inhibitor e.g. imatinib, lapatinib, erlotinib, sunitinib, sorafenib, etc. • 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) • No chemotherapy two weeks before study entry • 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. med. Stefan Fröhling 2. Universitätsklinikum Essen, Dr. med. Rainer Hamacher 3. Universitätsklinikum Ulm, Dr. Verena Gaidzik
CURRENT NUMBER OF PATIENTS INCLUDED	16

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:	auf Anfrage
Rekrutierungszeitraum:	2018 – 2020
Weitere Zentren:	sind möglich
Letzte Aktualisierung	Nov. 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
Das vollständige Kurzprotokoll finden Sie unter den Studien der Arbeitsgruppe **Translationale Forschung**.	

Young Medical Oncologists

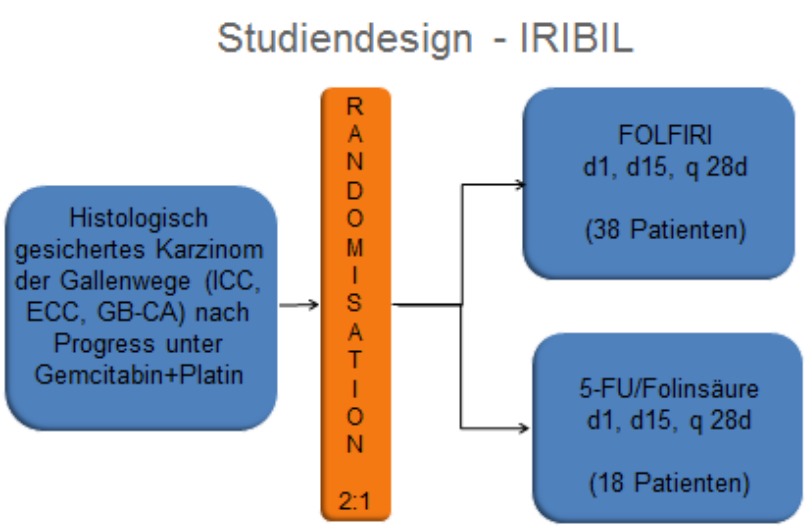
Biliäre Tumoren – 2nd-line

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 – 2019	
Patienten	geplant: 56	aktuell eingeschlossen: 13
Zentren	geplant:	initiiert:
Weitere Zentren:	sind leider nicht möglich!	
Letzte Aktualisierung	Nov. 2020	

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: 56 Patienten Bereits eingeschlossen: 5 (Stand Okt 2018) (in 4 Zentren)
Rekrutierungs-zeitraum	Erster Patient eingeschlossen: Mai 2016 Rekrutierungsdauer: 24 Monate Therapiedauer: 12 Monate Follow-up-Dauer: alle 6 Wochen bis Tod Studienende: Mai 2019 Gesamtdauer: 3 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 5-FU/folinic acid: 2 Monate 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: 38 Patientenzahl 5-FU/folinic acid 18

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: 17	initiiert: 10
Patienten:	geplant: 88	aktuell eingeschlossen: 5
Letzte Aktualisierung	16.10.2020	

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 ≥ 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 ohne onkogenen Treiber, metastasiert

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

AIO-Studie	Eine Studie der Young-Medical-Oncologists (YMO)	
Studiennummer/-Code:	AIO-YMO/TRK-0416 - DURATION	
Status:	In Rekrutierung	
Rekrutierungszeitraum:	2017 –2020	
Zentren:	geplant: 30	initiiert:
Patienten:	geplant: 200	aktuell eingeschlossen: 186
Weitere Zentren:	Leider nicht möglich	
Letzte Aktualisierung	Oktober 2020	

Study design	Open label, treatment stratified and randomized phase II study
National Coordinating Investigator	Dr. med. Jonas Kuon Internistische Onkologie der Thoraxtumoren Thoraxklinik – Universität Heidelberg Röntgenstrasse 1, 69126 Heidelberg jonas.kuon@med.uni-heidelberg.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 814534431, Fax +49 30 322932926 info@aio-studien-ggmbh.de
Anticipated start date	Q4/2017
Duration of study	Enrollment: 24 month Treatment and follow-up: 24 month
Indication	metastatic non-small cell lung cancer (NSCLC)
Target population	Frail or elderly patients with metastatic NSCLC with no targetable molecular alterations (EGFRwt; ALKtransl-) and not amenable to cisplatinum-based standard-combination chemotherapy but eligible for at-least mono-chemotherapy with gemcitabine or vinorelbine.
Primary objective	To assess the safety and tolerability of sequential therapy consisting of standard of care mono- or combination chemotherapy followed by durvalumab in comparison to standard of care mono- or combination chemotherapy in frail/elderly patients. For this purpose treatment related adverse events including those with a potential inflammatory or immune-mediated mechanism will be assessed. These include colitis, pneumonitis, ALT/AST increases, hepatitis, hepatotoxicity, neuropathy, neuromuscular toxicity (e.g. encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and myasthenia gravis), endocrinopathy (e.g. hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism), dermatitis, nephritis and pancreatitis.

Secondary objectives	To explore additional efficacy, safety and Quality of Life parameters and to investigate the utility of geriatric assessments for treatment guidance.
Exploratory objectives	predictive biomarkers for efficacy variables
Planned sample size	**N=200 randomized patients in total** Anticipated uninformative drop-outs: 15% Currently randomized: 186
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 ≥ 70 years at time of study entry and/or Charlson-Comorbidity-Index (CCI) >1 and/or Performance status ECOG >1 3. Histologically confirmed diagnosis of metastatic NSCLC and no targetable molecular alterations (EGFRwt; ALKtransl-) and not amenable to cisplatinum-based standard-combination chemotherapy. 4. Patients with measurable disease (at least one uni-dimensionally measurable target lesion not previously irradiated, by CT-scan or MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) are eligible. 5. A formalin fixed, paraffin-embedded (FFPE) tumor tissue block (fresh or archival less than 3 years old or recent) or a minimum of 10 unstained slides of tumor sample (slices must be 2-3 µm in thickness and less than 90 days old and collected on SuperFrost slides provided by the sponsor) must be available for biomarker (PD-L1) evaluation. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is inappropriate. 6. No prior chemotherapy or any other systemic therapy for metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for locally advanced disease are eligible, provided that progression has occurred >6 months from last therapy. 7. Prior radiotherapy and surgery are allowed if completed 4 weeks (for minor surgery and palliative radiotherapy for bone pain: 2 weeks) prior to start of treatment and patient recovered from toxic effects or associated adverse events. 8. Adequate blood count, liver-enzymes, and renal function: • Haemoglobin ≥ 9.0 g/dL • Absolute neutrophil count (ANC) ≥ 1.5 x 109/L (> 1500 per mm3) • Platelet count ≥ 100 x 109/L (>100,000 per mm3) • Serum bilirubin ≤ 1.5 x ULN. This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician. • AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN • Serum creatinine CL>30 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance 9. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits, examinations including follow up and appropriate contraception.
Exclusion criteria	1. Mixed small-cell lung cancer and NSCLC histology 2. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's correction, except for asymptomatic QTc prolongations. 3. History of another primary malignancy except local prostate cancer without need for systemic treatment (e.g. active surveillance, operation without need for adjuvant treatment) and malignancies treated with

	curative intent and with no known active disease >2 years befor the first dose of study drug and of low potential risk for recurrence, e.g. adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, adequately treated carcinoma in situ without evidence of disease (e.g. cervical cancer in situ) 4. Pre-existing peripheral neuropathy of Grade ≥ 2 5. Brain metastasis or spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatement. 6. Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded. 7. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis) 8. History of primary immunodeficiency 9. History of allogeneic organ transplant 10. History of hypersensitivity to durvalumab or any excipient 11. History of hypersensitivity to any of the comparator agents 12. Medication that is known to interfere with any of the agents applied in the trial. 13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent 14. Clinical diagnosis of active tuberculosis 15. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab 16. Male patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year) 17. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results 18. Participation in another clinical study with an investigational product during the last 30 days before inclusion 19. Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab 20. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid 21. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 21 days prior to the first dose of study drug or ≤4 half-lifes of the agent administered, which ever comes first. 22. Previous enrollment or randomization in the present study. 23. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff of sponsor and study site) 24. Patient who might be dependent on the sponsor, site or the investigator 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 form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG]. 27.
Investigational agent	• durvalumab (MEDI4736) Comparators and standard chemotherapies:

	• *nab*-Paclitaxel • gemcitabine • vinorelbine • carboplatin
Treatment schedule	Dosage/Timepoints Experimental arms: • Induction: 2 cycles of mono-chemotherapy or combination chemotherapy followed by two cycles durvalumab 1125 mg Q3W • Maintenance: durvalumab 1500 mg Q4W Treatment will be given until progression, intolerance/toxicity, or withdrawel of consent, whichever occurs first. Control arms -active comparators (SOC CTx): Mono-chemotherapies: • Vinorelbin 30 mg/m^2 D1 + D8 Q3W • Gemcitabine 1000 mg/m^2 D1 + D8 Q3W Combination chemotherapy: • *nab*-Paclitaxel: 100mg/m^2 D1,D8 + Carboplatin AUC 5.0 D1; Q3W Treatment will be given for a maximum of 4 cycles (chemotherapy) or until intolerance/toxicity, progressive disease or withdrawel of consent. **Key study procedures (and routine procedures):** • CARG-score for treatment (stratification) allocation • geriatric assessments (G8-questionnaire, Timed up&go, 6MWT) • HR-QOL (FACT-L) • tumor response evaluation • tumor tissue and blood biomarker assessments
Primary endpoint	Rate of treatment related Grade III/IV adverse events (CTCAE V4.03)
Secondary endpoints	• ORR according to RECIST 1.1 criteria • Progression free survival (PFS) • Overall survival (OS) • AEs / SAEs according to CTCAE 4.03 • Health related Quality of Life (HR-QoL)
Stratification	According to the predictive model for treatment-related toxicity in older adults (Hurria et al., JCO 2011), stratification will be performed with the following cut-offs: • Total risk score ≤ 3 → combination chemotherapy • Total risk score > 3 → mono-chemotherapy
Randomization procedure	1:1 after CARG-score stratification
Rationale	Metastatic non-small cell lung cancer (NSCLC) bears a dismal prognosis with a median survival not exceeding 10-12 month. The impact of combination chemotherapy is limited with median progression-free survival times ranging from 3-4 month. In subgroups of about 20% of adenocarcinoma patients, defined by molecular alterations (activating EGFR-mutation; ALK-translocation), treatment with tyrosine-kinase inhibitors impacts on prolonging median progression-free survival up to 9-11 months and median survival up in a range of 3 years. In the non-molecularly altered population chemotherapy-only is still the standard of care [1]. In patients aged over 70 years and those with a restricted performance score (ECOG-2) or “frail” physical condition mono-chemotherapy (e.g. Vinorelbine; e.g. Gemcitabine) [2, 3] or a dose adopted combination of carboplatin (AUC6) / Paclitaxel (90 mg/m2; d1+8+15) [4] is considered to improve prognosis. So, in a randomized trial, enrolling patients aged > 70 (> 80 years, 25%; PS-ECOG 2, 27%; Charlson-Comorbidity –Index > 2, 24%), superiority of the afore mentioned regimen compared to mono-chemotherapy (Gemcitabine; Vinorelbine) could be shown [4]: RR, 27% vs. 10%; PFS, 6.0 vs. 2.8 months (median), 13% vs. 2% (1-year-rate), 5% vs. 0.4% (2-year-rate); OS, 10.3 vs. 6.2 months (median), 44% vs. 25% (1-year-rate), 22% vs. 12% (2-year-rate). Moreover, a randomized phase II trial

	(Carboplatin, AUC5 / Vinorelbine, 25 mg/m2; d1+8 vs. Erlotinib, 150 mg daily) provided evidence on the feasibility of Carboplatin / Vinorelbine in patients aged > 70 [5], with efficacy-rates comparing to Carboplatin / Paclitaxel: RR, 28% PFS, 4.3 months (median), 15% (1-year-rate); OS, 17.7 months (median), 40% (1-year-rate), 25% (2-year-rate). In the recent past, with the impact-assessment of nab-paclitaxel, by head-to-head comparison of carboplatin/paclitaxel vs. carboplatin/nab-paclitaxel (n = 744), a superior response rate (25% vs. 33%, $p < 0.001$) paralleled by significantly lesser grade 3/4 neutropenia (47% vs. 58%, $p < 0.001$) and grade 3/4 neuropathy (18% vs. 9%, $p < 0.001$) in favor of nab-paclitaxel could be shown [6]. Moreover, in patients > 70 years (n = 105), overall survival favored carboplatin / nab-paclitaxel (HR = 0.58) [6]. However, due to the considerable toxicities choosing the appropriate chemotherapy regimen is still a notable clinical challenge. With the advent of immunooncology in the treatment of lung cancer, new options arise at the horizon. So checkpoint inhibition, targeting PD-1 and PD-L1, is advancing up to 1st line treatment in comparison to combination chemotherapy. Anti-PD-1/PD-L1 antibodies have demonstrated impressive efficacy results in NSCLC and first marketing approvals have been granted (nivolumab/Opdivo® and pembrolizumab/Keytruda®) [7-11]. The rate of treatment emergent adverse events is lower than with conventional chemotherapies and side effects of immune-checkpoint inhibitors are generally manageable. There is however, currently a lack of clinical evidence to assess the tolerability and safety of check-point inhibition as a treatment option in frail and elderly patients. Thus an appropriately defined patient population (EGFRwt; ALKtransl-), characterized by: age ≥ 70 and / or Charlson-Comorbidity-Index (CCI) > 1 (frailty) and / or performance status ECOG > 1, not amenable to cisplatinum-based standard-combination chemotherapy, should be tested for treatment with PD-L1 – antibody - after an induction chemotherapy of 2 cycles (mono or combination chemotherapy) in comparison to either mono-chemotherapy or combination therapy (Carboplatin/nab-Paclitaxel). It is expected, that two cycles of induction chemotherapy lead to a prompt disease stabilizing effect, which can be efficaciously extended by a consecutive durvalumab monotherapy with even less toxicity in comparison with standard of care chemotherapy. In frail and elder patients with NSCLC two cycles of chemotherapy is well feasible, side effects are manageable, and no or minor alteration in QoL should be expected. To assort patient to treatments (combination vs. mono) by stratification, an adopting scoring system will be employed (Hurria 2011). In both strata PD-L1 – antibody treatment given after 2 cycles of chemotherapy (mono or combination) will serve as a comparator. This will give the opportunity to assess the “extent of frailty/comorbidity” and the potential impact of PD-L1 – antibody treatment 1st line in those patients. **Hypothesis:** We hypothesize that PD-L1 checkpoint blockade (durvalumab) given after induction of 2 cycles of chemotherapy will lead to a reduced rate of CTC grade III/IV toxicity and improves the overall survival when compared to standard of care mono- or combination chemotherapy.
Safety data	• AEs, SAEs and Treatment Emergent Adverse Events according to CTC 4.03 • Frequency of abnormal laboratory parameters • Immune related (ir)AEs of special interest will require additional reporting (colitis, hepatitis, hypophysitis, uveitis or pneumonitis, pancreatitis)
Sample size	Sample size calculation: The primary safety endpoint for the study is the occurrence of a CTC grade

and statistical analysis considerations	III/IV toxicities assessed from first dose up to 90 days after last dose of IMP. This is also the primary study endpoint on which the sample size calculation is based. According to the results of Rizvi presented at ASCO 2015 it is assumed that the probability for a CTC grade III/IV toxicity for patients from the pooled experimental arms B+C receiving durvalumab amounts to PB+C=0.18. It is furthermore assumed from reported data of selected treatment related adverse events (combination chemotherapy nab-paclitaxel / carboplatin: Socinski, JCO 2012, mono-chemotherapy gemcitabine / vinorelbine: Quoix, Lancet 2011) that the rate of patients with a CTC grade III/IV toxicity in the pooled control arms A+D receiving chemotherapy only amounts to PA+D=0.35. With the planned number of patients of N=200, the assumed difference between these two groups can be detected using a Chi-square test at a two-sided significance level of α=10% with a probability of 1-β=0.80, also taking a dropout rate of 15% into account. Sample size calculation was performed using ADDPLAN v6.1. It should be noted that the study is not powered to detect significant differences with regard to the efficacy endpoints, since its primary aim is to assess safety and tolerability. Hence, no confirmatory evidence can be drawn from the efficacy evaluation. Accordingly, all p-values for efficacy outcomes are only to be interpreted descriptively and no adjustment for multiple testing will be done. Statistical analysis considerations for the primary endpoint: The null hypothesis for the primary (safety) endpoint of the trial is defined as H0: PB+C = PA+D (i.e., the rate of patients with a CTC grade III/IV toxicity is equal in the pooled experimental arms B+C and the pooled control arms A+D), which is tested against its alternative H1: PB+C ≠ PA+D (i.e., there is a difference between the pooled experimental arms B+C and the pooled control arms A+D with regard to the rate of patients with a CTC grade III/IV toxicity). These hypotheses will be assessed at a two-sided significance level of α=0.1 using a Mantel-Haenszel Chi-square test adjusting for the stratum “adopted combination/not prone to combination”. Furthermore, the odds ratio and risk ratio will be calculated together with the corresponding 90% confidence interval. 90% confidence intervals will also be determined for the estimated grade III/IV toxicity in the pooled arms A+B and C+D and for the estimated grade III/IV toxicity in the four separate treatment arms. The analysis of the primary endpoint will be based on the Safety Population.
Biomarker measurements	• PD-L1 expression and optionally other biomarkers in tumor tissue samples Optional: • phenotypical analysis of lymphocytes by FACS • analysis of T-cell receptor specificities (T-cell receptor sequencing) • mRNA profiling of T-cells • soluble pro- and anti-inflammatory markers and Glycodelin • Analysis of mutational load based on cfDNA
QoL measurements	FACT-L
Study plan / time lines	First Patient In (FPI): Q4/2017 Last Patient In (LPI): after approx. 36 month Last Patient Last Visit (LPLV): after approx. 60 month End of follow-up period after LPLV: after approx. 60 month Study report: after approx. 72 month Publication: after approx. 75 month

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:	von: 2020		bis: Mrz. 2022
Anzahl Zentren:	geplant: 8	aktuell initiiert: 0	aktiv rekrutierend: 0
Weitere Zentren:	erwünscht		
Anzahl Patienten:	geplant: 60	aktuell eingeschlossen: 0	
Letzte Aktualisierung	Oktober 2020		

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 - NICITA		
Status:	in Rekrutierungsphase		
Rekrutierungszeit:	von: Q1-2020	bis: Q1-2022 (24 Monate)	
Anzahl Zentren:	geplant: 12	aktuell initiiert: 10	aktiv rekrutierend: 6
Weitere Zentren:	Evtl. möglich		
Anzahl Patienten:	geplant: 92	aktuell eingeschlossen: 13	
Letzte Aktualisierung	09.10.2020		

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:	in Vorbereitung	
Rekrutierungzeit:		
Anzahl Patienten:	geplant: 153	aktuell eingeschlossen:
Anzahl Zentren:	geplant: 40	initiiert:
Weitere Zentren:	sind erwünscht	
Letzte Aktualisierung	Okt. 2020	

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:	in Vorbereitung	
Rekrutierungszeitraum:	Q4/2020 – Q4/2022	
Zentren:	geplant: 6	initiiert:
Patienten:	geplant: 132 (Max 200)	aktuell eingeschlossen:
Weitere Zentren:	Aktuell leider nicht möglich	
Letzte Aktualisierung	26.10.20	

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 2020

Studiendesign	Multizentrische, prospektive Studie
Verantwortlicher Studienleiter nach AMG	PD Dr. med. Michael Quante, II. Medizinische Klinik der Technischen Universität München, Klinikum rechts der Isar
Kontaktadresse/ Kontaktperson:	PD Dr. med Michael Quante Klinikum rechts der Isar - Technische Universität München II. Medizinische Klinik, Ismaninger Straße 22, 81675 München michael.quante@tum.de
Studienziele/ Objectives	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: 806 (Stand 18.10.2020) Anzahl Studienvisiten: 1092 (Stand 18.10.2020)
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: 0

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 2020

Art der Studie Study Type	Retrospective and prospective registry study
Kontaktadresse/ Kontaktperson:	Prof. Dr. Dr. Matthias Kroiß Tel.: 089/4040-52221 Email: matthias.kroiss@med.lmu.de Julia Wendler Tel.: 0931/201-39717 Email: Wendler_J@ukw.de LMU Klinikum der Universität München Medizinische Klinik und Poliklinik IV Endokrinologie/Diabetologie Ziemssenstr. 1 803360 München
Studienziele/ Objectives	Primary objectives: 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 Secondary objectives: 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: 268 ATC, 645 MTC, 263 RDTC, 82 PaTC
Rekrutierungzeitraum von/bis period of	retrospective: 2000 – 2013 prospective: 2014 – 2023 (Zwischenevaluierung)

Weitere teilnehmende Zentren erwünscht? More centres?	current centers (10/2017): - Universitätsklinikum Würzburg - Universitätsklinikum Augsburg - Universitätsklinikum Düsseldorf - Universitätsklinikum Gießen und Marburg – Standort Marburg - Universitätsklinikum Greifswald - Endokrinologische-Nuklearmedizinische Gemeinschaftspraxis Heidelberg - Universitätsklinikum Leipzig - Klinikum der Universität München - Campus Großhadern - 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	

Arbeitsgruppe ZNS-Tumoren/Meningeosis

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 2020

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. 30 Patienten pro Jahr prospektiv eingeschlossen werden. Aktuell sind **268** Pat. eingeschlossen (Stand Oktober 2020).
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:	in Vorbereitung	
Rekrutierungszeitraum:	2019 - 2024	
Weitere Zentren:	sind sehr erwünscht	
Patienten:	geplant: 200	aktukell eingeschlossen:
Letzte Aktualisierung	25.01.2019	

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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