AIO-KRK-0320ass: 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)

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-KRK-0320ass / GOBLET**
Status:	in Rekrutierung
Rekrutierungszeit:	von: Q3/2021 bis: Q4/2023
Anzahl Zentren:	geplant: 13 aktuell initiiert: 12 aktiv rekrutierend: 12
Weitere Zentren:	Nicht benötigt
Anzahl Patienten:	geplant: 55 aktuell eingeschlossen: 41
Letzte Aktualisierung	Oktober 2023

PRINCIPAL INVESTIGATOR	Prof. Dr. med. Dirk Arnold Director, Asklepios Tumorzentrum Hamburg Head of Oncology, Hematology and Palliative Care Asklepios Klinik Altona Paul-Ehrlich-Strasse 1 22763 Hamburg, Germany
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	**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	open-label, non-randomized, phase 1/2, multiple-indication platform, multi-center study
PRIMARY OBJECTIVE	**Safety** To evaluate the tolerability of pelareorep plus atezolizumab in combination with SOC chemotherapy (only cohort 1 and 3). **Efficacy** Cohort 1, 2 and 4: To evaluate the response to treatment measured by ORR at week 16. Cohort 3: Evaluate the response to treatment measured by DCR at week 16.

SECONDARY OBJECTIVES	To assess the anti-tumor activity of the treatment combinations based on: • Progression-free survival (PFS) • Duration of response (DOR) • Overall survival (OS) • Overall response rate (ORR) • Overall disease control rate (DCR)
EXPLORATORY OBJECTIVES	To evaluate the immunological changes within tumor tissue and peripheral blood and to examine potential biomarkers of response to treatment in each cohort
PRIMARY ENDPOINT	**Primary Safety Endpoint** All Cohorts, All Phases: • Serious and non-serious AEs (clinical and laboratory), laboratory parameters, treatment exposure (total delivered dose and dose modifications), and reasons for treatment discontinuation. All observed AEs and ≥grade 3 lab abnormality AEs will be documented and graded according to NCI CTCAE v5.0. **Primary efficacy endpoint** Cohorts 1, 2, and 4, Phase 2: • ORR (complete response [CR], partial response [PR]) assessed by the investigators and/or central reader according to RECIST v1.1 at week 16 (within each cohort) Cohort 3, Phase 2: • DCR (complete response [CR], partial response [PR], and stable disease [SD]) according to RECIST v 1.1 at week 16.
SECONDARY ENDPOINTS	**Secondary endpoints, All Cohorts, Phase 2:** • PFS defined as the duration from the date of first treatment to the date of progressive disease or death from any cause • DOR per RECIST v 1.1. • OS defined as the time from date of first treatment to death from any cause • ORR, defined as the percentage of patients with a best overall response of complete response [CR] or partial response [PR] according to RECIST v 1.1, and confirmed ORR, defined as the percentage of patients with a CR or PR at two or more consecutive evaluation timepoints. • Overall DCR, defined as the number of patients with a best overall response of CR, PR, or SD according to RECIST v. 1.1
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
EXPLORATORY ANALYSIS / TRANSLATIONAL RESEARCH ENDPOINTS	• Examine the expression of immune-related biomarkers, such as PD-1 and PD-L1 • Identify biological changes, as defined by changes in gene expression, within the TME and peripheral blood mononuclear cells (PBMCs), between baseline and on-treatment specimens • Compare changes in the T cell repertoire between pre-treatment and on-treatment tumor biopsies, examining common T cell clones between tumor tissue and peripheral blood samples • Compare changes in the T cell repertoire between pre-treatment and on-therapy peripheral blood samples

	• Examine tumor mutational burden and prevalent deoxyribonucleic acid (DNA) mutations in all patients from circulating tumor deoxyribonucleic acid (ctDNA) • Examine if quantifiable changes in ctDNA correlate with treatment outcome • Develop new classifiers to predict therapeutic response, using quantum cascade laser-based infrared microscopy for label-free and automated cancer classification in tissue sections • Measure the ability of a microbiome signature to predict clinical efficacy
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 (CTLA-4) 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 'primed' 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). This study will explore if the oncolytic virus, pelareorep, can sensitize GI tumors to checkpoint blockade, thereby improving responses and increasing the number of patients who can be treated. Specifically, the study will explore pelareorep's potential to enhance the activity of the checkpoint inhibitor atezolizumab in four different locally advanced or metastatic cancer settings: 1. 1L PDAC (C1): Checkpoint inhibitor therapy is indicated for PDAC patients with MSI-H/dMMR tumors; however, fewer than 2% of PDAC patients are eligible based on this criterion. This study will assess whether the addition of pelareorep to atezolizumab may allow PDAC patients to benefit from checkpoint inhibitor therapy regardless of MSI/dMMR status. 2. 1L mCRC with MSI-H/dMMR tumors (C2): Checkpoint inhibitor therapy is indicated as first-line therapy in MSI-H/dMMR colorectal cancer. However, in the pivotal study supporting this indication, KEYNOTE-177, 56% of MSI-H/dMMR tumors did not respond to checkpoint inhibitor therapy and more than 40% of patient progressed within 6 months of beginning checkpoint inhibitor therapy. Therefore, this study will assess whether the addition of pelareorep may increase the proportion of responding patients.

	3. 3L mCRC (C3): Similar to PDAC, only a low proportion (approximately 5%) of mCRC patients are eligible for checkpoint inhibitor treatment based on MSI/dMMR status. This study will assess whether pelareorep can enable atezolizumab to benefit mCRC patients regardless of MSI/dMMR status. 4. ≥2L SCCA (C4): Treatment options for ≥2L SCCA are limited. Checkpoint inhibitors have shown some promise in pretreated patients, but tumor response rates remain low. This study will assess whether the combination of pelareorep and atezolizumab may provide tumor response in these patients. 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.
INCLUSION CRITERIA	**Cohort 1: 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. **Cohort 2: Metastatic Colorectal Cancer 1L (MSI-H/dMMR)** Patients with histologically or cytologically confirmed metastatic colorectal adenocarcinoma (mCRC) with MSI-H/dMMR tumors and no prior systemic treatment for metastatic disease. **Cohort 3: 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. (See Appendix 6 for guidance on determining eligibility for this cohort). **Cohort 4: 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. **<u>All Cohorts:</u>** **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 measurable lesions per RECIST v1.1 5. Have adequate organ function at the time of enrollment as defined by: • Absolute neutrophil count ≥1200/mm^3 • Platelet count ≥7.5 × 10^4/mm^3 • 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. 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.
EXCLUSION CRITERIA	**<u>All Cohorts</u>** **Patients must not have:** 1. Undergone systemic chemotherapy, radiotherapy, or surgery, <4 weeks before study treatment. **In Cohort 3 only:** patients must not have received previous treatment with trifluridine/tipiracil. 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). Patients with a known history of brain metastasis must be assessed by MRI during screening. 9. Interstitial lung disease with symptoms or signs of activity.

	10. **In Cohort 1, Cohort 2, and Cohort 3 only:** known active Hepatitis B (HBV) or Hepatitis C (HCV) infection that requires anti-viral treatment. Testing for HBV/HCV is not required in the absence of clinical suspicion. **In Cohort 4 only:** Prior HIV infection 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 within 28 days prior to first treatment or during the first cycle of study treatment. 21. Legal incapacity or limited legal capacity to consent. 22. Life expectancy less than 3 months
TRIAL DURATION	Enrollment: 14 months Total study duration: ~50 months
SAMPLE SIZE ESTIMATION	A potential total of 206 patients across all four cohorts will be analyzed. The initial Phase 1b and Phase 2 Stage 1 will include a total of 55 evaluable patients (i.e., patients with week 8 imaging assessments) across all 4 cohorts (C1=12; C2=19; C3=14; C4=10), with the option for extension to Phase 2 Stage 2 (C1=32; C2=42; C3=37; C4=40)
PARTICIPATING CENTERS	12
FURTHER CENTERS DESIRED?	no
NUMBER OF PATIENTS	Stage 1: 55 Stage 2: 151