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 beendet	
Rekrutierungszeitraum:	28.10.2020 - 11.08.2021	
Zentren:	geplant: 7	initiiert: 7
Patienten:	geplant: 20	aktuell eingeschlossen: 20
Weitere Zentren:	keine	
Letzte Aktualisierung	06.09.2021	

STUDY TYPE	Non-randomized, open-label, multicenter pilot study
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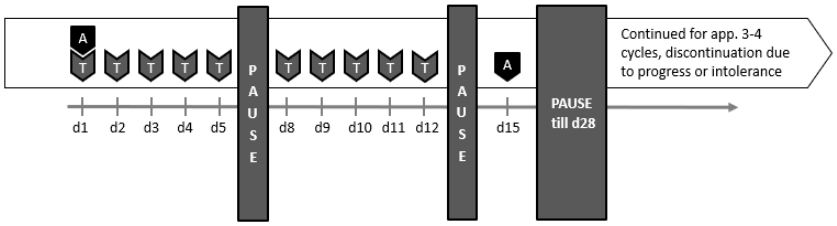
TRIAL OFFICE	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
SPONSOR	Institut für Klinisch-Onkologische Forschung (IKF) Krankenhaus Nordwest gGmbH Steinbacher Hohl 2-26 60488 Frankfurt/Main
CONDITION	advanced or metastatic adenocarcinoma 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.  A = Antibodytherapy with Ramucirumab T = TAS102 (2x tgl.) d = Tag 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 **Exclusion Criteria** 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.