AIO-STO-0315/ass: Perioperative RAMucirumab in combination with FLOT versus FLOT alone for reSEctable eSophagogastric adenocarcinoma – RAMSES – A phase II/III trial of the AIO

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-STO-0315/ass - RAMSES – FLOT7	
Status:	Rekrutierung beendet	
Rekrutierungszeitraum	2016 - 2019	
Zentren:	Anzahl:	initiiert:
Patienten:	geplant: 180	aktuell eingeschlossen: 180
Weitere Zentren:	sind leider nicht mehr möglich!	
Letzte Aktualisierung	08.10.2020	

Study type	Multicenter, randomized, open label phase II/III study
Investigational and control drugs	Ramucirumab FLOT (backbone therapy)
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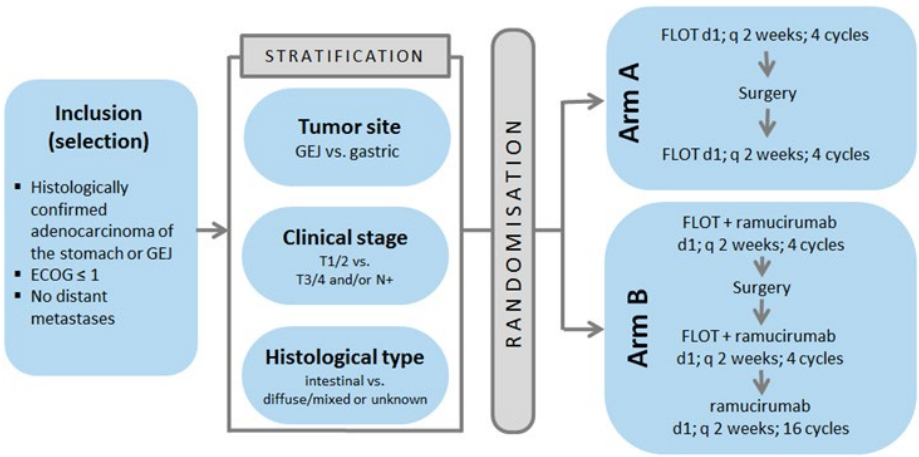
Study Management	Sascha Herzer, Ulli S. Bankstahl Dr. Claudia Pauligk Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26, 60488 Frankfurt am Main Tel.: +49 69 7601-4281, -4596, -3906; Fax -3655 Email: herzer.sascha@ikf-khnw.de; bankstahl.ulli@ikf-khnw.de; pauligk.claudia@ikf-khnw.de
Objectives	Phase II: • To compare rate of pathological complete or subtotal responses (pCR/SR) in patients treated with ramucirumab plus FLOT versus patients treated with FLOT alone. • To determine R0 resection rates, progression-free survival (PFS), overall survival (OS) Phase III: • To compare OS in both trial arms • To determine R0 resection rates, pathological response rates, PFS and OS rates at 3 and 5 years and PFS. Safety Objectives (phase II and III) • To evaluate the safety and tolerability of the ramucirumab plus FLOT compared with FLOT in patients with adenocarcinoma of the stomach and GEJ, focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities • To evaluate the perioperative morbidity and mortality of the regimens described above

Study design	This is a multicenter, randomized, controlled, open-label study including patients with locally advanced adenocarcinoma of the stomach and GEJ scheduled to receive perioperative chemotherapy. The scope of the phase II portion of the trial is to evaluate pathological response rates of either regimen assessed by a centralized pathology and evaluate safety and tolerability. Patients with locally advanced esophagogastric adenocarcinoma (i.e. cT2 any N or any T N-positive) with exclusion of distant metastases will be included in this trial. Patients will be centrally reviewed and then stratified by tumor site (GEJ vs. gastric), histological type (intestinal vs. diffuse/mixed or unknown) and clinical stage (T1/2 vs. T3/4 and/or N+) and randomized 1:1 to receive either FLOT (Arm A) or FLOT/ramucirumab (Arm B). Arm A (FLOT) Patients randomized to Arm A will receive 4 pre-operative cycles (8 weeks) of biweekly FLOT (Docetaxel 50 mg/m² in 250 ml NaCl 0.9%, iv over 1 h; Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2h; Leucovorin 200 mg/m² in 250 ml NaCl 0.9%, iv over 30 min; 5-FU 2600 mg/m², iv over 24 h, q2wk) of the preoperative treatment phase. Surgery in Arm A is planned to occur 4 to 6 weeks after d1 of last FLOT. Patients will receive 4 additional post-operative cycles (8 weeks) of FLOT in the post-operative treatment phase. Post-operative treatment should start 6 to 8 weeks, but at maximum 12 weeks after surgery. Arm B (FLOT/ramucirumab) Patients randomized to Arm B will receive ramucirumab 8mg/kg i.v. over 60 min in combination with the FLOT regimen, which is administered identical to Arm A as described above. Surgery in Arm B is planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients will receive 4 additional post-operative cycles (8 weeks) of FLOT/ramucirumab in the post-operative treatment phase followed by a total of 16 cycles of ramucirumab as a monotherapy (q2wk), starting 2 weeks after d1 of the last cycle of FLOT/ramucirumab. In both of the arms, tumor assessments (CT or MRI) are performed before randomization and prior to surgery, and then every 3 months thereafter until progression/relapse, death or end of follow-up. A change from CT into MRI in the follow up period is possible at any time. During treatment, clinical visits (blood cell counts, detection of toxicity) occur prior to every treatment dose. Safety of FLOT/ramucirumab will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.  Figure 1: Study Flow Chart. When the recruitment of the phase II portion is completed, the primary end point of the phase II portion will be analyzed, along with all relevant safety outcome measures. A continuation to phase III will be recommended if the phase II portion

	observes a positive efficacy signal in terms of pCR/pSR rates, and if FLOT/ramucirumab is shown to be feasible and is not associated with relevant increase in postsurgical morbidity or mortality (for further information s. protocol). If decided to continue the trial into phase III and this is confirmed and accepted by Lilly Deutschland GmbH, further efficacy endpoints will not be analyzed at this time. The transition into phase III will be performed via an amendment of the study protocol, considering a new sample size calculation taking into account the results of the FLOT4. For the phase III part, additional centers in representative parts of the world will be recruited. The phase II/III design is not alpha-spending. In case of continuation, only pathologic response and safety will be analyzed at the end of the phase II portion. All other efficacy parameters such as OS, PFS etc. will not be analyzed. Therefore, alpha level for the primary endpoint of phase III which is OS will not be affected by the phase II/III design and is at p=0.05.
Rationale	FLOT is regarded a standard chemotherapy regimen in Germany according to German S3 guidelines. The use of FLOT in the perioperative setting has become German wide practice. Within the framework of the AIO FLOT4 study, the FLOT regimen is currently compared against another standard for perioperative treatment, ECF. Interim results showed that FLOT is safe. More patients undergo postoperative chemotherapy with FLOT (ASCO 2012). Interim results from the phase II part of the FLOT4 trial also show that FLOT was associated with significantly more pathologic complete and subtotal response.
Chemotherapy schedule	**FLOT** · Docetaxel 50 mg/m², iv over 1 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 (d15) Patients in arm B (ramucirumab/FLOT parallel group) will receive ramucirumab 8mg/kg iv over 60 min in combination with FLOT on d1 (i.e. parallel to the 4 cycles of FLOT scheduled pre- and postoperatively) followed by a total of 16 cycles as monotherapy every 2 weeks, starting 2 weeks after the last cycle of FLOT.
Inclusion criteria	1. Histologically confirmed, resectable adenocarcinoma of the gastroesophageal junction (AEG/GEJ-type II-III) or the stomach (uT2, uT3, uT4, any N category, M0), or any T N+ M0 patient, with the following specifications: a. Medical and technical operability, according to the techniques described in Chapter 12 Surgical Therapy that are subtotal, total or transhiatal extended gastrectomy (patients planned to receive transthoracic esophagectomy are not eligible for the study) b. Participating sites in PETRARCA study: Negative HER-2 detection (score IHC HER-2 0 or IHC HER-2 1+); IHC HER-2 2+ and negative by FISH, SISH or CISH1 2. No preceding cytotoxic or targeted therapy 3. No prior partial or complete tumor resection 4. Female and male patients ≥ 18 and ≤ 70 years. Patients in reproductive age must be willing to use adequate contraception during the study and for 7 months after the end of ramucirumab treatment (Appropriate contraception is defined as surgical sterilization (e.g., bilateral tubal

[1] HER-2 positive patients are recruited in the German PETRARCA study (EudraCT: 2014-002695-86) sponsored by the IKF. So this study is restricted for HER-2 negative patients at sites where PETRARCA is recruiting.

	ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)). Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start.2 5. ECOG ≤ 1 6. Exclusion of distant metastasis by CT of thorax and abdomen, bone scan or MRI (if osseous lesions are suspected due to clinical signs). Exclusion of the infiltration of any adjacent organs or structures by CT or MRI. 7. Laparoscopic exclusion of peritoneal carcinomatosis, if suspected clinically 8. Adequate haematological, 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. 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 must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to randomization. c. Serum creatinine ≤ 1.5 x upper limit of normal d. Urinary protein ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol). e. Bilirubin ≤ 1.5 x upper limit of normal, AST and ALT ≤ 3.0 x upper limit of normal, alkaline phosphatase ≤ 6 x upper limit of normal 9. Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures
Exclusion criteria	1. Known hypersensitivity against ramucirumab, 5-FU, leucovorin, oxaliplatin, or docetaxel 2. Other known contraindications against ramucirumab, 5-FU, leucovorin, oxaliplatin, or docetaxel 3. Patients with esophageal cancer and those with adenocarcinoma of GEJ type I and all patients who are planned to have transthoracic esophagectomy. 4. Clinically significant active coronary heart disease, clinically active cardiomyopathy or congestive heart failure, peripheral artery occlusive disease (PAOD, German pAVK), or any history of aortic aneurysm 5. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina 6. Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management. 7. Clinically significant valvular defect 8. Past or current history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix 9. Radiologically documented evidence of major blood vessel invasion or encasement by cancer. 10. Patients with involved retroperitoneal (e.g. para-aortal, paracaval or interaortocaval lymph nodes) or mesenterial lymph nodes (distant metastasis!) 11. Known brain metastases 12. Other severe internal disease or acute infection 13. Peripheral polyneuropathy ≥ NCI Grade II

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

	14. Chronic inflammatory bowel disease 15. Grade 3-4 GI bleeding within 3 months prior to enrollment. 16. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment. 17. The patient has undergone major surgery within 28 days prior to enrollment. 18. Receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted. 19. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) during the 3 months prior to randomization. 20. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis. 21. On-treatment participation in another clinical study in the period 30 days prior to inclusion and during the study 22. Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment. 23. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) 24. Any other concurrent antineoplastic treatment including irradiation 25. Current chronic alcohol, nicotine or drug abuse or history of chronic alcohol abuse during last 12 months. Nicotine abuse is defined as ≥ 25 pack-years (Willigendael et al., 2004).
Sample size	A total of n = 150 patients with adenocarcinoma of the stomach and GEJ type II and III will be included the phase II portion of the study. The 28 patients of GEJ type I randomized before protocol version 2.0 will be replaced by additional 30 patients of the current study population. Therefore n = 180 patients will be included in total. Approximately 758 additional patients will be included in the phase III portion (total number n = 908). However, the final number will be reassessed based on the results of the randomized phase II part, and the final data of the FLOT4 trial.
Duration of the study (planned)	Recruitment duration will be 1 year for phase II and 2.5 years for phase III = recruitment duration for phase II/III is 3.5 years The follow-up time for the phase III is 2 year after last patients in, resulting in a total study duration of 5.5 years (3.5+2) for phase II/III study Note: If the phase II study part continues to phase III, there are no specific follow-up times for the phase II part. If continuation is not proposed, at least a two years follow-up (counted from last patient in) will be applicable. So the length of the phase II study will be 3 years.
Anzahl eingeschl. Pat.	180 (Stand 08.10.2020)