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
The Phase II/III RAMIRIS STUDY (RAMIRIS)

AIO-Studie	
Studiennummer/-Code:	AIO-STO-0415 - RAMIRIS
Status:	in Rekrutierung
Rekrutierungszeitraum	2019 - 2024
Weitere Zentren:	erwünscht
Zentren:	geplant: 48 in Deutschland, 12 weitere in Österreich und Italien. initiiert: 46 in Deutschland
Patienten:	geplant: Phase II: 111/Ph III: 318 aktuell eingeschlossen: 111 Phase II, 128 Phase III
Letzte Aktualisierung	März 2022

Study type	Randomized, multicenter phase II/III trial
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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 (that results in a failure rate of <1% per year) during the study and for 3 months after the end of ramucirumab treatment (appropriate contraception is defined as surgical sterilization (e.g. bilateral tubal ligation, vasectomy), hormonal contraception (including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants, intrauterine devices (IUDs) and intrauterine hormone-releasing system (IUS)), nonhormonal IUDs and complete abstinence). Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start. Female patients with childbearing potential need to have a negative pregnancy test within 7 days before study start. * There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. Histologically proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction 4. Metastatic or locally advanced disease, not amenable to potentially curative resection 5. Phase II only: Documented objective radiological or clinical disease progression during or within 6 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline or docetaxel. Neoadjuvant/adjuvant treatment is not counted unless progression occurs <6 months after completion of the treatment. In these cases neoadjuvant/adjuvant treatment is counted as one line. OR Phase III only: Radiological or clinical disease progression during or after the last dose of a first-line platinum, fluoropyrimidine-containing therapy. Patients must also have received a taxane with the first-line or during their adjuvant or neoadjuvant therapy or both. Neoadjuvant/adjuvant platinum containing therapy is permitted and is counted as first-line therapy if progression occurs <12 months after completion of the treatment. If progression occurred ≥12 months after completion of neoadjuvant/adjuvant therapy, the therapy is not counted as a treatment line. At decision of the investigator, different regimens can be considered as one line of prior treatment, in case these were administrated as a sequential or alternating therapy. 6. Measurable or non-measurable but evaluable disease 7. ECOG performance status 0-1 8. Life expectancy > 12 weeks 9. Adequate hematological, hepatic and renal functions: • Absolute neutrophil count (ANC) ≥ 1.5 x 109/L • Platelets ≥ 100 x 109/L • Hemoglobin ≥9 g/dL (5.58 mmol/L) • Total bilirubin ≤ 1.5 times the upper normal limit (UNL) • AST (SGOT) and ALT (SGPT) ≤ 3.0 x UNL in absence of liver metastases, or ≤ 5 x UNL in presence of liver metastases; AP ≤ 5 x UN • Serum creatinine ≤ 1.5 x upper limit of normal, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed) • Urinary protein ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol) • Adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5, and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients

	receiving warfarin/ phenprocoumon must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy. 10. Ability to comply with scheduled assessments and with management of toxicities **Exclusion** Patients with any of the following will not be eligible for participation: 1. Other tumor type than adenocarcinoma (e.g. leiomyosarcoma, lymphoma) or a second cancer except in patients with squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been effectively treated. Patients curatively treated and disease-free for at least 5 years will be discussed with the sponsor before inclusion 2. Squamous gastric cancer 3. Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol 4. Phase II only: Previous therapy with paclitaxel or FOLFIRI Phase III only: Previous therapy with FOLFIRI 5. Current treatment with any anti-cancer therapy ≤ 2 weeks prior to study treatment start unless rapidly progressing disease is measured 6. Concurrent treatment with any other anti-cancer therapy 7. Previous exposure to a VEGF or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study 8. Patient has undergone major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to first dose of protocol therapy. The patient has elective or planned major surgery to be performed during the course of the clinical trial 9. Grade 3-4 GI bleeding within 3 months prior to enrollment 10. History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) during the 3 months prior to first dose of protocol therapy 11. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis. 12. Known brain or leptomeningeal metastases 13. Known allergic/ hypersensitivity reaction to any of the components of the treatment 14. Contraindications to the use of atropine 15. Other serious illness or medical conditions within the last 12 months prior to study drug administration 16. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol 17. The patient has uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management 18. Active uncontrolled infection 19. Current history of chronic diarrhea 20. Active disseminated intravascular coagulation 21. Any other serious concomitant disease or medical condition that in the judgment of the investigator renders the subject at high risk of treatment complication or reduced the probability of assessing clinical effect 22. Known Dihydropyrimidine dehydrogenase (DPD) deficiency 23. Prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation. 24. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy

	25. The patient is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted 26. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to treatment start or at the same time as this study 27. Lack of resolution of all toxic effects (excluding alopecia) of prior chemotherapy, prior radiotherapy or surgical procedure to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade < 1. Note: Neuropathy due to prior chemotherapy is allowed if not > NCI Grade II according to CTCAE version 4.03 28. Subject pregnant or breast feeding, or planning to become pregnant within 3 months after the end of treatment 29. Subject (male or female) is not willing to use highly effective methods of contraception (per CTFG-Guideline) during treatment and for 3 months (male or female) after the end of treatment 30. Patients known to have a HER 2 positive Cancer who have not been treated already with a HER 2 targeting agent. 31. Patients with a psychiatric illness or patients imprisoned or working in the institution of the treating physician.
Investigational and Control Arm, Dose, Regimen, treatment cycle	Randomisation 1:1 Each Cycle: either: • Experimental Treatment: Arm A (FOLFIRI + Ramucirumab) Ramucirumab 8 mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle Plus FOLFIRI (Irinotecan 180 mg/m^2; i.v. bolus of 5-FU 400 mg/m^2, i.v. infusion of leucovorin* 400 mg/m^2, followed by a 46-hour continuous administration of 5-FU 2400 mg/m^2 on day 1 and 15 of a 28-day cycle) or • Standard Treatment: Arm B (Paclitaxel + Ramucirumab) Ramucirumab 8mg/kg i.v. infusion on day 1 and 15 of a 28-day cycle Plus Paclitaxel 80 mg/m^2 on day 1, 8, 15 Each cycle will be repeated after 28 days (from day 1) until the patient experiences progress (*) Note: Leucovorin can be replaced by sodium folinate that is given according to local guideline.
Sample size calculation	**Phase II portion:** According to these parameters, and using a standard single-stage phase II design by FLEMING (1981), n = 67 patients evaluable for efficacy have to be recruited in the R-FOLFIRI arm. About n = 34 patients are to be allocated to the reference R-Pac arm, according to the 2:1 randomization. The final conclusion of the phase II trial will depend on the definite OS rate (and its confidence interval), the respective findings in the R-Pac reference arm, as well as the information on type, frequency and severity of toxicities. Thus, a total number of about 67 + 34 = 101 evaluable patients is required. Assuming a 10% drop out rate we are planning to include 111 pts **Phase III portion:**

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