AIO-KRK-0316/ass: Phase III study of Ramucirumab in combination with TAS102 vs. TAS102 monotherapy in chemotherapy refractory metastatic colorectal cancer patients [RAMTAS]

AIO-assoziierte Studie		
Studiennummer/-Code:	AIO-KRK-0316/ass - RAMTAS	
Status:	in Rekrutierung	
Rekrutierungszeitraum	2018 - 2022	
Weitere Zentren:	sind leider nicht möglich	
Zentren:	geplant: 50	initiiert: 46
Patienten:	geplant: 426	aktuell eingeschlossen: 317
Letzte Aktualisierung	März 2022	

Condition	metastatic colorectal cancer (mCRC)
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Study group	Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft e.V.
Sponsor Project Management Sponsor	Institut für Klinische Krebsforschung IKF GmbH am 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	Primary objective: To determine the efficacy of Ramucirumab in combination with TAS102 vs. TAS102 monotherapy in patients with refractory mCRC. Primary endpoint will be overall survival (OS) according to Kaplan-Meier. Secondary objectives: Overall Response Rate (ORR) (complete remission and partial remission) Disease control rate (DCR) (complete remission, partial remission and stable disease) Progression Free Survival (PFS) OS rate at 6 and 12 months Efficacy (ORR, PFS, OS) in patients who develop neutropenia ≥ grade 2 (ANC≤1500/µl) in cycle 1 Toxicity/safety Quality of life (QoL) Tanslational research program
Study type	An interventional, prospective, randomized (1:1), controlled, open label, multicenter phase III study
Rationale	Patients with mCRC who have progressed on/after Fluoropyrimidins, Oxaliplatin, Irinotecan, anti-angiogenic and anti-EGFR therapies have limitied therapeutic options with a dismal prognosis and a median overall survial below 6 months (1,2). Recently TAS102, an oral agent that combines trifluridine and tipiracil hydrochloride significantely improved overall survival in patients with refractory

	mCRC (1). In addition the anti-angiogenic drugs Bevacizumab, Aflibercept, Regorafenib and Ramucirumab are effective beyond progression on prior anti-angiogenic therapies (2-5). The combination of TAS102 and the anti-VEGFR2 antibody Ramucirumab is the next logical step to improve efficacy and prevent resistance in mCRC.
Inclusion criteria	1. Metastatic and inoperable, colorectal cancer who has progressed on/after or did not tolerate, refuse or have contraindications to: - fluoropyrimidins, oxaliplatin, irinotecan, anti-angiogenic therapies (bevacizumab, aflibercept, regorafenib or ramucirumab) and if indicated anti-EGFR antibodies (cetuximab or panitumumab) Intolerance is defined as a permanent discontinuation of the respective treatment resulting from toxicity 2. Signed informed consent before start of specific protocol procedure 3. Histologically or cytologically documented diagnosis of adenocarcinoma of the colon or rectum 4. Presence of at least one measurable site of disease following RECIST 1.1 criteria 5. ECOG performance 0-1 6. Known RAS and BRAF V600E mutational status 7. Life expectancy of at least 3 months 8. Adequate hematological, hepatic and renal function parameters: a. Leukocytes ≥3000/mm³, platelets ≥100,000/mm³, neutrophil count (ANC) ≥1500/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/ phenprocoumon must be switched to low molecular weight heparin and have achieved a stable coagulation profile prior to first dose of protocol therapy c. Serum creatinine ≤1.5 x upper limit of normal or 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) 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, ≤5xULN if liver metastasis present, 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 10. Female and male patients ≥18. 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 ligation, vasectomy) or hormonal contraception (implantable, patch, oral). Women who use a hormonal contraception method should use an additional barrier method like 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.
Exclusion criteria	1. Known hypersensitivity against ramucirumab or TAS102 2. Other known contraindications against ramucirumab, TAS102, or other anti-angiogenic therapies 3. Prior therapy with TAS102

	4. Drug-related severe adverse events upon pretreatment with anti-angiogenic drugs that would require permanent discontinuation and not allow re-challenge with the same class of drug (i.e. ramucirumab) such as noncontrollable severe hypertension or thromboembolic events (see Table 15 on p. 63 for additional examples) 5. Any antineoplastic treatment including irradiation within 14 days (42 days for mitomycin c) prior to start of therapy. 6. Major surgery within 4 weeks of starting therapy within this study, 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 7. during the course of the clinical trial 8. Symptomatic brain metastasis 9. Clinically significant cardiovascular disease - NYHA>II°, myocardial infarction within 6 months prior study entry - Known clinically significant valvular defect - Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or >100 mmHg diastolic for >4 weeks) despite standard medical management - 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 - History of deep vein thrombosis (DVT), symptomatic 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 10. Active clinically serious infections (> grade 2 NCI-CTC version 4.0) 11. Chronic inflammatory bowel disease 12. History of uncontrolled HIV infection or chronic hepatitis B or C 13. Patients with evidence of bleeding diathesis 14. Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy 15. 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 16. History of gastrointestinal perforation or fistulae in past 6 months or risk factors for perforation 17. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy 18. 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 or bladder, or low/intermediate risk prostate cancer (Gleason score ≤7) with normal PSA levels 19. Any condition that could jeopardize the safety of the patient and their compliance of the study 20. Medical, psychological or social conditions that may interfere with the participation in the study 21. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or ascites. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis

	22. On-treatment participation in another clinical study or received investigational drug therapy in the period 30 days prior to inclusion and during the study 23. Subject pregnant or breast feeding, or planning to become pregnant within 7 months after the end of treatment 24. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) 25. Any other concurrent antineoplastic treatment including irradiation
Sample Size	426 patients (randomization 1:1) Strata: previous anti-angiogenic therapies ≥ or <12 months in total; BRAF/RAS mutation status
Interventions	Arm A: ▪ Ramucirumab 8 mg/kg d1+15, q4w ▪ TAS102 35mg/m^2 BID d1-5, 8-12, q4w Arm B ▪ TAS102 35mg/m^2 BID d1-5, 8-12, q4w Safety analyses after 20 and 40 patients
Sample Size and Statistical Analyses	According to results of the RECOURSE trial the median OS upon TAS102 treatment will be 7.1 months with a 6- and 12-months survival probability of 58% and 27%, respectively (1). An expected improvement in OS, corresponding to an increased rate after 6 months from 58% to 70% could be detected with a power of 80% and a significance level of 0,025 with a logrank test (one-sided), if 213 patients per treatment group (426 in total) are included in the study. This calculation assumes an exponential shape of the survival curves, an accrual time of 36 months and a total observation time, i.e. maximum follow-up duration, of 48 months.
Time schedule	Start of trial/First patient in (FPI): QI/2019 Last patient in (LPI) QIII /2022 LPLV (last patient last visit) date QIII/2023 Recruitment period (months): 36 months Minimum follow-up-period: 12 months
Number of enrolled pts.	317
Participating centers	50 in total

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