AIO-KRK-0117: Aflibercept and 5-FU vs. FOLFOX as 1st line treatment option for elderly or frail elderly patients with metastatic colorectal cancer

AIO-Studie		
Studiennummer/-Code:	AIO-KRK-0117	
Status:	Rekrutiert	
Rekrutierungszeitraum:	09/2018 – erweitert bis 06/2022 (geplant)	
Zentren:	geplant: 40	initiiert: 39
Patienten:	geplant: 124	bereits eingeschlossen: 109
Weitere Zentren:	Keine weiteren Zentren mehr gesucht	
Letzte Aktualisierung:	März 2022	

Phase	Randomized phase II
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Study design	This is a controlled, open-label, randomized phase- II trial (1:1 randomization) investigating 5-FU + aflibercept and 5-FU + oxaliplatin in elderly and frail elderly patients with mCRC scheduled to receive first line treatment.
Duration of study	4,5 years
Indication	Metastatic colorectal cancer
Country Total number of sites	Germany 40 sites
Primary objective	To assess the rates of progression-free survival at six months calculated from the start of treatment in elderly / frail elderly patients with metastatic colorectal cancer undergoing a 1st line treatment.
Secondary objectives	To compare the treatment arms with respect to: **Safety** - Dose intensities of study medication - Type, incidence and severity of AEs and SAEs - Laboratory parameters **Efficacy** - Response rate assessed by the local investigators - Overall and progression-free survival **Patient reported outcomes** - Quality of life - Geriatric assessment - Overall treatment utility
Primary endpoint	Rate of patients free of progression at the time point of 6 month calculated from the start of treatment. Response assessment will be done in a standardized manner using CT scan.
Secondary endpoints	**Safety**

	• Dose intensities of study medication • Type, incidence and severity of AEs, SAEs (CTCAE version 4.03) • Dose reduction or discontinuation of study drug due to adverse events • Rate of treatment discontination due to toxicity • Type, incidence and severity of laboratory abnormalities **Efficacy** • Response rates (response will be assessed by the local investigator using RECIST criteria v. 1.1; CT scans are conducted at 3 and 6 months and every three months thereafter) • Overall and progression-free survival (OS) **Patient reported outcomes** • Quality of life using EQ5D • Geriatric assessment using G8, ADL and IADL • Overall treatment utility (as defined in FOCUS2 trial)
Planned sample size	176 evaluable patients total (88 per arm). Assuming a 10% drop out rate a total of 196 patients were planned to be recruited. However, due to the slow recruitment process, sample size estimation was adjusted to 62 patients per treatment arm, and a total of 124 patients are recruited.
Target population	Elderly or frail elderly patients with metastatic colorectal cancer scheduled to undergo palliative 1st line chemotherapy.
Inclusion Criteria	1. To enter this trial the oncologist has to confirm, that the reason for entering the trial was advanced age alone or both age and frailty. As an operational definition for frailty the G8 screening tool will be used upon inclusion of the patient in a standardized manner. Briefly, G8 is an established screening tool that includes seven items from the Mini Nutritional Assessment (MNA) and an age-related item (<80, 80 to 85, or 85 years). The total score can range from 0 to 17. The result on the G8 is considered abnormal if the score is ≤14, indicating a geriatric risk profile. Due to age or frailty, the patient might not be a candidate for standard full-dose combination therapy. 2. Patients have to have histologically confirmed mCRC with unidimensionally measurable inoperable metastatic disease 3. ECOG performance status of 2 or better. 4. Life expectancy of 3 months or longer at enrolment 5. Patients ≥70 years with no upper age limit 6. Previous adjuvant chemotherapy is allowed if completed more than 6 months before randomisation 7. Previous rectal (chemo)radiotherapy is allowed if completed more than 6 months before randomisation 8. Hematological status: • Neutrophils (ANC) ≥ 1.5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Hemoglobin ≥ 9 g/dL 9. Adequate renal function: • Serum creatinine level ≤ 1.5 x upper limit normal (ULN) 10. Adequate liver function: • Serum bilirubin ≤ 1.5 x upper limit normal (ULN) • Alkaline phosphatase < 5 x ULN • AST and ALT < 3 x ULN (unless liver metastases are present then < 5 x ULN in that case) 11. Proteinuria < 2+ (dipstick urinalysis) or ≤ 2 g/24hour 12. Signed and dated informed consent, and willing and able to comply with protocol requirements 13. Regular follow-up feasible 14. Male patients with a partner of childbearing potential must agree to use effective contraception (Pearl Index < 1) during the course of the trial and at least 3 months after last administration of the study drug.

Exclusion Criteria	1. Prior systemic chemotherapy for mCRC 2. Other concomitant or previous malignancy, except: • Adequately treated in-situ carcinoma of the uterine cervix • Basal or squamous cell carcinoma of the skin • Cancer in complete remission for > 3 years 3. Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 days before start of study treatment 4. History or evidence upon physical examination of CNS metastasis unless adequately treated (irradiation and no seizure with appropriate treatment) 5. Uncontrolled hypercalcemia 6. Pre-existing peripheral neuropathy (NCI grade ≥2) resulting from previous therapy 7. Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy), 8. Treatment with any other investigational medicinal product within 28 days prior to study treatment. 9. Significant cardiovascular disease: • Cardiovascular accident or myocardial infarction or unstable angina ≤6 months before start of study treatment • Severe cardiac arrhythmia • New York Heart Association grade ≥2 congestive heart failure • Uncontrolled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), or history of hypertensive crisis, or hypertensive encephalopathy. • History of stroke or transient ischemic attack ≤6 months before start of study treatment • Coronary/peripheral artery bypass graft ≤6 months before start of study treatment. • Deep vein thrombosis or thromboembolic events ≤1 month before start of study treatment 10. Patients with known allergy to any excipient to study drugs, 11. Any of the following within 3 months prior to randomization: Grade 3-4 gastrointestinal bleeding/hemorrhage, treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event. 12. Bowel obstruction before start of study treatment. 13. Treatment with CYP3A4 inducers unless discontinued > 7 days prior to randomization 14. Known dihydropyrimidine dehydrogenase (DPD) deficiency 15. Involvement in the planning and/or conduct of the study (applies to both Sanofi staff and/or staff of sponsor and study site) 16. Patient who might be dependent on the sponsor, site or the investigator 17. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.

	18. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
Treatment schedule after randomization	**Arm A (mFOLFOX7):** Patients in the 5-FU / oxaliplatin arm receive modified (m) FOLFOX 7: Folinic acid 350 mg/m² and oxaliplatin 68 mg/m² by concurrent 2-h intravenous infusion, 5-fluorouracil 1920 mg/m² 46-h intravenous infusion. This regimen represents the 80% dosage reduced mFOLFOX 7. The 80% dose reduction was shown to be a tolerable regimen in frail elderly patients in the FOCUS 2 study. **Arm B (Aflibercept + mLV5FU2):** Patients in the 5-FU / aflibercept arm receive aflibercept 4mg/kg as 1-h infusion followed by folinic acid 350 mg/m² by 2-h intravenous infusion, 5-fluorouracil 1920 mg/m² 46-h intravenous infusion (mLV5FU2). The decision to use reduced doses of 5-FU and folinic acid was made to have comparable doses to the reduced FOLFOX 7. Chemotherapy doses in both arms may be starting at 100% (beginning from C1D1), at the discretion of the investigator.
Scientific rationale	The current trial seeks to evaluate a new treatment option for elderly / frail elderly patients with mCRC including 5-FU – better tolerated than capecitabine in the FOCUS2 study – in conjunction with aflibercept, a broad active anti-angiogenic drug within a randomized phase-II setting. Patients will be randomized using a 1:1 randomization between 5-FU / aflibercept and 5-FU / oxaliplatin using the oxaliplatin-based regimen established in FOCUS2 trial. Main goal is to estimate the 6-months PFS rate with 5-FU / Aflibercept and the safety of this regimen. The decision to use a randomized phase-II design using the “FOCUS2- FOLFOX” is based on two assumptions; (i) Bias can be better controlled by using a randomized phase-II design (ii) A clear standard regimen in frail elderly cannot be defined, but FOLFOX was superior to 5-FU alone in FOCUS2 and the patient population included in the FOCUS2 study represents the patient population scheduled to be included in the current trial. Provided the randomized phase-II study shows adequate efficacy of 5-FU / aflibercept and a tolerable safety profile, a subsequent phase-III trial may be planned. Description of the terms and conditions to expand the current trial are not part of this protocol.
Randomization and stratification procedures	After the initial screening procedure, eligible patients will be randomized in a ratio of 1:1 to receive either mFOLFOX7 or Aflibercept + mLV5FU2. Permuted block randomization will be applied. Stratification factors: G8 score ≤14 versus 15-17 & ECOG 0/1 versus 2

Statistical considerations and sample size calculation	**Sample Size Estimation:** The aim of the randomized phase-II trial is to gain a precise estimation of 6 months progression free-survival (PFS) rate of 5FU-Aflibercept for planning of a following phase III study in elderly and frail elderly patients with mCRC scheduled to receive first line treatment. Sample size calculation was done using R version 4.0.3 (R Core Team (2014). http://www.R-project.org/.).Assumptions: • Uniform recruitment of patients during randomized phase II-part • PFS exponential distribution PFS(t)=exp(rt) • Median $PFS_{5FU\text{-}Aflibercept}$=6 months equivalent to a mean $PFS_{5FU\text{-}Aflibercept}$=8.7 months With 88 evaluable patients in the 5-FU / aflibercept arm and an accrual of 24 months the lower limit of the 95% confidence limit for the 6 months PFS is 42.4%. Randomization of a total 176 patients will be stratified by G8 score and ECOG and will be performed on a 1:1-basis. Assuming a 10% drop out rate a total of 196 patients were planned to be recruited. However, due to the slow recruitment process, sample size estimation was adjusted to 62 patients per treatment arm In summary, with 62 evaluable patients in the 5-FU / aflibercept arm and an expected accrual duration of 39 months, the lower limit of the 95% confidence limit for the 6 months PFS is 41.3%. A total of 124 patients are recruited and randomized on a 1:1 basis. Stratification factors: G8 score ≤14 versus 15-17 & ECOG 0/1 versus 2
	Safety The dose intensities of study medication will be calculated over the whole study duration and will be summarized descriptively by summary statistics. AEs, will be summarized by presenting the number and percentages of patients having any AE and having an AE in each NCI-CTC category. Summaries will also be presented for AEs by severity and relationship to study medication. Tables will be broken down by study arm. All deaths and serious adverse events will be listed and briefly described. Laboratory evaluations will be analyzed by summary statistics per parameter, visit and treatment group. **Others** Vital signs will be analyzed using summary statistics broken down per treatment group and visit. Physical examination as well as ECOG will be analyzed by calculating frequencies and percentages broken down per treatment group and visit.
Number of patients, and location	Total number of patients: 124 Location of sites: Germany