AIO KRK-0116: Randomised study to investigate FOLFOXIRI plus Cetuximab vs. FOLFOXIRI plus bevacizumab as first-line treatment of BRAF-mutated metastatic colorectal cancer (FIRE-4.5)

AIO-Studie

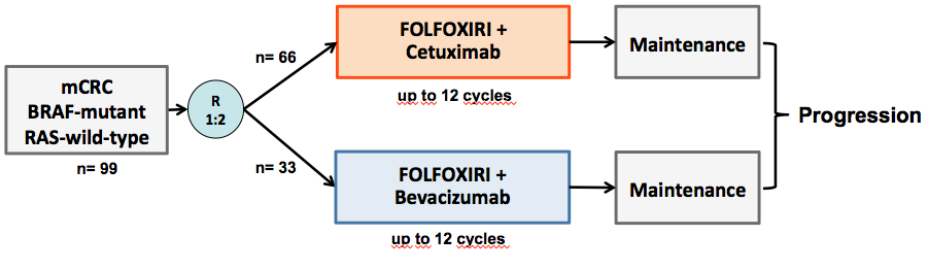
Studiennummer/-Code:	AIO-KRK-0116 - FIRE-4.5	
Status:	Rekrutierung der FIRE-4.5 Studie ist am 18. Dezember beendet worden	
Rekrutierungszeitraum	2016 - 2020	
Zentren:	geplant: 150	initiiert: 150
Patienten:	geplant: 108	aktuell eingeschlossen: 101
Weitere Zentren:	Aktuell keine neuen Zentren benötigt	
Letzte Aktualisierung	Dezember 2020	

Study Type	Randomisierte, multizentrische Phase-II Studie
Verantwortlicher Studienleiter nach AMG	Klinikum der Universität München Marchioninistraße 15, 81377 München Vertreten durch: Prof. Dr. med. Volker Heinemann
Objectives	<u>Primäres Studienziel:</u> Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 under treatment with FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab. <u>Sekundäre Studienziele:</u> • Progression-free survival (PFS) from randomisation • Overall survival (OS) from randomisation • Investigation of early tumour shrinkage (ETS) and depth of response (DpR) • Study of molecular biomarkers for prediction of sensitivity and secondary resistance of an anti-EGFR treatment with cetuximab (including tumour biopsies and liquid biopsies from blood samples) • Investigation of progressive analysis of tumour marker evolution (CEA and CA 19-9) • Recording of the safety and tolerance (NCI-CTCAE version 5.01 criteria) of the treatment
Objectives	- Objective response rate (ORR) - Progression-free Survival (PFS) and Overall Survival (OS) - Safety and Toxicity
Number of patients	Geplant: 99 Patienten Bereits eingeschlossen: 68 (Oktober 2019)

Key inclusion criteria	- Histologically confirmed, UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer, mCRC), primarily non-resectable or surgery refused by the patient
	- RAS wild-type tumour status (KRAS and NRAS exons 2, 3, 4) (proven in the primary tumour or metastasis)
	- BRAF-mutated (V600E) tumour (proven in primary or metastasis)
	  ○ Age ≥18 years
	  ○ ECOG performance status 0-1
	- Patient's written declaration of consent obtained

	- Presence of at least one measurable reference lesion according to the RECIST 1.1 – criteria (chest X-ray in two planes or chest CT and abdominal CT 4 weeks or less before randomisation)
	- Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of the tumour material.
	- Adequate haematopoietic function:
	  o Leukocytes ≥ 3.0 x 10^9/L with neutrophils ≥ 1.5 x 10^9/L
	  o Thrombocytes ≥ 100 x 10^9/L,
	  o Haemoglobin ≥ 5.6 mmol/L (equivalent to 9 g/dL)
	- Adequate hepatic function:
	  o Serum bilirubin ≤ 1.5 x upper limit of normal (ULN),
	  o ALAT and ASAT ≤ 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT ≤ 5 x ULN)
	- INR < 1.5 and aPTT < 1.5 x ULN (patients without anticoagulation). Therapeutic anticoagulation is allowed if INR and aPTT have remained stable within the therapeutic range for at least 2 weeks.
	- Adequate renal function:
	  o Serum creatinine ≤ 1.5 x ULN or creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50ml/min.
	- Adequate cardiac function: ECG and echocardiogram with a LVEF of ≥55%
	- No previous chemotherapy for metastatic disease. One cycle (cycle 0) of either FOLFOX, FOLFIRI, or FOLFOXIRI is allowed prior to randomisation.
	- Time since last administration of any previous adjunctive chemotherapy >6 months
	- Any significant toxicities of previous treatments must have subsided to grade 0

Key exlusion criteria	- Grade III or IV heart failure (NYHA classification) - Myocardial infarction, unstable angina pectoris, balloon angioplasty (PTCA) with or without stenting within the past 12 months before randomisation - Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study - Additional cancer treatment (chemotherapy, radiation, immune therapy or hormone treatment) during the study treatment. Treatments that are conducted as part of an anthroposophic or homeopathic treatment approach, e.g. mistletoe therapy do not represent an exclusion criterion). - Previous chemotherapy for the colorectal cancer with the exception of adjunctive treatment, completed at least 6 months before entering the study. - Participation in a clinical study or experimental drug treatment within 30 days prior to study inclusion or within a period of 5 half-lives of the substances administered in a clinical study or during an experimental drug treatment prior to inclusion in the study, depending on which period is longest or simultaneous participation in another clinical study while taking part in the study - Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, cetuximab, irinotecan, bevacizumab, oxaliplatin, and chemically related substances and/or hypersensitivity to any of the excipients of any of the aforementioned substances - Known hypersensitivity to CHO (Chinese hamster ovary cells) - cellular products or other recombinant human or humanised antibodies - Patients with confirmed cerebral metastases. In case of clinical suspicion of brain metastases, a cranial CT or MRI must be performed to rule out brain metastases before study inclusion. - History of acute or subacute intestinal occlusion or chronic inflammatory bowel disease or chronic diarrhoea. - Symptomatic peritoneal carcinosis - Severe, non-healing wounds, ulcers or bone fractures - Patients with active infection (including confirmed HIV and/or HBV/HCV infection). In case of clinical suspicion of the presence of HIV or HBV/HCV infection, the latter should be ruled out before study inclusion. - Requirement for immunisation with live vaccine during the study treatment.

	- Uncontrolled hypertension - Marked proteinuria (nephrotic syndrome) - Arterial thromboemboli or severe haemorrhage within 6 months prior to randomisation (with the exception of tumour bleeding before tumour resection surgery) - Haemorrhagic diathesis or tendency towards thrombosis - Known DPD deficiency (specific screening not required) - Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required) - History of a second malignoma during the 5 years before inclusion in the study or during participation in the study, with the exception of a basalioma, spinalioma or cervical carcinoma in situ, if these were treated curatively. - Known history of alcohol or drug abuse - A significant concomitant disease which, especially chronic hepatic or renal disease, chronic inflammatory or autoimmune diseases, in the investigating physician's opinion, rules out the patient's participation in the study - Absent or restricted legal capacity
Scheme of therapy	**FOLFOXIRI plus bevacizumab up to 12 cycles** one cycle (cycle duration 14 days) consists of: • Irinotecan 150 mg/m² iv, 30 - 90 min. day 1 • Folinic acid (racemic) 400 mg/m² iv, 120 min. day 1 • Oxaliplatin 85mg/m² day 1 • 5-FU 3000 mg/m² iv over 48 h days 1-2 • Bevacizumab 5 mg/kg BW iv over 30 to 90* min day 1 **FOLFOXIRI plus cetuximab up to 12 cycles** one cycle (cycle duration 14 days) consists of: • Irinotecan 150 mg/m² iv, 30 - 90 min. day 1 • Folinic acid (racemic) 400 mg/m² iv, 120 min. day 1 • Oxaliplatin 85mg/m² day 1 • 5-FU 3000 mg/m² iv over 48 h days 1-2 • Cetuximab initially 400 mg/m² with infusion rate of ≤5 mg/min., subsequently 250 mg/m² iv with infusion rate of ≤10 mg/min.days 1+8 **Study design**  **Primary Objective:** Prospective investigation of the overall response rate (ORR) according to RECIST 1.1 during treatment with FOLFOXIRI plus bevacizumab versus FOLFOXIRI plus cetuximab.
Criteria for evaluation	After treatment week 8, 16, 24 and every 12 treatment weeks thereafter tumor response evaluation according to RECIST 1.1
Rationale	The question of the right treatment for BRAF-mutated colorectal cancer is currently the subject of scientific discussion. No clinical data are available to date for treatment with FOLFOXIRI plus bevacizumab. A retrospective analysis of 10 patients with BRAF-mutated tumours was able to show that it is possible to achieve a response (ORR) in 90% (9 patients), a median PFS of 12.8 months and a median OS of 23.8 months [Masi G et al Lancet Oncol 2010]. A validation

	study based on 15 patients was able to confirm the efficacy in BRAF-mutated patients of FOLFOXIRI plus bevacizumab, which resulted in a tumour response of 60%, a median PFS of 9.1 months and a median OS of 24.1 months [Loupakis F. et al Eur J Cancer 2014]. Furthermore, retrospective data from the TRIBE study are available, which suggest greater efficacy of FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab in 28 patients with BRAF-mutated tumours [Cremolini C et al Lancet Oncol 2015]. In this case, it was possible to demonstrate response rates of 56% versus 42%, median PFS times of 7.5 months versus 5.5 months and median OS times of 19.0 months versus 10.7 months, repectively [Cremolini C et al Lancet Oncol 2015]. However, none of the differences reached the significance level, owing to the small number of cases. Given the study design, it is not possible to make any statement concerning the additional benefit of bevacizumab in combination with FOLFOXIRI. A pooled retrospective assessment of the TRIP and MCBETH studies is available for colorectal tumour patients treated with FOLFOXIRI plus anti-EGFR antibodies [Salvatore L et al Annaös of Oncology (2014) 25 (suppl_4)]. Only RAS/BRAF wild-type patients were assessed in this case. The response rates were around 82% versus 71 in comparison of anti-EGFR plus FOLFOXIRI with FOLFOXIRI plus Bevacizumab. PFS and OS data were not presented.
Statistik	This is a randomised, phase II trial, intended to study the efficacy of the two regimens - FOLFOXIRI plus cetuximab or FOLFOXIRI plus bevacizumab - as part of first-line treatment with reference to the endpoint of tumor response (ORR according to RECIST 1.1) in patients suffering from BRAF-mutant colorectal cancer. The efficacy of FOLFOXIRI plus cetuximab will be assessed as promising if: • The null hypothesis (ORR in the FOLFOXIRI plus cetuximab arm ≤ 55%) can be rejected at a significance level of 0.1 and • Response (ORR) in the FOLFOXIRI plus cetuximab arm is greater than in the FOLFOXIRI plus bevacizumab arm. Hence, the hypotheses to be tested are: • H0: ORR (arm B) ≤ 55% • H1: ORR (arm B) ≥70% Since an ORR of ≥70% is expected in the FOLFOXIRI plus cetuximab arm, 53 patients are required in the FOLFOXIRI plus cetuximab arm in order to reject the null hypothesis with a power of 80% at a significance level of 0.1 (two-stage design according to Fleming with 20 patients in the first stage and 53 patients in the second stage). The null hypothesis would be rejected if at least 17 out of the first 20 patients (85%) or at least 33 patients (62.5%) in the second stage (total evaluable n=53) show a tumour response according to RECIST 1.1 (partial (PR) or complete response (CR)) and, at the same time, response (ORR) in the FOLFOXIRI plus cetuximab arm is numerically greater than in the FOLFOXIRI plus bevacizumab arm. If less than 12 patients of the first 20 patients show tumor response according to RECIST 1.1 the study would be terminated due to “futility”. 27 further patients are used as a control arm with the standard recommended therapy of FOLFOXIRI and bevacizumab according to Loupakis et al. (TRIBE study) to investigate efficacy and safety of both study arms.