AIO KRK-0118: Avelumab added to FOLFIRI plus Cetuximab followed by Avelumab maintenance in patients with previously untreated RAS wild-type colorectal cancer. The phase II FIRE-6-Avelumab study

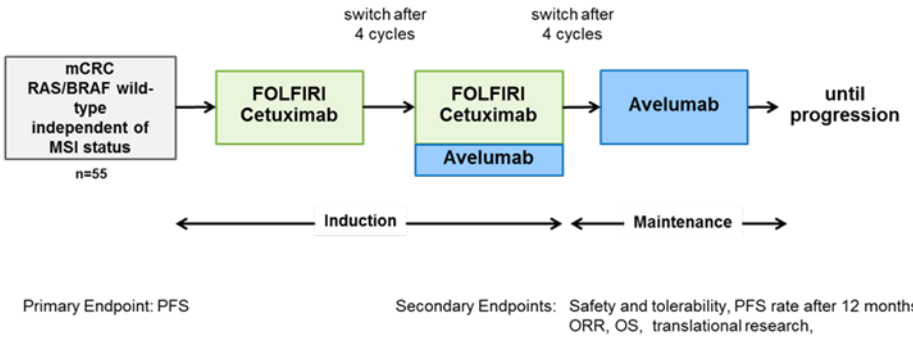
AIO-Studie

Studiennummer/-Code:	AIO-KRK-0118 - FIRE-6	
Status:	Studie fertig rekrutiert und geschlossen	
Rekrutierungszeitraum	2019 - 2020	
Zentren:	geplant: 15	initiiert: 15
Patienten:	geplant: 55	aktuell eingeschlossen: 57
Weitere Zentren:	sind derzeit nicht möglich	
Letzte Aktualisierung	Juni 2021	

Study Type	Einarmige, multizentrische Phase-II Studie
Verantwortlicher Studienleiter nach AMG	Klinikum der Universität München Marchioninistraße 15, 81377 München Vertreten durch: Prof. Dr. med. Sebastian Stintzing
Objectives	<u>Primäres Studienziel:</u> Progression Free Survival (PFS) according to RECIST v1.1 <u>Sekundäre Studienziele:</u> • Safety and tolerability (acc. to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters (oxygen saturation) and feasibility of the regimen) • Progression-free survival (PFS) according to immune-modified RECIST (imRECIST) • Response Rate (RR) according to RECIST v1.1 and (imRECIST) • Progression Free Survival Rate after 12 months of treatment (PFSR@12) (acc. to RECIST v1.1) • Overall survival (OS) • Translational research (PD-L1, PD-1 expression, TIL´s within the tumor specimen, neutrophil/leukocyte ratio and use of antibiotics as predictive marker for avelumab)
Objectives	- Progression-free Survival (PFS) - Objective response rate (ORR) and Overall Survival (OS) - Safety and Toxicity
Key inclusion criteria	- Histologically confirmed, UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer), metastases primarily non-resectable or surgery refused by the patient - RAS wild-type tumour status (KRAS and NRAS exon 2, 3, 4) (proven in the primary tumour or metastasis) - Age ≥18 - ECOG performance status 0-1 - Patients suitable for chemotherapy administration - Patient's written declaration of consent obtained - Estimated life expectancy > 3 months - Presence of at least one measurable reference lesion according to the RECIST 1.1 criteria

	- Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of tumour material. Molecular profiling of blood samples is optionally performed. - Females of childbearing potential (FCBPs) and men must agree to use highly effective contraceptive measures (Pearl index <1) or practice true abstinence from any heterosexual intercourse (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject) for the duration of the study treatment and for at least 6 months after the last administration of study medication. A woman will be considered as being of childbearing potential unless she is at least 50 years old and moreover has gone through menopause for at least 2 years or has been surgically sterilised. - Adequate bone marrow function: - Leukocytes ≥ 3.0 x 109/L with neutrophils ≥ 1.5 x 109/L - Thrombocytes ≥ 100 x 109/L - Haemoglobin ≥ 5.6 mmol/L (equivalent to 9 g/dL) - Adequate hepatic function: - Serum bilirubin ≤ 1.5 x upper limit of normal (ULN) - 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: - Creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50 mL/min - Adequate cardiac function: ECG and echocardiogram with a LVEF of ≥ 55% - No previous chemotherapy for metastatic disease. Patient with need of immediate treatment (high tumour load, symptoms) may have received one application of FOLFIRI prior to study entry. - Time interval since last administration of any previous neoadjuvant/adjuvant chemotherapy or radiochemotherapy of the primary tumour in curative treatment intention ≥ 6 months. - Any relevant toxicities of prior treatments must have resolved - Patient affiliated to a public health insurance coverage
Key exlusion criteria	- Proof of a RAS mutation (KRAS or NRAS, exons 2, 3, 4 in the tumor (proven in the primary tumor or metastasis) or absence of testing for RAS mutation - Primarily resectable metastases and the patient wishes for resection - ≥ Grade II heart failure (NYHA classification) - Myocardial infarction, balloon angioplasty (PTCA) with or without stenting, and cerebral vascular accident/stroke within the past 12 months before start of study treatment, unstable angina pectoris, serious cardiac arrhythmia according to investigator's judgement requiring medication. - Pre-existing pulmonary fibrosis or immune pneumonitis - Active autoimmune disease that might be negatively affected by an immune checkpoint inhibitor. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible. - Prior organ transplantation, including allogeneic stem cell transplantation - Current use of immunosuppressive medication, except for the following: - Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); - Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication). - Pregnancy (absence of pregnancy to be ascertained by a negative beta hCG test) or breast feeding - Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study

	- Additional cancer treatment (chemotherapy, radiation, immunotherapy or hormone treatment) during the study treatment in first-line (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 adjuvant treatment, completed at least 6 months before entering the study - Toxicity > Grade 1 that has not yet resolved, attributed to a previous treatment or measure for treatment of the CRC. However, alopecia (all grades) and oxaliplatin-induced neurotoxicity ≤ Grade 2 are acceptable. - 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 study while taking part in the study - Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, capecitabine, cetuximab, irinotecan, avelumab and chemically related substances and/or hypersensitivity to any of the components in the formulations of the aforementioned substances, including known hypersensitivity reactions to monoclonal antibodies NCI CTCAE Grade ≥ 3. - Known hypersensitivity to Chinese hamster ovary cell (CHO) – cellular products or other recombinant human or humanised monoclonal antibodies - Patients with known brain metastases. In case of clinical suspicion of brain metastasis a cranial CT or MRI must be performed to rule out brain metastasis before study inclusion. - History of acute or subacute intestinal occlusion, inflammatory bowel disease, immune colitis or chronic diarrhoea - Symptomatic peritoneal carcinosis - Severe, non-healing wounds, ulcers or bone fractures - Patients with active infection requiring systemic therapy - Known history of testing positive for HIV or known acquired immunodeficiency syndrome. - Active or chronic Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive; serologic tests required). - Requirement for immunisation with live vaccine under the study treatment. - Haemorrhagic diathesis or known thrombophilia - Known DPD deficiency (specific screening not required) - Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required) - History of a second primary malignancy during the past 5 years before inclusion in the study or during participation in the study, with the exception of a basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ, if these were treated curatively. - Known history of alcohol or drug abuse - Any other severe acute or chronic concomitant disease or medical condition including psychiatric conditions (including recent i.e. within the past year or active suicidal ideation or behavior) or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. - Absent or restricted legal capacity
Scheme of therapy	All eligible patients will receive cetuximab and FOLFIRI until the first follow up examination for the first 4 cycles (2 months). Patients with a cycle 0 of FOLFIRI will also receive 4 cycles of FOLFIRI plus cetuximab within the study. Patients that have not progressed will receive FOLFIRI and cetuximab in combination with avelumab from the fifth cycle onwards for a total of 4 cycles until the second

	follow up examination. Having not progressed for a total of 8 cycles, patients will then switch to avelumab single agent maintenance until progression of the disease. Study treatment will therefore be discontinued if one of the following events occur: • Progressive disease (according to RECIST 1.1) • Intolerable toxicity • Withdrawal of consent **Initial regimen (4 cycles):** **FOLFIRI plus cetuximab (administration to local standard)** One cycle (cycle duration 14 days) consists of: Irinotecan 180 mg/m² iv — day 1 Folinic acid (racemic) 400 mg/m² iv — day 1 5-FU 400 mg/m² bolus — day 1 5-FU 2400 mg/m² iv over 46h — day 1-2 Cetuximab initially 400 mg/m²; subsequently 250 mg/m² iv — day 1 + 8 **Switch after 4 cycles:** **FOLFIRI Cetuximab (administration to local standard) plus Avelumab (for 4 cycles)** One cycle (cycle duration 14 days) consists of: Irinotecan 180 mg/m² iv — day 1 Folinic acid (racemic) 400 mg/m² iv — day 1 5-FU 400 mg/m² bolus — day 1 5-FU 2400 mg/m² iv over 46h — day 1-2 Cetuximab 250 mg/m² iv — day 1 + 8 Avelumab at a dose of 10mg/kg IV — day 1 **Maintenance (starting at cycle 9) until progression:** Avelumab at a dose of 10mg/kg IV day 1 (repeat every 14 days) Study design **FIRE-6 Avelumab Study** **Phase-II Design** 
Criteria for evaluation	During treatment tumor response will be assessed by the investigator according to RECIST v1.1 (MRI (or CT scan if MRI is unavailable) of the chest, abdomen, pelvis and all other sites of disease) every 4 cycles (8 weeks ±7

	days) CT and/or MRI scans will be independently reviewed. The results ot the central review will not have an impact on the study treatment.
Rationale	Inhibition of the PD-1/L1 axis has shown to improve survival as single agent in a variety of tumor types (e.g. melanoma and lung cancer) (Robert, Long et al. 2014, Borghaei, Paz-Ares et al. 2015). The efficacy of single agent PD-1/L1 inhibition in patients with highly advanced and treatment refractory MCRC seems to be limited to those with hypermutated tumors characterized by mismatch repair deficiency (Le, Uram et al. 2015). After 4-6 months of doublet chemotherapy a de-escalation to a less toxic regimen is needed for most of the patient with mCRC. The addition of Avelumab to a cytotoxic chemotherapy regimen with FOLFIRI plus cetuximab followed by Avelumab maintenance has not been investigated so far. It is known that FOLFIRI plus cetuximab leads to necrosis and therefore tumor antigens that usually are not presented to the host immune system become recognizable. This effect of a triggered immune response after induction treatment with chemotherapy is currently investigated in other trials. The ongoing IMPALA trial (Cunningham, Zurlo et al. 2015) is testing the toll-like receptor (TLR)-9 agonist MGN1703 as maintenance treatment in patients that have responded to an induction doublet chemotherapy. This effect may be enhanced by the fact that Cetuximab in Combination with 5-FU and Irinotecan triggers immunogenic cell death (Pozzi, Cuomo et al. 2016). The lately published data from the interim analysis of the PACIFIC trial using the anti-PD L1 antibody durvalumab after chemoradiation in stage II non-small cell lung cancer (NSCLC) proofed the concept of an anti-PD L1 antibody as a maintenance treatment after chemoradiation. Durvalumab prolonged PFS significantly (HR 0.52, $p<0.001$) (Antonia, Villegas et al. 2017). The study is not limited to MSI-h and should be able to demonstrate Avelumab efficacy in MSS tumors when used in combination with cetuximab plus FOLFIRI. The lately presented data on the use of atezolizumab plus cobimetinib (NCT01988896, IMblaze370) (Bendell, Bang et al. 2018) in in heavily pretreated MSS mCRC patients showed a 12-month OS rate of 43% which was higher than the 24% seen for Regorafenib in the pivotal CORRECT trial. But its primary endpoint, a benefit in median OS, was not met (Bendell, Ciardiello et al. 2018). As the IMblaze370 trial was conducted in heavily pretreated patients without the combination of chemotherapy, it is worthwhile to test this concept in MSS and MSI-h mCRC. Furthermore part of the cetuximab as of the avelumab effect can be attributed to ADCC (antibody derived cellular cyctotoxicity) with again leads to necrosis of tumor cells and the release of antigens. Both effects together may be able to present enough tumor-neo-antigens. To boost the effect, Avelumab is able to inhibit the PD-1 derived inhibition of cytolysis and other tumor cells within the body may be attacked by the immune system which leads to an anti-tumor effect represented by a prolonged PFS and finally OS of the patients. Patients will be included independent of microsatellite instability (MSI) status. It is expected that within the trial population the MSI rate will be as reported in stage IV MCRC with about 5% (Venderbosch, Nagtegaal et al. 2014).
Statistik	It is intended to study the progression-free survival within the context of the first-line treatment and maintenance trial. The goal of this phase-II study is to detect non-sufficient treatment timely. With regard to FOLFIRI plus cetuximab a median PFS of 10 months has been reported before (FIRE-3 study) Thereby a median PFS of at most 8 months will be rated as non-sufficient, in contrast a median PFS of 12.88 months as sufficient..

	Hence the hypotheses to be tested are: H0: median PFS ≤ 8 months H1: median PFS ≥ 12.88 months PFS = period between start of treatment and progression or death. According to this hypothesis formulation, the tests of the objective (PFS) will be performed in line with a one-sided logrank test. Since a median PFS of ≥12.88 months is expected, 47 patients are required in order to reject the null hypothesis with a power of 80% at a one-tailed significance level of 0.025 (one sample testing using log-rank test) if an accrual period of 18 months and a minimum follow-up of 18 months is assumed. Due to possible drop-outs, a total of 55 patients (15% drop-out rate) are going to be included into this trial.