Coordinating Investigator	Priv. Doz. Dr. med Alexander Stein Hämatologisch-Onkologische Praxis Eppendorf Eppendorfer Landstrasse 42/Orchideenstieg 12; 20249/22297 Hamburg Tel: +49 (0) 40 36035220, Fax: +49 (0) 40 473547 stein@hope-hamburg.de
Sponsor:	AIO-Studien-gGmbH, Dr. Mischo Kursar Kuno-Fischer-Straße 8, 14057 Berlin Phone: +49 30 8145 344 67, Fax +49 30 3229 329 26 info@aio-studien-ggmbh.de
Study design	Single-arm, open label, multicentre, phase II trial
Duration of study	Duration of recruitment: 24 months at a rate of 2 patients/month (counted from first patient in). Treatment for 8 weeks neoadjuvant and additional 16 weeks postoperatively in patients with tumor regression grade of 2-4. Follow-up for survival until trial termination 2 years after last patient in. Expected total trial duration 4.5 years.
Indication	Patients with unresected BRAF mutated/pMMR localized colorectal cancer (CRC)
Target population	Radiologically (CT) staged disease as: T3-4 and/or nodal positive (N+), M0. BRAF V600E mutation and pMMR or MSS (determined by either IHC or PCR) ECOG Performance status ≤ 1 Life expectancy > 3 months
Total number of sites	16 sites in Germany and 4 sites in Austria planned
Number of patients	48 patients planned
Primary objective	The targeted triplet combination of encorafenib, binimetinib and cetuximab should improve clinically relevant tumor regression (TRG2-4) compared to the rate achieved with neoadjuvant fluoropyrimidines and oxaliplatin in the FOxTROT trial.
Secondary objective	The triplet combination of encorafenib, binimetinib and cetuximab should be feasible in the neoadjuvant treatment of localized CRC and should have a positive impact on DFS compared to previous data on neoadjuvant chemotherapy with fluoropyrimidines and oxaliplatin. Translational data will inform about molecular mechanisms of response/resistance to triplet combination and the potential utility of liquid biopsy monitoring during treatment.
Primary endpoint	• Tumor regression grade (TRG)
Secondary endpoints	• Safety and tolerability (according to NCI CTC AE v5) incl. vital signs, clinical parameters and overall feasibility of the regimen • Perioperative morbidity and mortality • R0-resection rate • Overall response rate (according to RECIST v1.1) • Disease free survival (according to RECIST v1.1) • Overall survival • Correlation of quantitative BRAF V600E levels (measured by ddPCR) with TRG • Evaluation of mechanism of relative resistance in patients with less response (evaluated by tumor and liquid biopsy NGS profiling at baseline and after treatment)

	• Comparison of ctDNA clearance and TRG with a BRAF mutant/pMMR cohort from the planned neoadjuvant PROTECTOR study receiving neoadjuvant chemotherapy
Translational Research	The following translational research is currently planned, but may be adapted taking into account new research data. • the role of monitoring BRAF V600E in the blood during treatment by ddPCR, • the correlation between BRAF levels in the blood and tumor regression grade • the possibility to evaluate mechanisms of resistance in patients with poor/less tumor regression grade
Inclusion criteria	1. Biopsy-confirmed adenocarcinoma of the colon or upper rectum if too high for radiotherapy. 2. Radiologically (CT) staged disease as: T3-4 and/or nodal positive (N+), M0. 3. BRAF V600E mutation and pMMR or MSS (determined by either IHC or PCR). 4. ECOG Performance status ≤ 1. 5. Life expectancy > 3 months. 6. Age ≥ 18 years. 7. Haematologic function as follows: ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x10^9/L. 8. Adequate liver function as measured by serum transaminases (AST & ALT) ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN. Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled. 9. Adequate renal function: serum creatinine ≤ 1.5 x ULN. 10. Negative serum pregnancy test at screening for women of childbearing potential. 11. Highly effective contraception for both male and female subjects if the risk of conception exists. (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required at least 21 days prior, throughout and for at least 30 days after study treatment and 6 months after standard chemotherapy. 12. Signed and dated written informed consent. 13. Ability to take oral medication. 14. Ability to comply with the protocol for the duration of the study, including hospital/office visits for treatment and scheduled follow-up visits and examinations.
Exclusion criteria	1. Any prior systemic therapy, surgery or radiotherapy of the colorectal cancer disease. 2. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes). 3. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent). 4. Known severe hypersensitivity reactions to monoclonal antibodies or BRAF-/MEK-inhibitors (grade ≥ 3 NCI-CTCAE v 5), any history of

	anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma). 5. Pregnancy or lactation. 6. Known alcohol or drug abuse. 7. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (≤ 6 months prior to enrolment); myocardial infarction (≤ 6 months prior to enrolment), acute coronary syndromes [including unstable angina, coronary artery bypass graft (CABG), coronary angioplasty or stenting) ≤ 6 months prior to enrolment]; congestive heart failure (≥ New York Heart Association Classification Class II); or history or current evidence of clinically significant arrhythmia and/or conduction abnormality (≤ 6 months prior to enrolment), except rate controlled atrial fibrillation and paroxysmal supraventricular tachycardia. 8. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy. 9. Impaired GI function or disease that may significantly alter the absorption of encorafenib or binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption). 10. History of thromboembolic or cerebrovascular events ≤ 6 months prior to enrolment, including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli. 11. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy). 12. Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. 13. All other significant diseases, which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment. 14. Any psychiatric condition that would prohibit the understanding or rendering of informed consent. 15. Any approved anticancer therapy, including chemotherapy, hormonal therapy or radiotherapy, within 5 half-lives or 4 weeks (the longer period applies) prior to initiation of study treatment. 16. Current treatment with a non-topical medication or current intake of herbal preparations / supplements / foods known to be a strong inhibitor of CYP3A4. However, patients who either discontinue such treatment/intake or switch to another medication at least 7 days prior to starting study treatment are eligible. 17. Concomitant use of St. John's Wort (hypericum perforatum).
Scheme of therapy	All eligible patients will receive encorafenib, binimetinib and cetuximab at the following dosage. **Encorafenib** tablets, dose of 300 mg qd **Binimetinib** tablets, dose of 45 mg bid **Cetuximab** infusion, weekly dose of 250 mg/m^2 (1st dose 400mg/m^2) Duration of treatment: Treatment will be administered for 8 weeks preoperatively and 16 weeks postoperatively in responding patients (TRG 2-4). In non-responding patients (TRG 0-1) standard chemotherapy with fluoropyrimidines and oxaliplatin (e.g. CAPOX) may be applied postoperatively outside the trial at Investigators discretion.

Rationale / Hypothesis	BRAF mutations confers a dismal prognosis in colorectal cancer (CRC) patients, in localized and particular metastatic disease. In localized CRC (stage II and III) the overlap with dMMR/MSI-H tumors (about 30%) results in a similar disease-free survival (DFS), but a worse survival after recurrence, compared to BRAF wildtype. Notably, the BRAF mutant and pMMR/MSS cohort (about 65%) is the subgroup with the worst DFS, even if treated with intensive adjuvant treatment like FOLFOX with or without cetuximab (Sinicrope, Shi et al. 2015, Taieb, Zaanan et al. 2016). In second and third line metastatic CRC (mCRC) as investigated in the BEACON phase III study, the triplet combination of encorafenib, binimetinib and cetuximab demonstrated superior efficacy in terms of response and survival compared to irinotecan-based chemotherapy and cetuximab (confirmed ORR 26% vs. 2%, p<0.001; OS median 9.0 vs. 5.4 months, HR 0.52, p<0.001) and a trend towards higher efficacy compared to the doublet combination (ORR 26% vs. 20%; OS median 9.0 vs. 8.4 months, HR 0.79, 95% CI 0.59-1.06); however, the study was not powered to compare triplet vs. doublet (Kopetz, Grothey et al. 2019). Despite the similar OS, based on the numerically better ORR of 26% with the triplet (27% updated) vs. 20% with the doublet, the triplet should be evaluated in this curative setting requiring maximum response (Tabernero, Grothey et al. 2021). Furthermore, in the curative and particular neoadjuvant setting response may have a closer correlation to survival compared to the metastatic setting. In a single arm study with 93 evaluable patients in the first line setting (ANCHOR trial) an confirmed ORR of 48% with 88% of patients showing some tumor regression or stability was noted with the triplet regimen (Van Cutsem, Taieb et al. 2021). These data clearly show the high efficacy of the triplet regimen with increasing response induction in earlier disease settings. In addition, the triplet showed a manageable safety profile with comparable incidence of higher grade (3/4) adverse events compared to control arm with chemotherapy (65.8 vs. 64.2) in the metastatic setting (Tabernero, Grothey et al. 2021). Discontinuation of all therapy primarily due to an adverse event was seen in 9% of patients in the triplet arm and 11% in the chemotherapy arm. Deaths resulting from AEs occurred in 5%, and 4% of patients treated with the triplet and control, respectively. Investigators deemed three of the deaths to be at least possibly related to treatment: one death was from colonic perforation (triplet), one was from anaphylaxis (control), and one was from respiratory failure (control). Based on these results in the metastatic setting, the safety profile of triplet combination of encorafenib, binimetinib and cetuximab is considered to be adequate, justifying its use in the early treatment setting. Thus, the evaluation of the treatment known to have the highest efficacy in terms of tumor response and a manageable safety profile as evaluated in the metastatic setting in this prognostically dismal patient subgroup of BRAF mutant (pMMR/MSS) patients is warranted. The duration of neoadjuvant treatment of 8 weeks was chosen to align with other ongoing neoadjuvant trials with 8-12 weeks of treatment (AIO Protector trial, AIO-KRK-0620) and to allow for the development of relevant response, which were noted in the metastatic trials only after at least 6 weeks of treatment (Pierre Fabre Pharma GmbH. 2020). Recently presented results of the FOxTROT trial paved the way for neoadjuvant treatment by showing a beneficial impact for 6 weeks of neoadjuvant (and adjuvant) chemotherapy with 5FU and oxaliplatin compared to adjuvant chemotherapy alone in terms of recurrence rate at 2 years (HR 0.75, p=0.08) (Seymour et al ASCO 2019). In the FOxTROT trial, patient with neoadjuvant showed significantly improved tumor regression grade (TRG). Notably, TRG was clearly associated with cumulative recurrence rate.

	Based, on the above mentioned very poor prognosis, the efficacy of the triplet combination in mCRC and the positive trend for neoadjuvant start of chemotherapy in stage III, the evaluation of the triplet as neoadjuvant treatment in BRAF mutant and pMMR/MSS patients is proposed, aiming to further improve tumor regression with a targeted and chemo-free treatment compared to chemotherapy. The clinical data for BRAF mutant/pMMR stage III patients obtained from the FOxTROT trial, the AIO Colopredict registry and a parallel BRAFmutant/pMMR cohort within the planned neoadjuvant AIO FOxTROT trial receiving neoadjuvant chemotherapy and liquid biopsy monitoring and central pathological evaluation will inform about the comparative efficacy of this approach. After surgery tumor regression grade will inform about further treatment, in case of TRG2-4 (indicating response to neoadjuvant treatment, referring to figure 1) the triplet will be continued postoperatively for further 16 weeks for overall 24 weeks/6 months of molecular targeted treatment. In case of insufficient response to neoadjuvant triplet (TRG0-1) chemotherapy with oxaliplatin should be applied, in general 3 (6) months CAPOX (duration: investigator decision). Based on the above-mentioned background, neoadjuvant treatment with the triplet combination of encorafenib, binimetinib and cetuximab is aimed at improving clinically relevant tumor regression (TRG 2-4) compared to the rate achieved with neoadjuvant fluoropyrimidines and oxaliplatin in the FOxTROT trial. Rational: The triplet combination has a more than 10 times higher efficacy in terms of RECIST response in the metastatic setting and at least in the metastatic setting response to standard chemotherapy in BRAF mutants is very limited. TRG has demonstrated a close correlation to relapse rate in the FOxTROT trial (figure 3) and thus serves as a validated and early assessable endpoint. The choice of dosing of encorafenib, binimetinib and cetuximab is based on the above-mentioned phase III BEACON trial with a change to the cetuximab schedule (Kopetz, Grothey et al. 2019). In the pivotal licensing trials cetuximab was applied in a weekly schedule with 250mg/m^2 after an initial loading dose of 400mg/m^2. Based on the relative impractical close meshed schedule, later pharmacokinetic and -dynamic trials evaluated a biweekly schedule with 500mg/m^2 to improve feasibility of the regimen and limit outpatient visits, which is of particular value taking into account public emergencies as pandemics (Tabernero, Cervantes et al. 2010, Tabernero, Ciardiello et al. 2010). The biweekly schedule of cetuximab is a widely adopted standard of care. Thus, for NeoBRAF a biweekly cetuximab schedule in combination with the established encorafenib (1x300mg) and binimetinb (2x45mg) dose was chosen.
Sample size estimation and statistical analysis considerations	With neoadjuvant chemotherapy a tumor regression grade (TRG) of at least 2 (moderate regression or more) was achieved in 20% of pMMR/MSS patients treated with chemotherapy (Seymour and Morton 2019). The triplet combination of encorafenib, binimetinib and cetuximab should achieve a TRG of at least 2 in 35% of patients. Thus, by applying a phase II single stage design according to A'Hern with a one-sided test, an alpha of 0.1 and a beta of 0.2 (power 80%) 44 evaluable patients need to be included, with a 10% drop out rate 48 patients should be included (Stat. Med. 2001, 20:859-866).