**AIO-KRK-0212: Randomized phase II study for evaluation of efficacy and safety of maintenance treatment with 5-FU/FA plus panitumumab vs. 5-FU/FA alone after prior induction treatment with mFOLFOX6 plus panitumumab and re-induction with mFOLFOX6 plus panitumumab in case of progression for first-line treatment of patients with metastatic colorectal cancer (PanaMa)**

**AIO-Studie**

| | |
|---|---|
| Studiennummer/-Code: | AIO-KRK-0212 - PanaMa |
| Status: | Rekrutierung abgeschlossen am 01.02.2021 |
| Rekrutierungszeitraum | 2014 –2021 |
| Zentren: | initiiert: 98 |
| Patienten: | geplant: 387 eingeschlossen, 266 rand. |
| Weitere Zentren: | Leider nicht mehr möglich |
| Letzte Aktualisierung | Oktober 2021 |

| | | |
|---|---|---|
| Study design | Phase II, randomized, multi-center, open-label, parallel-group | |
| National Coordinating investigator | Prof. Dr. med. Dominik Paul Modest | |
| Sponsor | AIO-Studien-gGmbH, Kuno-Fischer-Straße 8, 14057 Berlin<br>Phone: +49 30 814534435; Fax: +49 30 322932926 | |
| Translational research committee | Prof. Dr. Stefan Kasper, Prof. Dr. Dominik Modest, Prof. Dr. Sebastian Stintzing, Dr. Tanja Trarbach. | |
| Quality of life committee | Dr. T. Trarbach | |
| Status: | • LPI 01-Feb-2021 / Recruitment completed<br>• 98 Study Sites initiated<br>• 387 Patients enrolled<br>• 266 Patients randomized / 218 events documented | |
| Duration of study | Duration of accrual | 84 months |
| | Final Analysis of primary study endpoint with 218 events: | 88 months after start of enrollment |
| | End of FU (observation period of at least 24 months after randomization for each patient): | 108 months after start of enrollment |
| | End of study: | 24 months after last randomization |
| Total number of centers | Approx. 95 | |
| Study population | Patients with metastatic colorectal cancer (wild-type RAS) in palliative first-line therapy | |

| | |
|---|---|
| Primary objective | To assess the efficacy of panitumumab plus 5-FU/ FA as maintenance after an induction treatment of 12 weeks with mFOLFOX6 plus panitumumab in the first-line treatment of RAS wild-type metastatic colorectal cancer patients compared to 5-FU/ FA maintenance alone in terms of progression-free survival. |
| Secondary objectives | To compare maintenance arms with respect to:<br>• Time from randomization until failure of treatment strategy (death/ progression)<br>• Progression-free survival of re-induction<br>• Objective response after 12 weeks of induction chemotherapy<br>• Objective best response during maintenance and re-induction<br>• Overall survival measured from time of randomization and from time of registration<br>• Safety<br>• Health and skin related Quality of life |
| Exploratory objectives | • Translational research parameters as defined in the respective section<br>• Central review of CT/MRI scans<br>• Depth of response (during induction and maintenance therapy) |
| Planned sample size | Approx. 400 patients will be enrolled to reach the planned number of 272 randomizations. |
| Inclusion criteria | • Signed written informed consent<br>• Male or female ≥ 18 years of age<br>• Histologically proven metastatic colorectal cancer<br>• Molecular testing showing RAS wild-type in colorectal carcinoma cells<br>• Life expectancy > 12 weeks<br>• At least one measurable lesion according to RECIST 1.1<br>• Adequate bone marrow, liver, kidney, organ and metabolic function<br>o Bone marrow function<br>o leukocyte count > 3.0 × 109/L<br>o ANC > 1.5 x 109/L<br>o platelet count ≥ 100 × 109/L<br>o hemoglobin ≥ 9 g/dL or 5.59 mmol/L (may be transfused or treated with erythropoietin to maintain/ exceed this level)<br>o Hepatic function<br>o Total bilirubin ≤ 1.5 × UNL<br>o ALT and AST ≤ 2.5 × UNL (or ≤ 5 × UNL in presence of liver metastases)<br>o AP ≤ 5 × UNL<br>o Renal function<br>o Creatinine clearance ≥ 50 mL/ according to Cockroft-Gault formula or serum creatinine ≤ 1.5 × UNL<br>o Metabolic function<br>o Magnesium ≥ lower limit of normal<br>o Calcium ≥ lower limit of normal<br>• ECOG performance status 0 - 1<br>• Women of child-bearing potential must have a negative pregnancy test |
| Exclusion criteria | • Previous treatment for colorectal cancer in the metastatic setting with the exception that patients with urgent need of immediate treatment (high tumor load, symptoms) may have received one cycle of any FOLFOX regimen (no capecitabine!) in case of yet unconfirmed RAS status.<br>• Previous EGFR-targeting therapy<br>• < 6 months after end of adjuvant therapy (previous chemoradiation for rectal cancer is accepted for inclusion into the trial and does not account as adjuvant therapy) |

| | |
|---|---|
| | • Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids<br>• Chronic inflammatory bowel disease<br>• Peripheral neuropathy ≥ NCI-CTCAE V 4.03 grade 2<br>• Other previous malignancies with the exception of a history of previous curatively treated basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix or other curatively treated malignant disease without recurrence after at least 5 years of follow-up<br>• Significant disease that, in the investigator's opinion, would exclude the patient from the study<br>• History of cardiac disease; defined as:<br>o Congestive heart failure > New York Heart Association (NYHA) class 2<br>o Active coronary artery disease (myocardial infarction more than 6 months prior to start of study treatment is allowed)<br>o Cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)<br>o Uncontrolled hypertension (defined as blood pressure > 160 mmHg systolic and/or > 90 mmHg diastolic on medication)<br>• Patients with interstitial lung disease, e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan<br>• Known HIV, hepatitis B or C infection<br>• Known hypersensitivity reaction to any of the study components<br>• Radiotherapy, major surgery or any investigational drug 21 days before registration<br>• Pregnancy or lactation or planning to be pregnant during treatment and within 6 months after the end of treatment<br>• Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for at least an additional 6 months after the end of treatment<br>• Known alcohol or drug abuse<br>• Any condition that is unstable or could jeopardize the safety of the patient and his compliance in the study |
| Treatment scheme | <u>Induction chemotherapy</u><br>6 cycles mFOLFOX6 plus panitumumab for 12 weeks<br>Panitumumab 6mg/kg BW<br>mFOLFOX6:<br>85 mg/m² Oxaliplatin 2h d1<br>400 mg/m² folinic acid 2h d1<br>2400mg/m² 5-FU over 46 h d1 -2<br>Q2w<br><br><u>Maintenance</u><br>Patient with CR, PR and SD after 12 weeks of induction treatment, will be randomized in a 1:1 ratio to receive either 5-FU/FA + panitumumab q2w (arm A) or 5-FU/FA alone q2w (arm B) until tumor progression.<br>Patient with curative resection within 12 weeks of induction therapy do not qualify for randomization.<br><br><u>Re-induction:</u><br>After tumor progression, a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression<br><br><u>Concomitant therapy:</u><br>Prophylactic management program for panitumumab-related acute and late skin toxicities (see section 6.5.2, 6.5.3) |

| | |
|---|---|
| Primary parameter | Progression-free survival during maintenance therapy defined as time from randomization until disease progression or death, whatever occurs first. |
| Secondary parameters | • Time from randomization until failure (death/ progression) of treatment strategy<br>• Progression-free survival of re-induction<br>• Objective response after 12 weeks of induction chemotherapy<br>• Objective best response during maintenance and re-induction<br>• Overall survival measured from time of randomization and from time of registration<br>• Safety<br>• Health and skin related Quality of life |
| Exploratory parameters | Translational research analysis in tumor tissue, circulation tumor cells, circulating tumor DNA and blood cells. These investigations will include DNA, RNA, immunohistochemistry, FISH, Sequencing from tumor/or blood cells as well as evaluations of laboratory markers (tumor markers).<br><br>Central review of CT/MRI scans for resectability, volumetry and further related parameters (i.e. depth of response etc.) |
| Study procedures | After the initial screening procedure, eligible patients will be registered for study participation.<br><br>The patient receives chemotherapy consisting of 6 cycles mFOLFOX6 plus panitumumab every 2 weeks. Patients showing CR, PR or SD after induction therapy and qualifying for subsequent maintenance treatment and re-induction treatment with all potential drug components, will be randomized to receive a maintenance regimen of 5-FU/FA + panitumumab or 5-FU/FA alone until tumor progression.<br><br>After tumor progression a reinduction with mFOLFOX6 plus panitumumab will be started and patients will receive this regimen until tumor progression.<br><br>Tumor assessments will be performed 12 weeks after treatment start with induction therapy and every 8 weeks during maintenance therapy and re-induction.<br><br>All patients will have an end of treatment visit 4 weeks (+ 7 days) after the last dose of the study agent. Thereafter, all patients will be followed up for survival every 3 months. |
| Randomization procedure | Permuted block randomization will be applied to guarantee balanced group numbers throughout enrollment period. To increase homogeneity between treatment arms, randomization will be stratified by<br>1. Response to induction therapy at time of randomization (CR/PR vs. SD)<br>2. Prior oxaliplatin-containing adjuvant therapy (yes vs. no)<br>3. Planned starting dose of panitumumab for maintenance therapy, if patient will be assigned to arm A (full dosage vs. reduced dosage)<br><br>Randomization will be performed in the subgroup of patients achieving CR, PR or SD 12 weeks after start of induction therapy qualifying for maintenance treatment and re-induction treatment with all potential drug components. |
| Sample size calculation | With a total number of 218 events (progressions or death, whichever occurs first), a logrank test for testing superiority of progression-free survival with a 10% one-sided significance level will have 80% power to reject the null-hypothesis if the true median progression-free survival times in patients treated with maintenance alone and maintenance plus panitumumab are 7.5 and 10 months, respectively. A total of approx. 400 patients eligible for induction |

| | |
|---|---|
| | therapy should be accrued for randomisation of 272 patients needed to reach the required number of events. |
| Planned interim analysis | No confirmatory interim analyses for efficacy with the aim to stop the trial prematurely are foreseen within this study protocol. |