AIO-KRK-0116

FOLFOXIRI Plus Cetuximab vs. FOLFOXIRI Plus Bevacizumab 1st-line in BRAF-mutated mCRC

NCT-Nummer:
NCT04034459

Studienbeginn:
November 2016

Letztes Update:
26.07.2019

Wirkstoff:
Bevacizumab, Irinotecan, Folinic Acid, Oxaliplatin, 5-FU, Cetuximab
Indikation (Clinical Trials):
Colorectal Neoplasms

Geschlecht:
Alle

Altersgruppe:
Erwachsene (18+)

Phase:
Phase 2

Sponsor:
Ludwig-Maximilians - University of Munich, Ludwig-Maximilians - University of Munich

Collaborator:
-

Studien-Informationen

Brief Summary:

Once randomisation has been completed, the study treatment should be started preferably immediately; at the latest within one week following randomisation.

The patients will be randomised in a ratio of 1:2 to the following two treatment arms.

Patients in both treatment arms will receive standard chemotherapy with FOLFOXIRI as background treatment, which can be de-escalated to FOLFIRI in case of toxicity.

Standard arm A:

The patient will be treated with FOLFOXIRI plus bevacizumab for up to 12 cycles (24 weeks) or until progression (if the latter occurs before completing the 12 cycles). Within the 12 cycles, the FOLFOXIRI plus bevacizumab regimen may be de-escalated, owing to toxicity, to FOLFIRI and bevacizumab at the treating physician's discretion.

After 12 cycles of the study treatment, a switch to a maintenance regimen with a fluoropyrimidine (5-FU infusion or capecitabine) plus bevacizumab, administered until progression occurs, is recommended. The recommended maintenance phase of the study is not part of the study treatment. However, maintenance therapy will be counted as first-line therapy.

Experimental arm B:

The patient will be treated with FOLFOXIRI plus weekly administration of cetuximab for up to 12 cycles (24 weeks) or until progression (if the latter occurs before completing the 12 cycles). Within the 12 cycles, the FOLFOXIRI plus cetuximab regimen may be de-escalated owing to toxicity, to FOLFIRI and cetuximab at the treating physician's discretion.

After 12 cycles, a switch to a maintenance regimen with 5-FU and cetuximab or with irinotecan and cetuximab, administered until progression occurs, is recommended. The recommended maintenance phase of the study is not part of the study treatment. However, maintenance therapy will be counted as first-line therapy.

Ein-/Ausschlusskriterien

Inclusion Criteria:

- Histologically confirmed UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer [mCRC]); metastases 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-mutant (V600E) tumour (proven in the primary tumour or metastasis)

- Age ≥18 years

- 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 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. Molecular profiling of blood samples is optionally performed.

- Females of childbearing potential (FCBP) and men must agree to use effective contraceptive measures (Pearl index <1) for the duration of the study treatment and for at least 6 months after last administration of the study medication. A female subject will be considered to be of child-bearing potential unless she is ≥ 50 years of age as well as has had a natural 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 case of hepatic metastasis, 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:

- 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 (prior radiotherapy of metastasis/metastases without application of chemotherapy permitted provided that no irradiated metastasis is selected as target lesion)

- Time interval since last administration of any previous neoadjuvant/adjuvant chemotherapy or radiochemotherapy ≥6 months

- Any relevant toxicities of previous treatments must have subsided to grade 0

Exclusion 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

- Pregnancy (absence of pregnancy has to be ascertained by a 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, immune therapy or hormone treatment) during the study treatment. Treatments that are conducted as part of an anthroposophical or homeopathic treatment approach, e.g. mistletoe therapy, do not represent an exclusion criterion.

- Previous chemotherapy for the colorectal cancer with exception of chemotherapy or radiochemotherapy given as neoadjuvant or adjuvant treatment with curative intent, completed ≥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) - cell 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 thromboembolism 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 malignancy during the 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

- A significant concomitant disease, in particular chronic hepatic or renal disease, chronic inflammatory or autoimmune diseases, ruling out the patient's participation in the study according to investigator's judgement.

- Absent or restricted legal capacity

Studien-Rationale

Primary outcome:

1. Overall Response Rate (ORR) (Time Frame - up to 48 months):
(overall response rate) measured in percentage of all treated patients according to RECIST 1.1 criteria

Secondary outcome:

1. Progression Free Survival (PFS) (Time Frame - up to 60 months):
Investigation of progression-free survival (PFS) from randomisation

2. Overall Survival (OS) (Time Frame - up to 60 months):
Investigation of overall survival (OS) from randomisation

3. Investigation of Early Tumour Shrinkage (ETS) as early-on-Treatment predictor for treatment (Time Frame - up to 48 months):
Investigation of early tumour shrinkage (ETS)

4. Investigation of Depth of Response (DpR) to define nadir for tumour response. (Time Frame - up to 48 months):
Investigation of depth of response (DpR)

5. Investigation of Molecular Biomarkers for Prediction of an Anti-EGFR Treatment (Time Frame - up to 48 months):
Investigation 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)

6. Prospective Analysis of Tumour Marker Level Evolution (CEA and CA 19-9) (Time Frame - up to 48 months):
Investigation of prospective analysis of tumour marker level evolution (CEA and CA 19-9)

7. Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability] (Time Frame - up to 48 months):
Recording of the safety and tolerability (NCI-CTCAE version 4.03 criteria) of the treatment

Studien-Arme

- Active Comparator: FOLFOXIRI plus bevacizumab
  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 *1st administration 90 min.; in case of good tolerability, second administration 60 min.; further administrations 30 min. Repeat administration every 2 weeks for a maximum of 12 cycles Dose adaptation at the treating physician's discretion. Switch to the recommended maintenance treatment with fluoropyrimidine and bevacizumab after the 8th cycle (following 2nd staging after baseline) is possible at the treating physician's discretion if response according to RECIST 1.1 (CR or PR) has been achieved.*
- Experimental: FOLFOXIRI plus cetuximab
  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 Repeat administration every two weeks up to a maximum of 12 cycles. Dose adaptation at the treating physician's discretion. Switch to the recommended maintenance treatment with 5-FU and cetuximab or irinotecan and cetuximab after the 8th cycle (following 2nd staging after baseline) is possible at the treating physician's discretion if response according to RECIST 1.1 (CR or PR) has been achieved.

Geprüfte Regime

- Bevacizumab:
  Bevacizumab 5 mg/kg BW iv over 30 to 90 min day 1*
- Irinotecan:
  Irinotecan 150 mg/m² iv, 30 - 90 min. day 1
- Folinic acid:
  Folinic acid (racemic) 400 mg/m² iv, 120 min. day 1
- Oxaliplatin:
  Oxaliplatin 85mg/m² day 1
- 5-FU:
  5-FU 3000 mg/m² iv over 48 h days 1-2
- Cetuximab:
  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

Studienleiter

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Studienlocations (1 von 1)

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Status: Rekrutierend