Optimal Anti-EGFR Treatment of mCRC Patients With Low-Frequency RAS Mutation

NCT-Nummer:
NCT04034173

Studienbeginn:
August 2019

Letztes Update:
26.07.2019

Wirkstoff:
Panitumumab, Irinotecan, Folinic Acid, 5-FU
Indikation (Clinical Trials):
Neoplasms, Second Primary

Geschlecht:
Alle

Altersgruppe:
Erwachsene (18+)

Phase:
Phase 2

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

Collaborator:
Amgen, ClinAssess GmbH, , Amgen, ClinAssess GmbH

Studien-Informationen

Brief Summary:

The present hypothesis is that anti-EGFR agents are active in tumors with low-level RAS mutation when the majority of tumor cells is still sensitive. While response rate may be high and may reflect sensitivity to anti-EGFR agents, PFS is anticipated to be shorter than in RAS wild-type patients due to the faster development of resistance when sensitive cells are eradicated and when the RAS-mutant anti-EGFR resistant clones become predominant.

The characteristics of low-level RAS mutant tumors would be:

- Objective response rate (ORR) high (reflecting the sensitive clone)

- Progression-free survival (PFS) short (reflecting the more rapid outgrowth of RAS mutant clones)

Ein-/Ausschlusskriterien

Inclusion Criteria:

- Histologically confirmed, UICC stage IV metastatic adenocarcinoma of the colon or rectum

- Primarily non-resectable metastases or surgical resection refused by the patient

- RAS mutation determined by the local pathology

- Age ≥18

- ECOG performance status 0-2

- 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 tumor tissue available and patient consents to storage and molecular and genetic profiling of tumor material. Molecular profiling of blood samples is optionally performed.

- 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)

- Adequate renal function:

□ Creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50 mL/min

- No previous chemotherapy for metastatic disease. Patient with need of immediate treatment

(high tumor load, symptoms) may have received one application of FOLFIRI prior to study treatment.

Exclusion Criteria:

- Previous chemotherapy for metastatic disease with the exception of one cycle of FOLFIRI (e.g. while waiting for the result of RAS mutation frequency).

- Patients planned to be treated with FOLFOX or another oxaliplatin-based regimen as first-line treatment

- Primarily resectable metastases and the patient agrees to resection

- Grade III or IV heart failure (NYHA classification)

- Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study

- Previous chemotherapy for the colorectal cancer with the exception of adjuvant treatment, completed at least 6 months before entering the study

- Participation in an investigational 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 the investigational clinical study or during an experimental drug treatment prior to inclusion in the study, depending on which period is longest

- Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, panitumumab, irinotecan, and chemically related substances and/or hypersensitivity to any of the excipients of any 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

- History of uncontrolled bronchial asthma

- Patients with interstitial pneumonitis or pulmonary fibrosis

- Patients with known brain metastasis

- History of acute or subacute intestinal occlusion or chronic inflammatory bowel disease or chronic diarrhoea

- Symptomatic peritoneal carcinomatosis

- Severe, non-healing wounds, ulcers or bone fractures

- Patients with acute or chronic infection requiring systemic therapy

- Known history of positive testing for human immunodeficiency virus (HIV) or known acquired

immunodeficiency syndrome (AIDS)

- 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 in patients who receive study treatment).

- Known DPD deficiency (specific screening not required)

- Known glucuronidation deficiency (Gilbert's syndrome);(specific screening not required

- Treatment with sorivudine or brivudine within 28 days before study enrollment or requirement for concomitant antiviral treatment with sorivudine or brivudine

- 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 previous or ongoing alcohol or drug abuse

- Pregnant or breast-feeding patients

- Any other severe concomitant disease or disorder which, in the investigator's opinion, could influence the patient's ability to participate in the study or influence his/her safety during the study or interfere with interpretation of study results

- Both, absent and restricted legal capacity

Studien-Rationale

Primary outcome:

1. Overall Response Rate (Time Frame - up to 60 months):
As primary endpoint ORR according to RECIST 1.1 will be evaluated separately for each arm of patients with defined low-frequency RAS mutation

Secondary outcome:

1. Progression free survival (PFS) (Time Frame - up to 60 months):
PFS, separately for each arm of patients with defined low-frequency RAS mutation

2. Overall Survival (OS) (Time Frame - up to 60 months):
OS, separately for each arm of patients with defined low-frequency RAS mutation

3. Investigation of Early Tumor shrinkage (ETS) as an alternative early-on-treatment predictor of treatment efficacy (Time Frame - up to 48 months):
ETS, separately for each group of patients with defined low-frequency RAS mutation

4. Investigation of Depth of Response (DpR) to define the nadir of tumour response (Time Frame -

up to 48 months):
DpR, separately for each arm of patients with defined low-frequency RAS Mutation.

Studien-Arme

- Other: RAS mutations frequency <= 7%
  Panitumumab 6 mg/kg BW as 60-min i.v. infusion D1 *If the 1st infusion is well tolerated, all subsequent infusions can be applied over 30-60 minutes. Followed by FOLFIRI regimen Irinotecan 180 mg/m² BSA i.v., 30 - 90 min D1 Folinic acid (racemic) 400 mg/m²BSA i.v., 120 min D1 5-FU 400 mg/m² BSA, bolus, D1 5-FU 2400 mg/m² BSA i.v. infusion over a period of 46 h D1-2 q day 14*
- Other: RAS mutation frequency >7% to <=14%
  Panitumumab 6 mg/kg BW as 60-min i.v. infusion D1 *If the 1st infusion is well tolerated, all subsequent infusions can be applied over 30-60 minutes. Followed by FOLFIRI regimen Irinotecan 180 mg/m² BSA i.v., 30 - 90 min D1 Folinic acid (racemic) 400 mg/m²BSA i.v., 120 min D1 5-FU 400 mg/m² BSA, bolus, D1 5-FU 2400 mg/m² BSA i.v. infusion over a period of 46 h D1-2 q day 14*
- Other: RAS mutation frequency >14% to <=20%
  Panitumumab 6 mg/kg BW as 60-min i.v. infusion D1 *If the 1st infusion is well tolerated, all subsequent infusions can be applied over 30-60 minutes. Followed by FOLFIRI regimen Irinotecan 180 mg/m² BSA i.v., 30 - 90 min D1 Folinic acid (racemic) 400 mg/m²BSA i.v., 120 min D1 5-FU 400 mg/m² BSA, bolus, D1 5-FU 2400 mg/m² BSA i.v. infusion over a period of 46 h D1-2 q day 14*

Geprüfte Regime

- Panitumumab:
  Panitumumab 6 mg/kg BW as 60-min i.v. infusion D1 *If the 1st infusion is well tolerated, all subsequent infusions can be applied over 30-60 minutes.*
- Irinotecan:
  Irinotecan 180 mg/m² BSA i.v., 30 - 90 min D1
- Folinic acid:
  Folinic acid (racemic) 400 mg/m²BSA i.v., 120 min D1
- 5-FU:
  5-FU 400 mg/m² BSA, bolus, D1 5-FU 2400 mg/m² BSA i.v. infusion over a period of 46 h D1-2

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Studienlocations (1 von 1)

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Status: Noch nicht rekrutierend

Quelle: ClinicalTrials.gov