# Clinical trial results:
# Randomisierte Studie zur Wirksamkeit von FOLFIRI in Kombination mit Cetuximab vs. Bevacizumab in der Erstlinien-Behandlung des metastasierten kolorektalen Karzinoms

# English translation:
# Randomised study for efficiency of FOLFIRI in combination with Cetuximab vs. Bevacizumab in first-line-therapy of metastatic colorectal cancer

## Summary

| | |
|---|---|
| EudraCT number | 2006-004030-32 |
| Trial protocol | DE AT |
| Global end of trial date | 21 November 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 September 2021 |
| First version publication date | 29 September 2021 |
| Summary attachment (see zip file) | Final Report ACCORDING TO § 42B (2) German Drug Law (Fire3_CSR_Version_2.0_30-Jul-2019.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AIOKRK0306 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Klinikum der Universität München - Grosshadern |
| Sponsor organisation address | Marchioninistraße 15, München, Germany, 81377 |
| Public contact | Medizinische Klinik III<br>AG Onkologie, Klinikum der Universität München - Grosshadern, +49 89 4400 0, onkologiestudien@med.uni-muenchen.de |
| Scientific contact | Medizinische Klinik III<br>AG Onkologie, Klinikum der Universität München - Grosshadern, +49 89 4400 0, onkologiestudien@med.uni-muenchen.de |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric | No |

| | |
|---|---|
| investigation plan (PIP) | |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 30 July 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 November 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Comparative validation of antitumor efficacy measured by objective remissionrate defined by RECIST-criteria (OR= CR+ PR), assessed within intent-to-treat-collective.

Protection of trial subjects:

All adverse events (AEs) for each cycle were recorded from the first day of administration of study medication until the end of treatment. Adverse events, denoted as late toxicities were also recorded every
three months during follow up.
Signs, symptoms or medical conditions/diseases that were already present before a subject obtained study drug treatment were only recorded as AEs if they worsened during study treatment.
There were 27 preprinted terms for common adverse events that could be ticked off in each treatment cycle
with space to fill in other adverse events than those recorded with the preprinted terms. Other adverse events were coded by MedDRA preferred terms and assigned to the preprinted terms if appropriate. The severity of AEs had to be graded according to the NCI CTCAE version 3.0 whenever possible and the causal relationship to the investigational drugs to be evaluated. An AE was analysed as causally related to
study medication when the AE was evaluated by the investigator as causally related to at least one of the
investigational drugs (5-FU, folinic acid, irinotecan, cetuximab, bevacizumab) administered in the respective
treatment arm.
All recorded adverse events were summarized in frequency counts based on the preprinted terms and MedDRA preferred terms assigned to other adverse events on patient level. A preprinted term or preferred
term was counted only once per patient. A patient with several grades of a preferred term was counted once with the highest NCI-CTCAE grade.
In addition, the data of laboratory investigations were analysed.
Data from all patients who received at least one dose of any study drug were included in the safety analyses.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 January 2007 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 35 |
| Country: Number of subjects enrolled | Germany: 717 |
| Worldwide total number of subjects | 752 |
| EEA total number of subjects | 752 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 559 |
| From 65 to 84 years | 193 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 752 |
| Number of subjects completed | 752 |

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | FOLFIRI + Cet |

Arm description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

| | |
|---|---|
| Irinotecan 180 mg/m² i.v., 30 - 90 min | day 1 |
| Folinic acid (racemic) 400 mg/m² i.v., 120 min | day 1 |
| 5-FU 400 mg/m² bolus | day 1 |
| 5-FU 2400 mg/m² i.v. over a period of 46 h | day 1-2 |
| Cetuximab initially 400mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each | day 1 + 8 |

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

180 mg/m² i.v., 30 - 90 min day 1

| | |
|---|---|
| Investigational medicinal product name | Folinic acid (racemic) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Folinic acid (racemic) 400 mg/m² i.v., 120 min day 1

| | |
|---|---|
| Investigational medicinal product name | 5-FU bolus |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Injection |

Dosage and administration details:

400 mg/m² bolus day 1

| | |
|---|---|
| Investigational medicinal product name | 5-FU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

5-FU 2400 mg/m² i.v. over a period of 46 h day 1-2

| | |
|---|---|
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Cetuximab initially 400mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each day 1 + 8

| | |
|---|---|
| **Arm title** | FOLFIRI + Bev |

Arm description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

| | |
|---|---|
| Irinotecan 180 mg/m² i.v., 30 - 90 min | day 1 |
| Folinic acid (racemic) 400 mg/m² i.v., 120 min | day 1 |
| 5-FU 400 mg/m² bolus | day 1 |
| 5-FU 2400 mg/m² i.v. over a period of 46 h | day 1-2 |
| Bevacizumab 5 mg/kg of BW i.v. for 30 to 90* minutes | day 1 |

* The 1st administration is given over a period of 90 min, if tolerated well, the second administration over a period of 60 min and the further administrations over a period of 30 min each

Continuation of the treatment until:

• the tumor progresses
• inacceptable toxicity is observed
• confirmed CR is achieved
• a status for surgical treatment is achieved
• the patient asks to end the treatment
• the treating physician decides that the therapy should be withdrawn

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

180 mg/m² i.v., 30 - 90 min day 1

| | |
|---|---|
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

180 mg/m² i.v., 30 - 90 min day 1

| | |
|---|---|
| Investigational medicinal product name | Folinic acid (racemic) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |

| | |
|---|---|
| Routes of administration | Infusion |
| Dosage and administration details:<br>Folinic acid (racemic) 400 mg/m² i.v., 120 min day 1 | |
| Investigational medicinal product name | 5-FU bolus |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Injection |
| Dosage and administration details:<br>400 mg/m² bolus day 1 | |
| Investigational medicinal product name | 5-FU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |
| Dosage and administration details:<br>5-FU 2400 mg/m² i.v. over a period of 46 h day 1-2 | |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |
| Dosage and administration details:<br>Bevacizumab 5 mg/kg of BW i.v. for 30 to 90* minutes day 1 | |

| **Number of subjects in period 1** | FOLFIRI + Cet | FOLFIRI + Bev |
|---|---|---|
| Started | 380 | 372 |
| Completed | 380 | 372 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Trial |

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|---|---|---|---|
| Number of subjects | 752 | 752 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 559 | 559 | |
| From 65-84 years | 193 | 193 | |
| Not recorded | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| median | 64 | | |
| full range (min-max) | 27 to 79 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 240 | 240 | |
| Male | 509 | 509 | |
| unknown | 3 | 3 | |
| KRAS Status<br>Units: Subjects | | | |
| KRAS wild-typ | 593 | 593 | |
| KRAS mutation | 113 | 113 | |
| Not recorded | 46 | 46 | |
| ECOG Performance status<br>Units: Subjects | | | |
| ECOG 0 | 394 | 394 | |
| ECOG 1 | 340 | 340 | |
| ECOG 2 | 18 | 18 | |
| Not recorded | 0 | 0 | |

## End points

### End points reporting groups

| Reporting group title | FOLFIRI + Cet |
|---|---|

Reporting group description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

| | |
|---|---|
| Irinotecan 180 mg/m² i.v., 30 - 90 min | day 1 |
| Folinic acid (racemic) 400 mg/m² i.v., 120 min | day 1 |
| 5-FU 400 mg/m² bolus | day 1 |
| 5-FU 2400 mg/m² i.v. over a period of 46 h | day 1-2 |
| Cetuximab initially 400mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each | day 1 + 8 |

| Reporting group title | FOLFIRI + Bev |
|---|---|

Reporting group description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

| | |
|---|---|
| Irinotecan 180 mg/m² i.v., 30 - 90 min | day 1 |
| Folinic acid (racemic) 400 mg/m² i.v., 120 min | day 1 |
| 5-FU 400 mg/m² bolus | day 1 |
| 5-FU 2400 mg/m² i.v. over a period of 46 h | day 1-2 |
| Bevacizumab 5 mg/kg of BW i.v. for 30 to 90* minutes | day 1 |

* The 1st administration is given over a period of 90 min, if tolerated well, the second administration over a period of 60 min and the further administrations over a period of 30 min each

Continuation of the treatment until:

• the tumor progresses
• inacceptable toxicity is observed
• confirmed CR is achieved
• a status for surgical treatment is achieved
• the patient asks to end the treatment
• the treating physician decides that the therapy should be withdrawn

### Primary: objective response rate (ORR)

| End point title | objective response rate (ORR) |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

the number of patients with either complete (CR) or partial response (PR) relative to the total number of subjects in the study population of interest. Only the results from restaging examinations during study therapy and until 28 days after the end.

| End point values | FOLFIRI + Cet | FOLFIRI + Bev | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 298 | 295 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 62.1 (56.3 to 67.6) | 58.3 (52.4 to 64.0) | | |

## Statistical analyses

| **Statistical analysis title** | Efficacy Results to SAF Dataset |
|---|---|
| Statistical analysis description: | |
| 1-sided Fisher's exact test and alpha = 0.025 | |
| Comparison groups | FOLFIRI + Cet v FOLFIRI + Bev |
| Number of subjects included in analysis | 593 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.192 [1] |
| Method | Fisher exact |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.63 |
| Variability estimate | Standard error of the mean |

Notes:

[1] - Thus, the primary endpoint was not reached and the ORR was not improved in patients treated with
FOLFIRI plus cetuximab.

## Secondary: progression free survival (PFS)

| End point title | progression free survival (PFS) |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |

End point timeframe:

PFS was defined as the time from randomisation until first occurrence of PD or death, whichever occurred
first. Subjects alive and without progression at the last date of assessment were censored.

| **End point values** | FOLFIRI + Cet | FOLFIRI + Bev | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| PFS | 10.1 (8.7 to 10.9) | 10.5 (9.9 to 11.5) | | |

## Statistical analyses

| **Statistical analysis title** | KRAS-wild-type patients, SAF |
|---|---|
| Comparison groups | FOLFIRI + Cet v FOLFIRI + Bev |
| Number of subjects included in analysis | 400 |
| Analysis specification | Post-hoc |
| Analysis type | equivalence |
| P-value | = 0.46 |
| Method | Fisher exact |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.26 |
| Variability estimate | Standard deviation |

| **Secondary: overall survival** | |
|---|---|
| End point title | overall survival |

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

OS was defined as the time from randomisation to the date of death of any cause. Subjects who were alive
at the date of the last assessment were censored.

| **End point values** | FOLFIRI + Cet | FOLFIRI + Bev | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| OS | 27.9 (23.7 to 31.7) | 25.6 (23.2 to 28.2) | | |

## Statistical analyses

| **Statistical analysis title** | KRAS-wild-type patients, SAF |
|---|---|
| Comparison groups | FOLFIRI + Cet v FOLFIRI + Bev |
| Number of subjects included in analysis | 400 |
| Analysis specification | Post-hoc |
| Analysis type | equivalence |
| P-value | = 0.05 |
| Method | Fisher exact |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.706 |
| upper limit | 1.001 |
| Variability estimate | Standard deviation |

## Secondary: Time to failure of strategy of the first-line treatment

| End point title | Time to failure of strategy of the first-line treatment |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

TFS was defined as the duration from randomisation to the date of death or start of a new systemic anticancer therapy that contained a substance not included in the study therapy (start of second-line therapy).

| **End point values** | FOLFIRI + Cet | FOLFIRI + Bev | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| TFS | 11.4 (10.1 to 12.6) | 12.1 (11.1 to 13.1) | | |

### Statistical analyses

| **Statistical analysis title** | Time to failure of strategy of the first-line trea |
|---|---|
| Comparison groups | FOLFIRI + Cet v FOLFIRI + Bev |

| | |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Post-hoc |
| Analysis type | equivalence |
| P-value | = 0.42 |
| Method | Fisher exact |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.27 |
| Variability estimate | Standard deviation |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) for each cycle were recorded from the first day of administration of study medication until the end of treatment. Adverse events, denoted as late toxicities were also recorded every
three months during follow up.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 13.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | adverse events according to SAF |

Reporting group description: -

| Serious adverse events | adverse events according to SAF | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 252 / 734 (34.33%) | | |
| number of deaths (all causes) | 13 | | |
| number of deaths resulting from adverse events | 13 | | |
| Injury, poisoning and procedural complications | | | |
| Bone fracture | | | |
| subjects affected / exposed | 3 / 734 (0.41%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 6 / 734 (0.82%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorder | | | |
| subjects affected / exposed | 10 / 734 (1.36%) | | |
| occurrences causally related to treatment / all | 4 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 26 / 734 (3.54%) | | |
| occurrences causally related to treatment / all | 3 / 26 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| handfoot syndrom | | | |
| subjects affected / exposed | 1 / 734 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neurotoxicity | | | |
| subjects affected / exposed | 3 / 734 (0.41%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Thromboembolic event | | | |
| subjects affected / exposed | 66 / 734 (8.99%) | | |
| occurrences causally related to treatment / all | 25 / 66 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Haematotoxicity | | | |
| subjects affected / exposed | 10 / 734 (1.36%) | | |
| occurrences causally related to treatment / all | 8 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bleeding | | | |
| subjects affected / exposed | 2 / 734 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Edema peripheral | | | |
| subjects affected / exposed | 3 / 734 (0.41%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorder | | | |
| subjects affected / exposed | 1 / 734 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |

| | | | | |
|---|---|---|---|---|
| Fatigue | | | | |
| subjects affected / exposed | 4 / 734 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypertension | | | | |
| subjects affected / exposed | 3 / 734 (0.41%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mucositis | | | | |
| subjects affected / exposed | 6 / 734 (0.82%) | | | |
| occurrences causally related to treatment / all | 5 / 6 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Nail changes | | | | |
| subjects affected / exposed | 2 / 734 (0.27%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| other | | | | |
| subjects affected / exposed | 54 / 734 (7.36%) | | | |
| occurrences causally related to treatment / all | 15 / 54 | | | |
| deaths causally related to treatment / all | 1 / 6 | | | |
| Psychiatric disorder | | | | |
| subjects affected / exposed | 4 / 734 (0.54%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune system disorders | | | | |
| Fever without neutropenia | | | | |
| subjects affected / exposed | 20 / 734 (2.72%) | | | |
| occurrences causally related to treatment / all | 6 / 20 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Allergic reaction | | | | |
| subjects affected / exposed | 11 / 734 (1.50%) | | | |
| occurrences causally related to treatment / all | 11 / 11 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Electrolyte imbalance | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 734 (0.95%) | | |
| occurrences causally related to treatment / all | 2 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fever with neutropenia | | | |
| subjects affected / exposed | 4 / 734 (0.54%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 40 / 734 (5.45%) | | |
| occurrences causally related to treatment / all | 38 / 40 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bleeding respected to GI tract | | | |
| subjects affected / exposed | 11 / 734 (1.50%) | | |
| occurrences causally related to treatment / all | 6 / 11 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| fistula perforation | | | |
| subjects affected / exposed | 6 / 734 (0.82%) | | |
| occurrences causally related to treatment / all | 3 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 5 / 734 (0.68%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstipation | | | |
| subjects affected / exposed | 8 / 734 (1.09%) | | |
| occurrences causally related to treatment / all | 4 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 734 (0.82%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|---|---|---|
| liver toxicity | | | |
| subjects affected / exposed | 4 / 734 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 5 / 734 (0.68%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin disorder | | | |
| subjects affected / exposed | 1 / 734 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound healing problems | | | |
| subjects affected / exposed | 4 / 734 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrotoxicity | | | |
| subjects affected / exposed | 4 / 734 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| infection without neutropenia | | | |
| subjects affected / exposed | 57 / 734 (7.77%) | | |
| occurrences causally related to treatment / all | 13 / 57 | | |
| deaths causally related to treatment / all | 1 / 3 | | |
| infections with neutropenia | | | |
| subjects affected / exposed | 9 / 734 (1.23%) | | |
| occurrences causally related to treatment / all | 5 / 9 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Product issues | | | |
| medical device complication | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 734 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | adverse events according to SAF | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 734 (4.50%) | | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 33 / 734 (4.50%) | | |
| occurrences (all) | 33 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 20 April 2007 | After authorization of cetuximab (Erbitux®) as 5 mg/ml solution for infusion by the European Medicines Agency (EMA) (Doc.Ref. EMEA/CHMP/280402/2008) cetuximab was provided as 5 mg/ml solution for the trial instead of the previously used 2 mg/ml solution that had been used initially. |
| 03 September 2008 | • Trials had shown that patients with mutated KRAS did not respond to anti EGFR treatment. Treatment with cetuximab was to be confined to KRAS-wildtype patients. Thus the in- and exclusion criteria were amended accordingly to include only patients with KRAS wild-type. Patients with mutated KRAS had to discontinue treatment with cetuximab.<br>• The planned primary statistical analysis was modified to take into account only patients with KRAS wild-type disease, whereas already included patients with mutated KRAS status would be analysed only by means of descriptive analyses. The sample size was increased from 147 to 284 evaluable patients per treatment arm.<br>• Also, all subsequently as well as prior obtained tumour samples were to be analysed regarding the KRAS mutation status.<br>• A variation for the cetuximab (Erbitux®) marketing authorization was authorized (Doc.Ref. EMEA/CHMP/280402/2008) in 2008.<br>Additional indication of cetuximab: treatment of patients with epidermal growth factor receptor (EGFR) - expressing, KRAS wild-type metastatic colorectal cancer in combination with chemotherapy.<br>Therefore cetuximab was no longer supplied as study medication, but had to be prescribed.<br>• Additional collection of copies of CT images for planned independent review at a later time point. |
| 25 January 2011 | • Addition of a translational research project to search for predictors for response to<br>cetuximab and bevacizumab in the treatment of mCRC patients. Pharmacogenetic factors were to be analysed in an additionally collected blood sample.<br>• The accountability of the biostatistics and data management services were transferred from „Wissenschaftlicher Service Pharma (WiSP) GmbH“ to „ClinAssess GmbH“. |
| 20 April 2012 | • Two secondary endpoints were added:<br>- Time to failure of strategy“ (TFS) for first-line treatment<br>- Depth of remission (maximum percentage decrease of tumour size compared to baseline tumour size).<br>Planned statistical analysis of the secondary endpoints was added.<br>• From the updated SmPCs new information regarding safety was introduced for FOLFIRI, cetuximab and bevacizumab.<br>• An independent radiological review for the evaluation of tumour response was established. Tumour response in the independent review was to be evaluated according to RECIST 1.1 (in contrast to local assessment of tumour response with RECIST 1.0)<br>• K-RAS genotyping had revealed a proportion of 144 patients with mutated or unknown K-RAS genotype (patients included before Amendment 2) and actual data to the number of drop outs were evaluable.<br>Thus, the number of patients was increased to 800 patients overall, to obtain the required 256 evaluable KRAS wild-type patients per treatment arm.<br>• Duration of patient recruitment time was extended from 48 to 72 months. |
| 19 April 2013 | • Change from trial phase II to trial phase III according to the number of recruited patients |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/25088940