REPORT ACCORDING TO § 42B (2) GERMAN DRUG LAW

Name of Sponsor/Company: Klinikum Großhadern Klinikum der Ludwig-Maximilians Universität Munich Marchioninistr. 15, 81377 München, Germany	Individual Study Table Referring to Part of the Dossier Volume: Page: n.a.	*(For National Authority Use Only)*
Name of Finished Products: Irinotecan (Campto and all products authorised in Germany), cetuximab (Erbitux), bevacizumab (Avastin), 5-fluorouracil (e.g. 5-FU medac, all products authorised in Germany), folinic acid (e.g. Leucovorin, all products authorised in Germany)		
Name of Active Ingredients: Irinotecan, cetuximab, bevacizumab, 5-fluorouracil, folinic acid		

Protocol code No.: AIOKRK0306

EudraCT No.: 2006-004030-32

Title of Study:

German title of the study:

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

Abbreviated title of the study:

FIRE-3

Protocol version 1.4 of October 31, 2006 was the version first approved by the German competent authority on December 04, 2006. There were several amendments to this protocol version that are compiled in Annex I in Table A.1.

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Heinemann V, Stintzing S, Modest DP, Giessen-Jung C, Michl M, Mansmann UR. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). *Eur J Cancer*. 2015;51(14):1927-1936

Modest DP, Stintzing S, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Kahl C, Seipelt G, Kullmann F, Scheithauer W, Moehler M, Holch JW, von Einem JC, Held S, Heinemann V. Exploring the effect of primary tumor sidedness on therapeutic efficacy across treatment lines in patients with metastatic colorectal cancer: analysis of FIRE-3 (AIOKRK0306). Oncotarget. **2017**;8(62):105749-105760.

Modest DP, Ricard I, Stintzing S, Fischer von Weikersthal L, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Kahl C, Seipelt G, Kullmann F, Scheithauer W, Moehler M, Westphalen CB, Holch JW, von Einem JC, Held S, Heinemann V; for FIRE-3/AIOKRK0306-investigators. Evaluation of survival across several treatment lines in metastatic colorectal cancer: Analysis of the FIRE-3 trial (AIO KRK0306). Eur J Cancer. **2017**;84:262-269.

Modest DP, Stintzing S, Fischer von Weikersthal L, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Scheithauer W, Kirchner T, Jung A, Stauch M, von Einem JC, Moehler M, Held S, Heinemann V; FIRE-3 study investigators. Relation of early tumor shrinkage (ETS) observed in first-line treatment to efficacy parameters of subsequent treatment in FIRE-3 (AIOKRK0306). Int J Cancer. **2017**;140(8):1918-1925

Modest DP, Stintzing S, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Held S, Möhler M, Jung A, Kirchner T, Heinemann V. Impact of Subsequent Therapies on Outcome of the FIRE-3/AIO KRK0306 Trial: First-Line Therapy With FOLFIRI Plus Cetuximab or Bevacizumab in Patients With *KRAS* Wild-Type Tumors in Metastatic Colorectal Cancer. J Clin Oncol. **2015**;33(32):3718-26

Stintzing S, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Held S, Giessen-Jung C, Moehler M, Jagenburg A, Kirchner T, Jung A, Heinemann V; FIRE-3 investigators. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final *RAS* wild-type subgroup of this randomised open-label phase 3 trial. Lancet Oncol. **2016**;17(10):1426-1434.

Studied period:

Date of first-patient-first visit (FPFV): January 23, 2007

Date of last-patient-last visit (LPLV): November 21, 2017

The study was not interrupted temporarily nor terminated early.

Phase of development:

Phase II, since Amendment 5 Protocol V 4.0 phase III

Objectives:

***Primary objective*:**

The primary objective of this trial was to compare the anti-tumour efficacy of cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI. The analysis was performed based on the objective response rate (ORR = CR + PR) as assessed by the investigators in the intent-to-treat (ITT) population according to RECIST 1.0.

Secondary objectives:

Secondary objectives were:

- Progression-free survival (PFS)
- Overall survival (OS)
- Rate of secondary resections of liver metastases with potentially curative approach
- Evaluation of safety and tolerability according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0
- Time to Failure of Strategy (TFS) of the first-line treatment.
  This was an additional secondary objective introduced with Amendment 4 (Protocol V 3.0/ April 20, 2012)
- Depth of Response (maximum percentage of tumour shrinkage as compared to baseline).
  This was an additional secondary objective introduced with Amendment 4 (Protocol V 3.0/ April 20, 2012)
- Early Tumour Shrinkage (ETS).
  ETS was defined as tumour shrinkage of equal to or more than 20% at the first restaging during study therapy compared to baseline. This was an additional analysis in accordance with Statistical Analysis Plan (SAP v.1.0/ February 25, 2018)

Methodology:

FIRE-3 was a phase III, multicentre, open-label, randomized, controlled study comparing the efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab in patients with *KRAS* exon 2 wildtype mCRC (since Amendment 2).

Patients were randomized in a 1:1 ratio to one of the 2 treatment arms:

- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) plus cetuximab (Arm A)
- FOLFIRI plus bevacizumab (Arm B)

A stratified permuted block randomization procedure was employed to balance prognostic factors between treatment arms; the following strata were used: Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1 vs. 2), white blood cell (WBC) count (< 8000 /µL vs. ≥ 8000 /µL), alkaline phosphatase level (< 300 U/mL vs. ≥ 300 U/mL), and number of metastatic sites (1 vs. > 1).

Initially, enrolment of patients was independent of any biomarker assessment. As per Amendment 2, enrolment was restricted to subjects with a tumour *KRAS* exon 2 wild-type status; this was defined as the ITT population (primary analysis population). Since then, all subjects were to be prospectively assessed for their tumour *KRAS* exon 2 mutation status. Subjects enrolled before Amendment 2 were to be tested retrospectively in case their tumour tissue was available. Patients with mutated *KRAS* exon 2 status had to discontinue treatment with cetuximab.

During the course of the study the importance of additional *RAS* mutations in determining the efficacy of epidermal growth factor receptor (EGFR) inhibitors including cetuximab became apparent and led to the requirement of extended *RAS* mutation testing. Since November 2013 the licenced indication for cetuximab was restricted to patients with wild-type *RAS* (wild-type *KRAS* exon 2, 3, 4 and *NRAS* exon 2, 3, 4). As the last patient had already been randomized at this time point, the inclusion criteria were not amended.

Based on the results of the *KRAS*/*RAS* mutation analyses of the tumour tissue, the following subgroups of patients were analysed according to SAP v.1.0/ February 25, 2018:

- *KRAS* wild-type (exon 2) patients
- *KRAS* mutant patients (exon 2) patients

- *RAS* wild-type patients (*KRAS* exon 2, 3, 4 and *NRAS* exon 2, 3, 4)

Treatment in Arm A (FOLFIRI plus cetxuximab) and Arm B (FOLFIRI plus bevacizumab) was given in 14-day cycles and was to be continued until progression, unacceptable toxicity, complete response (CR) or achievement of surgical resectability.

After discontinuation of the treatment, follow-up examinations were conducted every three months for a maximum of five years or until the patient's death, whichever occurred first.

The first restaging for tumour response was performed after 3 treatment cycles (i.e. after 6 weeks) of FOLFIRI and the second restaging followed after 6 cycles (i.e. after 12 weeks). Subsequently, restaging was performed after every 10 treatment weeks.

Tumour response was evaluated at the local trial site according to RECIST 1.0.

Since Amendment 2, the additional collection of copies of CT images for a planned independent review at a later time point was performed. An independent radiological review for evaluation of tumour response according to RECIST 1.1, depth of response and early tumour shrinkage was established with Amendment 4.

Number of patients:

The planned number of patients in the first approved study protocol v.1.4 of October 31, 2006 was 294 subjects (147 evaluable patients per treatment arm).

With Amendment 2 (study protocol v.1.7 of September 3, 2008), the planned number of patients was increased to 568 patients with a *KRAS* exon 2 wild-type tumour status (284 subjects per treatment group).

With Amendment 4 (study protocol v.3.0 of April 20, 2012), the planned number of patients was increased to 800 patients overall to obtain 284 evaluable *KRAS* wild-type patients per treatment arm (a total of 568 patients with *KRAS* wild-type status = population for the intent-to-treat analysis).

Number of patients randomized:

Overall, 752 patients were randomized, thereof 735 patients had been treated: 373 with FOLFIRI plus cetuximab and 362 with FOLFIRI plus bevacizumab.

593 treated patients with *KRAS* exon 2 wildtype mCRC were analysed in the ITT population (298 subjects in the FOLFIRI plus cetuximab group and 295 subjects in the FOLFIRI plus bevacizumab group).

Diagnosis and main criteria for inclusion:

Diagnosis

Metastatic colorectal cancer (mCRC)

Main criteria for inclusion

- Histologically confirmed adenocarcinoma of the colon or rectum, stage IV.
- Proven wild-type *KRAS* mutation status in the tumour (primary tumour or metastasis). (Additional inclusion criterion since Amendment 2)
- General performance status: 0-2 (ECOG/World Health Organization)
- Fit for treatment with a chemotherapy regimen
- Subject's written informed consent (first-and second-line therapy)
- Age: 18-75 years
- Inpatient or outpatient treatment

- Estimated life expectancy > 3 months
- Presence of at least one measurable target lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST). Evaluation of the tumour lesions within 2 weeks before study enrollment.
- Effective contraception for men and women if conception was possible
- WBC count ≥ 3.0 x 10^9 /L, with neutrophils ≥ 1.5 x 10^9 /L, platelets ≥ 100 x 10^9 /L, hemoglobin ≥ 5.6 mmol/L (corresponding to 9 g/dL)
- Serum bilirubin ≤ 1.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) ≤ 2.5 x ULN. ALAT and ASAT ≤ 5 x ULN in the presence of liver metastases
- Serum creatinine ≤ 1.5 x ULN
- Surgery and fine needle biopsy had to be performed more than 4 weeks and more than 1 week before study enrollment. Surgical wounds had to be healed completely. No need for major surgery during the course of the study was to be expected, except for a possible resection of liver metastases. In the case of a secondary curative surgery, bevacizumab and cetuximab had to be discontinued 6-8 weeks and about 2 weeks before surgery, respectively.
- Relevant toxicities of prior therapies had to be resolved.

Main exclusion criteria

- Proof of *KRAS* mutation
- Prior anti- EGFR targeted therapy
- Prior bevacizumab treatment
- Prior chemotherapy of the colorectal cancer (CRC), except for adjuvant therapy completed at least 6 months before study enrollment
- Experimental drug treatment within 30 days of enrollment
- Known hypersensitivity to any component of the investigational drugs
- Pregnant female (absence of pregnancy had to be confirmed with beta-human chorionic gonadotropin test) or lactating female
- Pre-existing or clinically suspected brain metastases
- Clinically relevant coronary heart disease, myocardial infarction within the past 12 months or high risk of uncontrolled arrhythmia
- Acute or subacute intestinal obstruction or history of chronic inflammatory disease or chronic diarrhea
- Symptomatic peritoneal carcinomatosis
- Severe, non-healing wounds, ulcers or bone fractures
- Uncontrolled hypertension
- Pronounced proteinuria (nephrotic syndrome)
- Arterial thromboembolism or severe hemorrhage within 6 months before study enrollment (except for tumour bleeding before tumour resection surgery)
- Hemorrhagic diathesis or thrombotic tendency
- Therapeutic anticoagulation (treatment with phenprocoumon, heparinization affecting the prothrombin time)
- Known dihydropyrimidine dehydrogenase deficiency (no special screening was required)

- Known glucuronidation defect (Gilbert-Meulengracht syndrome; no special screening was required)
- History of secondary malignancy within the past 5 years, except for basalioma of the skin or carcinoma in situ of the cervix uteri, if treated with curative intent
- Pre-existing alcohol or drug abuse
- Medical or mental impairments which prevented to obtain subject's consent or to conduct the study in due form
- A significant concomitant medical condition which the clinical investigator believed to preclude the subject from enrolling in the study
- Absent or limited legal competence

Test product, dose and mode of administration:

Treatment Arm A - One cycles consists of (see Table 1).

Table 1 FOLFIRI schedule plus cetuximab, every two weeks

Study Drug	Dose	Mode of administration
Irinotecan	180 mg/m²	i.v., 30-90 min, Day 1
Folinic acid	400 mg/m²	i.v., 120 min, Day 1
5-FU	400 mg/m²	Bolus, Day 1
5-FU	2400 mg/m²	i.v. Day 1-2, continuously over 46 h
Cetuximab	400 mg/m²	i.v. 120 min, initial dose only on Day 1 of Cycle 1
Cetuximab	250 mg/m²	i.v., 60 min, Day 8 of Cycle 1 and on Day 1 and Day 8 of each consecutive cycle

Reference Therapy, dose and mode of administration:

Treatment Arm B - One cycles consists of (see Table 2).

Table 2 FOLFIRI schedule plus bevacizumab, every two weeks

Study Drug	Dose	Mode of administration
Irinotecan	180 mg/m²	i.v., 30-90 min, Day 1
Folinic acid	400 mg/m²	i.v., 120 min, Day 1
5-FU	400 mg/m²	Bolus, day 1
5-FU	2400 mg/m²	i.v., Day 1-2, cont. 46h
Bevacizumab	5 mg/kg body weight	i.v., 30-90 min, Day 1*

* First administration over 90 minutes, second administration in case of good tolerability over 60 minutes, every subsequent administration over 30 minutes

Batch numbers:

All available trademarks or generic products for the combination chemotherapy (FOLFIRI) with approved marketing authorisation in Germany were allowed as test product. Thus, only the batch numbers for cetuximab are listed for the solutions of the test product provided by Merck. Cetuximab was provided as 20 ml and 100 ml solution for injection. In 2008, cetuximab was approved for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing *KRAS* wild-type mCRC in combination with chemotherapy. Therefore, cetuximab was no longer supplied as study medication, but had to be prescribed (see Amendment 2). The lot numbers for the supplied solutions are listed in Table 3.

Table 3 Lot numbers of the supplied test product cetuximab (2007-2009)

Volume	Lot numbers
20 ml solution	4900201, 4922601,4999701,7469201, 7469301, 7469501, 7469502, 7469606, 7600109, 7600201, 7600206, 7600301, 7600401, 7608501, 7650803, 7650901, 7655505, 7656103, 7657901, 7659108, 7659208, 7659701, 7661705, 7662202, 7662301, 7663603, 7663704, 7663903, 7664006, 7665203, 7666304, 7666605, 7667801, 7820201,7820301, 7820807
100 ml solution	4821403, 4821801, 4821805, 4821901, 4822001, 4837307, 4837401, 4837501, 4837603, 4852301, 4852401, 4861901, 4862001, 4862104, 4862201, 4862301, 4862505, 4873801, 4873901, 4874003, 4874101, 4874201, 4874301, 4913401, 4913501, 4913601, 4913802, 4914101, 4917102, 4923902, 4924004, 4924101, 4924201, 4924601, 4933902, 4934001, 4939903, 4940001, 4940101, 4940201, 4940305, 4959101, 4959301, 4975201, 4982302, 4999801, 6500603, 6554002, 7822301

Duration of treatment:

Treatment in Arm A (FOLFIRI plus cetxuximab) and Arm B (FOLFIRI plus bevacizumab) was given in 14-day cycles and was to be continued until occurrence of progressive disease (PD), observation of unacceptable toxicity, achievement of confirmed complete response (CR) or surgical resectability.

Criteria for evaluation:

Efficacy:

The tumour response and the occurrence of stable disease or progression were assessed in restaging examinations. Restaging was performed after Cycle 3 (i.e. after 6 weeks) and Cycle 6 (i.e. after 12 weeks of treatment). Thereafter, restaging was performed every 10 treatment weeks.

For restaging, imaging procedures (computed tomography [CT] of abdomen and pelvis as well as appropriate imaging of other body regions) affected by the tumour or suspected to be involved by the tumour were conducted.

The primary efficacy variable was the objective response rate (ORR) according to RECIST 1.0 as assessed at the local trial site. It is defined as 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 of the last cycle were taken into account.

The secondary endpoints included PFS, OS, TFS, depth of response, early tumour shrinkage and rate of secondary resections of liver metastases with a potentially curative intent.

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.

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.

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).

In addition to the assessment by the investigator, response was evaluated according to RECIST 1.1 by an independent review by board-certified radiologists, the corresponding measurements were used for the calculation of depth of response and early tumour shrinkage.

Safety:

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.

Statistical methods:

Analysis populations

All patients: All patients who were randomised were included in this analysis set. This analysis set was used for all demographic variables and disease characteristics as well as other baseline characteristics.

Safety Analysis Set (SAF) and Full Analysis Set (FAS) included all patients who had received at least one dose of study drug and, in this study, comprised the same set of patients which will be called SAF below.

The SAF was used for all demographic variables and disease characteristics as well as other baseline characteristics and for all safety parameters.

Efficacy parameter were analysed only in patients with confirmed *KRAS* wild-type status, as this had been defined as the primary analysis population in the study protocol.

Per Protocol (PP): All patients from the SAF with confirmed *KRAS* wild-type status who fulfilled the following criteria:

- At least ≥3 cycles of allocated combination therapy (FOLFIRI plus cetuximab/or FOLFIRI plus bevacizumab)
- At least 1 restaging by means of imaging procedures after baseline

The following subgroups were analysed according to *KRAS/RAS* mutation status:

- *KRAS* wild-type (exon 2)
- *KRAS* mutant (exon 2)
- *RAS* wild-type (*)

  *: *RAS* evaluable patients with a tumour showing no mutation in *KRAS* exons 2, 3, and 4, and *NRAS* exons 2, 3, and 4.

The primary objective of the study was to demonstrate with a power of 80% and a one-sided type I error of α=0.025 that the ORR was significantly superior in the FOLFIRI plus cetuximab arm compared to the FOLFIRI plus bevacizumab arm. The primary endpoint ORR was analysed in the SAF - population with *KRAS* exon 2 wild-type tumours using the one-sided Fisher's exact test (α=0.025).

Standard descriptive methods were used to present all relevant data.

The distributions of the time-to-event data (i.e. progression-free survival, overall survival, time to failure of the first-line strategy) were analysed using the product-limit method (Kaplan-Meier analysis). Median time to event estimates with the associated 95% confidence intervals were displayed. The log-rank test was used for the comparison of the treatment arms while hazard ratios were estimated using a Cox proportional hazards regression model.

Patients who did not have the event were censored with the last date at which they were known to be event-free.

The analyses of depth of response (DpR) and early tumour shrinkage (ETS) were performed with data from the independent central radiological review as per RECIST 1.1. This was a subset of patients of the SAF and PP of whom copies of CT images from baseline and/or restaging procedures had been obtained.

DpR was defined in the SAP as the maximum shrinkage of tumour size as compared to the tumour size at baseline. It was to be displayed as a continuous parameter in percent. For the calculations waterfall

analyses were performed and for the comparison between the treatment arms a two-sided Wilcoxon-Mann-Whitney test was used.

ETS was defined as tumour shrinkage of equal to or more than 20% at the first restaging during study therapy compared to baseline. As laid down in the SAP, ETS was displayed as a discrete parameter. For the comparison of both arms a two-sided Fisher's exact test was used.

SUMMARY – CONCLUSIONS

In total, 752 patients were randomized in 129 German centres and seven Austrian trial centres. Of these, 735 patients received at least one dose of study medication (SAF), thereof 373 patients had been randomized to the FOLFIRI plus cetuximab arm and 362 patients to the FOLFIRI plus bevacizumab arm. 17 patients had not been treated.

Independent radiological review of response was performed in 496 *KRAS* wild-type patients (237 patients of the FOLFIRI plus cetuximab arm and 259 patients of the FOLFIRI plus bevacizumab arm).

Patient characteristics

Of 735 patients in the SAF, 593 patients (80.7%) had a wild-type status in exon 2 of *KRAS.* Correspondingly, the FOLFIRI plus cetuximab arm had 298 (79.9%) *KRAS* wild-type patients and the FOLFIRI plus bevacizumab arm 295 patients (81.5%). 113 patients (15.4%) were carrier of mutations within the *KRAS* gene (exon 2, codon 12 and 13) with a comparable distribution in the two treatment arms (n= 58 [15.5%] in the FOLFIRI plus cetuximab arm versus n=55 [15.2%] in the FOLFIRI plus bevacizumab arm).

400 patients (54.4%) had *RAS* wild-type mCRC (n=199 [53.4% in the FOLFIRI plus cetuximab arm versus n=201 [55.5%] in the FOLFIRI plus bevacizumab arm).

The median age of all patients in the SAF and of those with *KRAS* wild-type tumours was 64 years for the FOLFIRI plus cetuximab arm and 65 years for the FOLFIRI plus bevacizumab arm. With an overall range from 27 to 79 years the sets differed only marginally. The proportions of elderly patients >65 years (46.1%-47%) to those ≤ 65 years (53% -53.9%) were similar in both treatment arms for all patient sets.

240 of 752 randomised patients (31.9%) were females and 509 (67.7%) males, gender was unknown in 3 patients. In all patients of the SAF, there were 113 females (30.3%) and 260 males (69.7%) in the FOLFIRI plus cetuximab arm versus 123 females (34.0%) and 239 males (66.0%) in the FOLFIRI plus bevacizumab arm. In the SAF with *KRAS* wild-type patients, there were 84 females (28.2%) and 214 males (71.8%) in the FOLFIRI plus cetuximab arm versus 99 (33.6%) females and 196 (66.4%) in the FOLFIRI plus bevacizumab arm.

Regarding the ECOG performance status (PS) of all randomised patients, the majority (n=394; 52.4%) had an ECOG PS of 0, 340 (45.2%) patients had an ECOG PS of 1 and only 18 patients (2.4%) had an ECOG PS of 2.

In the SAF with *KRAS* wild-type patients only, 317 patients (53.5%) had ECOG PS Grade 0, 265 patients (44.7%) had ECOG PS Grade 1 and 11 patients (1.9%) had ECOG Grade 2.

The different ECOG grades were equally distributed in both treatment arms.

In the subgroup of patients with *RAS* wild-type, 217 patients (54.3%) had ECOG PS Grade 0, 177 patients (44.3%) ECOG Grade 1 and 6 patients (1.5%) ECOG Grade 2.

In the SAF with *KRAS* wild-type tumours, the tumour was left-sided in 237 patients (79.5%) and right –sided in 58 patients (19.5%) of the FOLFIRI plus cetuximab arm versus left-sided in 215 patients (72.9%) and right-sided in 78 patients (26.4%) of the FOLFIRI plus bevacizumab arm.

In the subgroup of patients with *RAS* wild-type mCRC, the tumour was left-sided in 158 patients (79.4%) and right –sided in 38 patients (19.1%) in the FOLFIRI plus cetuximab arm versus left-sided in 149 patients (74.1%) and right-sided in 50 patients (24.9%) in the FOLFIRI plus bevacizumab arm.

Right-sided refers to tumours located in the caecum to transverse colon and left-sided to tumours from the splenic flexure to rectum.

EFFICACY RESULTS:

Primary endpoint: objective response rate in the SAF in patients with *KRAS* wild-type tumours

The ORR based on investigator's assessments was 62.1% (95% CI, 56.3 -67.6%; n =185 of 298) in patients receiving treatment with FOLFIRI plus cetuximab versus 58.3% (95% CI, 52.4 – 64.0%; n=172 of 295) in patients receiving treatment with FOLFIRI plus bevacizumab. There was no statistically significant difference between the treatment arms
(p = 0.192 with the 1-sided Fisher's exact test and alpha = 0.025). The odds ratio was 1.17 (95% CI, 0.84 - 1.63).
Thus, the primary endpoint was not reached and the ORR was not improved in patients treated with FOLFIRI plus cetuximab.

Objective response rate in other subgroups of the SAF and in the per-protocol analysis

Whereas the ORR based on investigator's assessments was not improved in the FOLFIRI plus cetuximab arm versus the FOLFIRI plus bevacizumab arm in the subgroup of patients with *RAS* wild-type mCRC of the SAF, a significant improvement of the ORR could be shown in the PP analyses for the subgroups of patients with *KRAS* wild-type and *RAS* wild-type disease. The respective data are displayed below.

RAS wild-type patients, SAF

The ORR was 65.8% (95% CI, 58.8 -72.4%; n =131 of 199) in the FOLFIRI plus cetuximab arm versus 58.7% (95% CI: 51.6 – 65.6%; n=118 of 201) in the FOLFIRI plus bevacizumab arm; p=0.15 with an odds ratio of 1.36 (95% CI: 0.9 – 2.03).

KRAS wild-type patients, PP

The ORR was 72.2% (95% CI, 66.2 -77.6%; n =184 of 255) in the FOLFIRI plus cetuximab arm versus 63.7% (95% CI, 57.7 – 69.4%; n=172 of 270) in the FOLFIRI plus bevacizumab arm; p= 0.04 with an odds ratio of 1.48 (95% CI: 1.02 – 2.14).

RAS wild-type, PP

The ORR was 76.9% (95% CI, 69.8 – 83.0%; n =130 of 169) in the FOLFIRI plus cetuximab arm versus 64.5% (95% CI, 57.1 – 71.4%; n=118 of 183) in the FOLFIRI plus bevacizumab arm; p = 0.014 with an odds ratio of 1.84 (95% CI: 1.15 – 2.93)

Duration of follow up

The median overall duration of follow up in the SAF population with *KRAS* wild-type mCRC (n=593) was 24.8 months (range 0.03 -105.4 months) and 25.9 months (range 0.03 -105.4 months) in the *RAS* wild-type subgroup.

Progression-free survival

PFS did not differ between the treatment arms FOLFIRI plus cetuximab and FOLFIRI plus bevacizumab in any of the different analyses (SAF and PP) nor in any of the subgroups analysed (patients with *KRAS* wild-type and *RAS* wild-type mCRC).

The respective data are displayed in detail below.

KRAS wild-type patients, SAF

The median PFS time of patients in the FOLFIRI plus cetuximab arm was 10.1 months (95% CI, 8.7 – 10.9 months) versus 10.5 months (95% CI, 9.9 – 11.5 months) in the FOLFIRI plus bevacizumab arm (HR 1.06 [95% CI, 0.90 – 1.26]; p = 0.46).

KRAS wild-type patients, PP

The median PFS time of patients in the FOLFIRI plus cetuximab arm was 10.1 months (95% CI, 8.7 – 10.9 months) versus 10.6 months (95% CI, 10.1 – 11.6 months) in the FOLFIRI plus bevacizumab arm (HR 1.12 [95% CI, 0.94 – 1.33]; p = 0.22).

RAS wild-type patients, SAF

The median PFS time of patients in the FOLFIRI plus cetuximab arm was 10.3 months (95% CI, 9.5 – 11.8 months) versus 10.4 months (95% CI, 9.8 – 11.7 months) in the FOLFIRI plus bevacizumab arm (HR 0.96 [95% CI, 0.79 – 1.18]; p = 0.71).

RAS wild-type, PP

The median PFS time of patients in the FOLFIRI plus cetuximab arm was 10.3 months (95% CI, 9.5 – 11.8 months) versus 10.7 months (95% CI, 9.9 – 11.8 months) in the FOLFIRI plus bevacizumab arm (HR 1.0 [95% CI, 0.81 – 1.24]; p = 0.998).

Overall survival

In patients with *KRAS* wild-type tumours, overall survival was not improved significantly in the FOLFIRI plus cetuximab arm versus the FOLFIRI plus bevacizumab arm.

However, overall survival was significantly prolonged in the subgroup of *RAS* wild-type patients. This was true for the SAF analysis as well as for the PP analysis.

The respective data are displayed in detail below.

KRAS wild-type patients, SAF

The median OS of patients in the FOLFIRI plus cetuximab arm was 27.9 months (95% CI, 23.7 – 31.7 months) versus 25.6 months (95% CI, 23.2 – 28.2 months) in the FOLFIRI plus bevacizumab arm (HR 0.84 [95% CI, 0.706 – 1.001]; p = 0.050).

KRAS wild-type patients, PP

The median OS of patients in the FOLFIRI plus cetuximab arm was 28.7 months (95% CI, 24.5 – 32.5 months) versus 26.1 months (95% CI, 23.7 – 28.6 months) in the FOLFIRI plus bevacizumab arm (HR 0.84 (95% CI: 0.698 – 1.010); p=0.06).

RAS wild-type patients, SAF

The median OS of patients in the FOLFIRI plus cetuximab arm was 31.1 months (95% CI, 25.2 – 36.4 months) versus 25.6 months (95% CI, 23.2 – 28.8 months) in the FOLFIRI plus bevacizumab arm (HR 0.76 [95% CI, 0.62 – 0.94]; p = 0.012).

RAS wild-type patients, PP

The median OS of patients in the FOLFIRI plus cetuximab arm was 32.5 months (95% CI, 25.9 – 38.3 months) versus 26.1 months (95% CI, 23.7 – 29.0) in the FOLFIRI plus bevacizumab arm (HR 0.75 [95% CI, 0.59 – 0.94]; p = 0.011).

Time to failure of strategy of the first-line treatment

The time to failure of strategy (TFS) of the first-line treatment was comparable between the treatment arms FOLFIRI plus cetuximab and FOLFIRI plus bevacizumab in the different analysis populations (SAF and PP) and in all the subgroups analysed (*KRAS* wild-type and *RAS* wild-type patients).

In the SAF with KRAS wild-type mCRC, the median TFS was 11.4 months (CI, 10.1-12.6 months) in patients of the FOLFIRI plus cetuximab arm versus 12.1 months (CI, 11.1-13.1 months) in patients of the FOLFIRI plus bevacizumab arm (HR 1.07 [95% CI, 0.91 – 1.27]; p = 0.42).

Depth of response

Analysis of depth of response was performed with a distinct data set from central radiological review of CT or MRI images according to RECIST 1.1

Depth of response was significantly increased in patients of the FOLFIRI plus cetuximab arm compared to patients of the FOLFIRI plus bevacizumab arm. This was true for the SAF and PP analyses and for the subgroups analysed (*KRAS* wild-type and *RAS* wild-type patients).

Data for the SAF analysis are displayed below in detail.

KRAS wild-type patients, SAF

Median tumour shrinkage compared to baseline tumour size was 45% in the FOLFIRI plus cetuximab arm versus 32.6% in the FOLFIRI plus bevacizumab arm (p = 0.0001).

RAS wild-type patients, SAF

Median tumour shrinkage compared to baseline tumour size was 49.4% in the FOLFIRI plus cetuximab arm versus 32.2% in the FOLFIRI plus bevacizumab arm (p < 0.0001).

Early tumour shrinkage

Analysis of early tumour shrinkage (ETS) was performed with a distinct data set from central radiological review of CT or MRI images according to RECIST 1.1.

The rate of early tumour shrinkage was significantly improved in the FOLFIRI plus cetuximab arm versus the FOLFIRI plus bevacizumab arm. This was true for the SAF and PP analyses and for both subgroups analysed (*KRAS* wild-type and *RAS* wild-type patients).

Data for the SAF analysis are displayed below in detail.

KRAS wild-type patients, SAF

ETS was observed in 62.4% of the patients in the FOLFIRI plus cetuximab arm (95% CI, 55.9% - 68.6%; n=148 of 237) versus 47.5% of the patients of the FOLFIRI plus bevacizumab arm (95% CI: 41.3% – 53.8%; n=123 of 259); p = 0.0009 with an odds ratio of 1.84 (95% CI: 1.29 – 2.63)

RAS wild-type patients, SAF

ETS was observed in 68.4% of the patients in the FOLFIRI plus cetuximab arm (95% CI, 60.5% - 75.5%; n=108 of 158) versus 48.9% of the patients of the FOLFIRI plus bevacizumab arm (95% CI: 41.2% – 56.5%; n=85 of 174); p = 0.0004 with an odds ratio of 2.26 (95% CI: 1.45 – 3.54).

Rate of secondary resections of liver metastases

There was no difference in the rate of secondary resections of liver metastases with potentially curative intent between the treatment arms FOLFIRI plus cetuximab arm and FOLFIRI plus bevacizumab in the different analysis populations (SAF and PP) and in all the subgroups analysed (*KRAS* wild-type and *RAS* wild-type patients).

In the SAF population with *KRAS* wild-type disease, 53 resections of liver metastases were performed in patients treated with FOLFIRI plus cetuximab (17.8%) and 52 resections in patients treated with FOLFIRI plus bevacizumab (17.6%; p> 0.999).

SAFETY RESULTS:

The mean treatment duration in the SAF patients with *KRAS* wild-type mCRC was 6.2 ± 5.6 months in the FOLFIRI plus cetuximab arm versus 6.4 ± 5.0 months in the FOLFIRI plus bevacizumab arm. The median treatment duration for these patients was 4.9 months with an overall range from 0.03 to 38.6 months versus 5.3 months with an overall range from 0.03 to 33.0 months.

Adverse events

All the patients (n=373; 100%) in the FOLFIRI plus cetuximab arm and all but one patients (n=361; 99.7%) patients in the FOLFIRI plus bevacizumab arm experienced at least one AE. Thereof, 372 patients (99.7%) in the FOLFIRI plus cetuximab arm and 357 patients (98.6%) in the FOLFIRI plus bevacizumab arm experienced at least one AE that was causally related to study medication.

The most common (in >50% of patients) AEs that were reported in the in the ***FOLFIRI plus cetuximab arm*** were haematotoxicity (n=347; 93%), liver toxicity (n=271; 72.7%); electrolyte imbalance (n=250; 67.0%), rash acneiform (n=296; 79.4%); diarrhoea (n=219; 58.7%), pain (n=208; 55.8%), dry skin (n=194; 52.0%), nausea (n=194; 52.0%) and fatigue (n=191; 51.2%).
The AE allergic reaction was reported in 30 patients (8.0%), thromboembolic events in 59 patients (15.8%), and hypertension in 86 patients (23.1%).

The most common (in >50% of patients) AEs that were reported in the in the ***FOLFIRI plus bevacizumab arm*** were haematotoxicity (n=336; 92.8%), liver toxicity (n=237; 65.5%); nausea (n=231; 63.8%), diarrhoea (n=234; 64.4%), pain (n=221; 61%) and fatigue (n=200; 55.2%).
The AE allergic reaction was reported in 3 patients (0.8%), thromboembolic events in 63 patients (17.4%), and hypertension in 140 patients (38.7%).

273 patients (73.2%) experienced an AE of the severity ≥ Grade 3 in the ***FOLFIRI plus cetuximab arm*** versus 239 patients (66.0%) in the ***FOLFIRI plus bevacizumab arm.***
Allergic reactions were of ≥ Grade 3 in 15 patients (4%) in the ***FOLFIRI plus cetuximab arm*** whereas no allergic reaction of ≥ Grade 3 occurred in the ***FOLFIRI plus bevacizumab arm.***

The frequency, severity and distribution of adverse events was comparable in all the patients of the Safety set, the SAF with *KRAS* wild-type patients, and the subgroup of *RAS* wild-type patients.

Serious adverse events

133 patients (35.7%) in the FOLFIRI plus cetuximab arm and 119 patients (32.9%) in the FOLFIRI plus bevacizumab arm experienced at least one SAE.

Thereof, 61 patients (16.4%) in the FOLFIRI plus cetuximab arm and 68 patients (18.8%) in the FOLFIRI plus bevacizumab arm experienced at least one SAE that was causally related to study medication.

The most common (in >2% of patients) SAEs that were reported in the ***FOLFIRI plus cetuximab arm*** were thromboembolic events (n=33; 8.8%), infection without neutropenia Grade 3/4 (n=28; 7.5%), diarrhoea (n=20; 5.4%), fever without neutropenia Grade 3/4 (n=14; 3.8%), pain (n=14; 3.8%), allergic reaction (n=11; 2.9%).
The SAE haematotoxicity was reported in 6 patients (1.6%), bleeding in the respiratory tract, gastrointestinal tract and genitourinary tract in 6 patients (1.6%). Liver toxicity was not reported as SAE.

The most common (in >2% of patients) SAEs that were reported in the in the ***FOLFIRI plus bevacizumab arm*** were thromboembolic events (n=33; 9.1%), infection without neutropenia Grade 3/4 (n=29; 8.0%), diarrhoea (n=20; 5.5%), pain (n=12; 3.3%).
The SAE haematotoxicity was reported in 4 patients (1.1%), bleeding in the respiratory tract, gastrointestinal tract and genitourinary tract in 5 patients (1.4%) and liver toxicity in 4 patients (1.1%). Allergic reaction was not reported as SAE.

The frequency and distribution of SAEs was comparable in all the patients of the Safety set, the SAF with *KRAS* wild-type patients and the subgroup of *RAS* wild-type patients.

Death and withdrawals due to adverse events

Thirteen patients died due to an adverse event from the first day of administration of study medication until the end of treatment.

In the ***FOLFIRI plus cetuximab arm*** 5 patients (1.3%) died due to the following adverse events:

- General physical health deterioration (2 patients) due to progression of the underlying tumour disease
- Ascites (1 patient) due to progression of the underlying tumour disease
- Pulmonary embolism (1 patient)
- Sudden death (1 patient)

Only the adverse event sudden death was assessed as causally related to study medication as sudden death occurred at home and no autopsy was performed. Thus a causal relationship to study medication could not be excluded.

In the ***FOLFIRI plus bevacizumab arm*** 8 patients (2.2%) died due to the following adverse events, thereof in 5 patients these events were assessed as causally related to the study medication (adverse reaction):

- Infection (pneumonia) with neutropenia Grade 3/4 (2 patients; thereof in one patient assessed as not related to study medication)
- Infection (pneumonia and sepsis; sepsis) without neutropenia Grade 3/4 (2 patients; thereof in one patient assessed as not related to study medication)
- Arrhythmia (1 patient)
- Tumour haemorrhage (1 patient)
- Cholestasis and consecutive sepsis (1 patient; assessed as not related to study medication)
- Mucositis/stomatitis (1 patient)

No patient died due to a thromboembolic event.

In the Safety population with *KRAS* wild-type mCRC, treatment was permanently discontinued due to an adverse reaction in 47 patients (15.7%) of the ***FOLFIRI plus cetuximab arm*** versus in 33 patients (11.2%) of the ***FOLFIRI plus bevacizumab arm.***

CONCLUSION:

The final analysis of the FIRE-3 suggests potential superiority of FOLFIRI plus cetuximab compared to FOLFIRI plus bevacizumab in the first-line treatment of mCRC with regard to ORR, early tumour shrinkage and depth of response as well as OS.

Although the primary endpoint ORR in the SAF population with *KRAS* exon 2 wild-type patients was not reached, a significant improvement of the ORR in patients treated with FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab was observed in the PP analysis including only patients who had received at least three treatment cycles and underwent at least one restaging after treatment.

This benefit for patients in the FOLFIRI plus cetuximab arm was also supported by a significantly higher rate of patients with early tumour shrinkage and an increase in depth of response.

Overall survival was significantly improved in patients treated with FOLFIRI plus cetuximab compared to patients treated with FOLFIRI plus bevacizumab in patients with *RAS* wild-type tumours although the final analysis failed to show this for patients with *KRAS* exon 2 wild-type patients. However, this is in line with the importance of additional *RAS* mutations limiting the efficacy of EGFR inhibitors that led to restriction of the licenced indication for cetuximab to patients with wild-type *RAS* in 2013.

PFS did not differ between the two treatment arms, although patients in the FOLFIRI plus cetuximab were more likely to obtain early tumour shrinkage and a deeper response.

A meta-analysis with data from three available head-to-head trials of EGFR inhibitors versus bevacizumab in combination with different background chemotherapy including the data of this FIRE-3, the PEAK study, and the CALGB/SWOG 80405 led to comparable results and suggested potential benefit of EGFR inhibitor plus chemotherapy versus bevacizumab plus chemotherapy in the first-line treatment of *RAS* wild-type mCRC [Heinemann, 2016].

Date of the report:

19th November 2018 (Version 1)
30th July 2019 (Version 2)

REFERENCES:

Heinemann V, Rivera F, O'Neil BH, et al. A study-level meta-analysis of efficacy data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in patients with RAS wild-type metastatic colorectal cancer. Eur J Cancer. 2016 Nov;67:11-20.

ANNEX I:

Protocol Changes

There were five amendments to the study protocol version 1.4 of October 31, 2006 as first authorized by the German competent authority on December 04, 2006. Key changes are summarized in Table A.1 for each amendment. Additional changes (not shown) were made for editorial consistency, clarity, and to enhance readability of the protocol in each amendment.

Table A. 1 Key Protocol Changes in Study FIRE-3

Protocol version/ version date	Key Changes
Original Protocol V 1.4/ 31-Oct-2006 approved on 4-Dec-2006	
Amendment 1 Protocol V 1.5/ 20-Apr-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.
Amendment 2 (V2.2) Protocol V 1.7/ 03-Sept-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. • 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. • Also, all subsequently as well as prior obtained tumour samples were to be analysed regarding the *KRAS* mutation status. • A variation for the cetuximab (Erbitux®) marketing authorization was authorized (Doc.Ref. EMEA/CHMP/280402/2008) in 2008. Additional indication of cetuximab: treatment of patients with epidermal growth factor receptor (EGFR) - expressing, *KRAS* wild-type metastatic colorectal cancer in combination with chemotherapy. Therefore cetuximab was no longer supplied as study medication, but had to be prescribed. • Additional collection of copies of CT images for planned independent review at a later time point.
Amendment 3 Protocol V 2.0/ 25-Jan-2011	• Addition of a translational research project to search for predictors for response to cetuximab and bevacizumab in the treatment of mCRC patients. Pharmacogenetic factors were to be analysed in an additionally collected blood sample. • The accountability of the biostatistics and data management services were transferred from „Wissenschaftlicher Service Pharma (WiSP) GmbH“ to „ClinAssess GmbH“.
Amendment 4	• Two secondary endpoints were added: - Time to failure of strategy“ (TFS) for first-line treatment

Protocol V 3.0/ 20-Apr-2012	- Depth of remission (maximum percentage decrease of tumour size compared to baseline tumour size). Planned statistical analysis of the secondary endpoints was added. • From the updated SmPCs new information regarding safety was introduced for FOLFIRI, cetuximab and bevacizumab. • 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) • *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. Thus, the number of patients was increased to 800 patients overall, to obtain the required 256 evaluable *KRAS* wild-type patients per treatment arm. • Duration of patient recruitment time was extended from 48 to 72 months.
Amendment 5 Protocol V 4.0/ 19-Apr-2013	• Change from trial phase II to trial phase III according to the number of recruited patients

Signatures

Title of the Study:

Randomized study to investigate the efficacy of 5-FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab versus FOLFIRI plus bevacizumab in the first-line treatment of metastatic colorectal cancer

EudraCT No.: 2006-004030-32

The signatories have read this clinical study report and hereby confirm that, to the best of their knowledge, it accurately describes the conduct and the results of the study.

Munich, 31.07.2019
Place, date

Coordinating investigator and sponsor's representative
Prof. Dr. V. Heinemann

Mainz, 31.07.19
Place, date

ClinAssess GmbH
Dr. B. Deuß

Leverkusen, 30.07.19
Place, date

Frau Swantje Held
Biometrician, ClinAssess GmbH