SYNOPSIS

Name of Sponsor/Company: **University Hospitals Leuven (U.Z. Leuven), Digestive Oncology Unit** Academic trial – the sponsor is not the Market Authorization Holder of any of the drugs involved. Research grant and study medication provided by Merck BV Belgium affiliate of Merck KGaA, Darmstadt, Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Products/Active ingredients: Cetuximab (Erbitux TM) provided by Merck Irinotecan (commercial) 5-fluorouracil (commercial) Leucovorin (commercial)	Volume: Page:	

Title of Study: **A two-arm phase II study of FOLFIRI in combination with standard or escalating dose of cetuximab as first line treatment of K-Ras wild type metastatic colorectal cancer: Everest 2.**

Study centres and Investigators:

BELGIUM: 100-01 - UZ Leuven - Prof. Dr. Eric Van Cutsem, Prof. Dr. SabineTejpar; 100-02 - Imelda Ziekenhuis Bonheiden - Dr. Veerle Moons; 100-04 - UCL Saint-Luc Bruxelles - Prof. Dr. Marc Van den Eynde; 100-05 - AZ Groeninge Kortrijk - Dr. Philippe Vergauwe; 100-06 - AZ Sint-Maarten Mechelen - Dr. Michel Ferrante; 100-08 - AZ Turnhout - Dr. Jos Janssens; 100-09 - OLV Ziekenhuis Aalst - Dr. Koen Hendrickx; 100-11 - UZ Gent - Prof. Dr. Karen Geboes; 100-13 - AZ Maria Middelares Gent - Dr. Erik Vanderstraeten; 100-14 - CUB Hôpital Erasme - Prof. Dr. Jean-Luc Van Laethem; 100-15 - AZ Delta Roeselare - Dr. Jochen Decaestecker; AUSTRIA: 200-01 - Landeskrankenhaus Salzburg - Prof. Dr. Richard Greil; 200-03 - AKH Linz - Dr. Michael Fridrik; 200-06 - St Vincent Krankenhaus Zams - Dr. Ewald Wöll; FRANCE: 300-01 - Hopital Européen Georges Pompidou Paris - Prof. Dr. Philippe Rougier, Prof. Dr. Julien Taieb; 300-07- Centre Eugène Marquis Rennes - Dr. Eveline Boucher, Dr. Marc Pracht; HUNGARY: 400-02 - National Institute of Oncology Budapest - Prof. Dr. István Láng; 400-06 - MH Honvédkórház - Dr. Zsuzsanna Pápai; SPAIN: 600-01 - Hospital Universitario Vall d'Hebron Barcelona - Dr. Teresa Macarulla; 600-02 - Hospital Clinico Universitario de Valencia - Dr. Andrés Cervantes; 600-03 - Hospital Universitario Virgen del Rocío Sevilla - Dr. Luisa Limón Mirón, Dr. Rocio Garcia-Carbonero; 600-04 - Institut Català d'Oncologia Barcelona - Dr. Ramon Salazar; 600-05 - Hospital Universitario Marqués de Valdecilla Satander - Dr. Fernando Rivera. ITALY: No patients accrued in Italy.

Publications (references):

One abstract/oral presentation at ESMO GI congress 2018. See document "Everest 2 publications".

Study period: Date of first signature of informed consent: 18-Jan-2011 Date of last end of treatment assessment: 25-Jul-2016 Date of last completed follow up (FU) expected: Jul-2019	**Phase of development:** two-arm, non-randomized, non-comparative, open-label phase II study

Objectives:

Considering that the severity of cetuximab-related skin toxicity might correlate with efficacy, this phase II trial aimed to assess feasibility and value of increasing the dose of cetuximab in patients without any drug-induced skin reaction at day 22 of treatment and to correlate clinical outcomes with molecular characteristics of tumours.

Endpoints:

Primary endpoint:

- To provide an estimate (+/- 15%) of the progression-free survival rate at 9 months, in patients without skin toxicity at 3 weeks treated with modified FOLFIRI + escalating dose of cetuximab (Arm A). It was expected that the progression free survival rate will be similar to that observed after standard cetuximab treatment + FOLFIRI in patients with grade 1-4 skin toxicity (NCI CTCAE version 4.0) in a K-Ras wild type population (CRYSTAL study).

Secondary endpoints:

- Safety profile of the combination in treatment arms
- Skin toxicity and correlations between outcome, pharmacokinetic (PK) results and dose escalation
- Overall response and response rate in liver-limited disease
- Disease control rates
- Duration of response
- Progression free survival (PFS) and overall survival (OS)
- General resection rate and R0 (resection margin tumour free) resection rate for metastatic lesions
- Pharmacokinetic parameters in patients in both treatment arms in selected centers.
- Exploratory biomarker studies: proteomics, microarray and polymerase chain reaction (PCR) studies on plasma and tumour and correlations with efficacy outcomes.

Methodology:

This two-arm, non-randomized, non-comparative, open-label phase II study aimed to investigate the strategy of increasing the dose of cetuximab in colorectal cancer patients without skin reactions after 22 days of treatment with modified FOLFIRI and weekly cetuximab at standard doses.

After completion of all pre-treatment screening procedures and signature of informed consent, eligible patients were treated with cetuximab 400 mg/m2 (loading at day 1) followed by 250 mg/m^2 weekly at day 8 and 15. FOLFIRI (simplified de Gramont) starting at day 15 was given every second week: irinotecan 180mg/m^2, leucovorin 400 mg/m^2 (racemic) or 200 mg/m^2 (L-form), 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 infusion over 46 hours. At day 22 (before the 4th cetuximab dose +/- 2 days) patients were classified as either eligible or ineligible for dose escalation and treatment arm was assigned based on the presence or absence of cetuximab-induced skin reactions during the first three weeks. The dose of cetuximab was escalated once to 350mg/m^2 if no skin reaction had occurred by day 22 and second time to 500mg/m^2 if no skin reaction had occurred by day 36. Patients in whom skin reactions of any grade were present continued cetuximab at standard dose. FOLFIRI was continued at standard doses.

Patients were evaluated weekly or every two weeks by standard tests. Recommendations for treatment adjustments in case of toxicity and use of certain concomitant medication were given in the protocol. Several blood samples and tumor biopsies were required for the translational component of the study. Patients received chemotherapy until disease progression, unacceptable toxicity or patient refusal to continue.

All patient data were collected in an electronic case report form (CRF). Automated selected datasets were pre-built for extraction in the electronic platform. Risk based monitoring of critical data was performed by independent monitors in all sites. Data verifications were also performed centrally by assigned CRO and sponsor. The database was locked on 09-07-2018. Final data sets were extracted, formatted, worked and summarized in comma separated values (CSV) files and analysed using the SAS statistical package version 9.2 (SAS Institute Inc. 2011. SAS® 9.2 Language Reference: Dictionary, Fourth Edition. Cary, NC: SAS Institute Inc.).

Statistical methods:

Standard cetuximab treatment in combination with FOLFIRI + cetuximab in K-Ras wild-type patients resulted in progression free survival rate at 9 months of 36% (95%CI 22–51%) in patients with skin toxicity

grade 0 at week 3 and 58% (95%CI 47-69%) in patients with skin toxicity grade 1-4 at week 3 (CRYSTAL study). Based on this observation:

It was estimated that after escalating the dose of cetuximab in patients with no skin toxicity at week 3 (Arm A) progression free survival rate at 9 months will be of 55% (+/-15%) in this group.

Assuming a PFS rate of 55% and a drop-out rate of 0.12 (both at 9 months), 44 evaluable subjects were to be included in the dose-escalation group in order to obtain a two-sided 95% confidence interval on the PFS rate of +/- 0.15 (i.e. distance from the estimate to the confidence interval limits of less than 0.15 in both directions).

A total of 124 patients were needed, 44 in Arm A and 80 in Arm B based on the proportion observed in the CRYSTAL study (Gr. 0/Gr. 1-4=0.55) with an estimated drop-out rate of 12% at 9 months.

In order to account for 5% of patients who drop-out before week 3 or have major protocol violations 130 patients were to be enrolled in the study (estimated per arm: 46 in Arm A and 84 in Arm B).

Analyses:

Primary endpoint:

- PFS rate at 9 months in Arm A - 95% confidence interval. Kaplan Meier for PFS.
- Multivariate analysis of PFS by Forward Stepwise Cox proportional hazard method to reveal prognostic factors (gender, age, metastases limited to liver at baseline, time between primary diagnosis/pathological confirmation and first administration of cetuximab, treatment arm).
- PFS for patients resected for metastatic lesions and for non-resected patients using Kaplan-Meier. Estimation of the hazard ratio, separately for resected and non-resected patients, using Cox proportional hazard method.

Secondary endpoints:

- OS – Kaplan Meier + multivariable per arm
- Response rate – descriptive per arm
- Response rate in liver limited disease – descriptive per arm
- Duration of response – Kaplan Meier, for all patients and for patients with liver-limited disease only.
- General safety and skin toxicity – descriptive per arm
- Time to first occurrence of skin reactions – Kaplan Meier.
- Efficacy in patients experiencing skin toxicity and patients not experiencing skin toxicity after dose escalation in Arm A – descriptive assessment.
- Number of resections for metastatic lesions and R0 rate
- PKs studies – specific PK calculations and qualitative assessment of linearity and predictability.
- Molecular studies and correlations with outcome.

Several subgroup analyses were planned, by demographic factors, disease site, skin toxicity, resection, etc.

Biomarkers were analyzed and described by the U.Z. Leuven's accredited lab for Human Genetics.

PK analyses were planned but not performed due to insufficient number of patients in Arm A.

The study was not powered to perform formal statistical comparisons of the treatment groups. Each treatment was described and presented separately.

Number of patients (planned and analysed):

130 patients planned (46 in Arm A, 84 in Arm B)

108 patients registered (8 in Arm A, 93 in Arm B, 7 not assigned dropped out before arm allocation).

Total Set: All patients who consented to participate in the study (Intent to treat ITT).

Safety Set: All patients for whom there is evidence they were administered any dose of Cetuximab or FOLFIRI on study. For this study, the ITT and the safety sets are identical. All patients have received at least one treatment dose and entered the safety analyses.

Full Analysis Set: All patients with skin toxicity data on D21 allowing assignment to Arm A or to Arm B. Patients who were not allocated into Arm A or Arm B (drop outs in the first three weeks or at day 22) will be excluded from this analysis set.

Per Protocol Set (PPS): All patients of the full analysis set without any major protocol deviation. Patients with incorrect treatment group allocation were also excluded from this analysis set.

All patients received at least one dose of treatment and entered the safety analyses. Safety set was the same as the intent to treat set in this study. All analyses were performed on the total (intent-to-treat) set.

Arm	Total Set	Safety Set	Full Analysis Set	Per Protocol Set
Arm A	8	8	8	8
Arm B	93	93	93	92
Not assigned	7	7	0	0
All patients	108	108	101	100

See document "Everest 2 CONSORT diagram" for patient distribution.

Eligibility deviations and exceptions:

Arm A: Patient 100-11-001 was escalated though having a mild rash acneiform on the face (chin), assessed to be possibly related to Cetuximab, that lasted for 5 days during the first 3 weeks. This was assessed to be a minor violation and therefore it was decided to keep the patient in the Per Protocol Set.

Arm B: Patient 300-07-001 was not escalated though at Infusion visit 4, no skin reaction grade 1 or higher had appeared. This was assessed to be no violation and therefore it was decided to keep the patient in the Per Protocol Set. Patient 600-01-032 was excluded from the Per Protocol Set because of treatment with FOLFOX given prior to enrolment.

All deviations are listed in document "Everest 2 protocol deviations".

Diagnosis and main criteria for inclusion:

Patients diagnosed with unresectable metastatic adenocarcinoma of the colon or rectum with K-Ras wild type tumours were considered eligible.

Other inclusion criteria were: age 18 years or older, body weight less than 120 kg, WHO performance status 0 or 1, adequate bone marrow, coagulation, hepatic and renal function, active contraception where applicable and ability to provide informed consent.

Patients previously treated for metastatic disease, patients with any dermatological condition grade higher than 1, as well as patients with other clinical or social conditions that would impede treatment were excluded.

Eligibility for arm allocation:

Arm A:

1. Absence of cetuximab-related skin reaction (grade 0; NCI-CTCAE v.4.0) at day 22.

and

2. No other (than skin) significant cetuximab related toxicity grade > 2. If mild or mild to moderate (grade 1 and, in some cases, grade 2 NCI-CTCAE v.4.0) cetuximab infusion related reactions occurred during the first three weeks of treatment, increasing the dose of cetuximab remained a clinical decision of the investigator. If severe (grade 3 and 4) cetuximab infusion related reactions occurred during the first three weeks the patient was NOT eligible for cetuximab dose escalation.

and

3. No significant FOLFIRI related toxicity or events requiring treatment discontinuation at day 22. If severe FOLFIRI related diarrhea (grade 3 or 4) occurs the patient was not eligible for dose escalation. As a general rule, FOLFIRI related toxicity other than severe diarrhea requiring dose adjustments of irinotecan or 5-FU did not impede escalation of cetuximab if the toxic events were not additive with cetuximab toxicity (e.g. hematologic reactions). Clinical judgement on a case to case basis was to be employed.

Arm B:

1. Skin reaction grade 1 or higher (NCI-CTCAE v.4.0) at day 22.

or

2. Other (than skin) cetuximab related toxicity requiring cetuximab treatment adjustments (i.e. cetuximab infusion related requiring reductions of infusion rate).

and/or

3. Significant FOLFIRI related toxicity impeding dose escalation.

and

4. Ability to continue treatment with cetuximab at standard or reduced dose and FOLFIRI at recommended or reduced doses. No toxic events requiring discontinuation at day 22.

Similar eligibility considerations applied for second dose escalation at day 36 (350 mg/m2 → 500 mg/m2) for patients in Arm A. If patients having already received cetuximab at 350 mg/m2 still fulfilled all criteria for Arm A above, they were eligible for the second dose escalation. If not, they continued at 350 mg/m2 unless a dose reduction was necessary.

Test product, dose and mode of administration, batch number:

Cetuximab (Erbitux TM) was provided by Merck. Cetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to the epidermal growth factor receptor (EGFR) with high affinity.

Formulation: Cetuximab is presented in 100 ml glass vials at a concentration of 5 mg/ml.

Route: IV

Doses: Cetuximab 400 mg/m2 (loading at day 1) followed by 250 mg/m2 weekly from day 8 onwards. FOLFIRI (simplified de Gramont) starting at day 15, given every second week: irinotecan 180mg/m2, leucovorin 400 mg/m² (racemic) or 200 mg/m² (L-form), 5-FU 400 mg/m² bolus and 2400 mg/m² infusion over 46 hours. After arm allocation the dose of cetuximab was increased to either 350 mg/m2 or 500 mg/m2 in eligible patients.

Multiple batches of study labelled medication were used. Detailed information is available upon request.

Modified FOLFIRI was administered as per routine practice. Regimen and doses are provided above and detailed in the protocol.

Duration of treatment:

Treatment was continued until one of the following occurred:

- Progression of disease documented by appropriate imaging techniques. If clinical progression was deemed and caused treatment discontinuation, a CT/MRI scan was required as soon as possible after cessation of treatment.
- Withdrawal of patient's consent.
- Occurrence of an exclusion criterion which was clinically relevant and affected patient's safety, if discontinuation was considered necessary by the investigator.
- Documented proof of mutant K-Ras status.
- Unacceptable toxicity attributed to study therapy.
- Occurrence of AEs, if discontinuation of cetuximab is considered necessary by the investigator and/or subject.
- Occurrence of pregnancy.
- Intake of non-permitted concomitant drug.
- Insufficient patient compliance (defined as missing more than two doses of cetuximab). However, if in these cases the patient is proven to be free of progression after this period (by CT- or MRI-scan) the investigator may request that the patient be allowed to continue to receive cetuximab (in these cases the investigator should first consult with the central PI).

A 30-day mandatory safety follow up period was foreseen.

Reference therapy, dose and mode of administration, batch number:

N/A

Criteria for evaluation:

Efficacy:

- Clinical response rates per arm (confidence intervals) and assessments of progression for progression free survival
- Median times to progression and death
- Duration of response or disease control

- Post-treatment resections of secondary lesions; R0 resection rates; median times to progression and death in resected patients
- Disease status and survival in follow up at 3 years

Safety:

- All observed adverse events (rates per arm, severity, duration, etc)
- Serious adverse events
- Severe adverse events that did not meet the seriousness criteria
- Deaths
- Laboratory abnormalities (hematology and biochemistry)

Translational research:

Tumour tissue samples by biopsy at 3 timepoints in consenting patients (baseline mandatory, week 4 and progression optional): DNA extended mutation analyses (RAS, BRAF, etc), acquired mutations on serial biopsy samples; RNA: gene expression profiling SNPs, gene fusion identification, novel transcript discovery, single nucleotide variation discovery; other biomarker and tumour immune microenvironment research.

Blood samples at 6 timepoints: immunoprofiling for biomarker research and correlations with molecular features in serial tissue samples.

DISCUSSION

It was initially planned to include 375 subjects (130 in the escalation Arm A). Based on previous larger studies (CRYSTAL and EVEREST), it was estimated that the ratio of assigned patients between the two arms will be Arm A/Arm B=0.55. Due to slow accrual, the sample size was subsequently amended to 130 subjects (46 in Arm A). 108 patients were registered, only 8 had no skin tox at week 3 and received 350mg/m2 cetuximab weekly; of these, 3 patients were escalated to 500 mg/m2 of cetuximab weekly. The observed proportion of patients with no skin toxicity after 3 weeks of treatment was 7.4%, much lower than expected. This represented the main limitation of the trial. A PK component was attached to this study but due to the small number of patients in Arm A the analysis was not performed. No formal statistical comparison was foreseen, nor possible between arms. Main strength of the study remains the availability of serial tissue samples at different timepoints prior, during and after treatment, matched with blood samples. The correlation between molecular results and clinical outcomes will be analyzed and reported separately.

Median study treatment duration was 6.3 months for all patients (range 0.2-29.3 months), with 6.5% remaining on treatment for more than 2 years. All patients discontinued treatment: 53 for disease progression, 12 for toxicity (2 allergic reaction, 3 severe gastrointestinal reactions, 3 severe skin reactions, 1 fever, 1 adult respiratory distress syndrome, 1 fatigue/weight loss and 1 multi organ toxicity), 6 for death, 16 undertook surgery and stopped treatment for more than 12 weeks, 8 withdrew consent, for 9 it was patient best interest, 2 patients had a complete response, 1 patient was lost to follow up. One patient discontinued due to early study closure.

Clinical results are presented descriptively in the report, per arm.

Efficacy results:

Progression free survival rate at 9 months was 45% in the dose escalation group and 58% in the standard dose group. Due to the low number of patients in Arm A, no conclusion could be drawn. The observed point estimate in arm B was consistent with previous reports. Progression free survival median time was about 11 months (95% CI 8.1-13.6) in all patients and increased to 14 months (95% 11.3-17.9) in the 17 patients resected for metastatic lesions per protocol (not censored at surgery). Overall survival median time was 30 months (95% CI 22.4-33.3) in all patients and was not reached in the resected subgroup. No significant effects of explanatory variables such as gender, age, liver limited disease at baseline were observed in COX proportional analysis models on OS or PFS.

Response was locally assessed by investigators. Response rate was 75% (95% CI 35-97%) in patients receiving higher doses of cetuximab, for a median duration of response of 8.3 months (95%CI 3.6-24.2) and 69% (95%CI 58-78%) in patients at standard dose levels for a median duration of 11.7 months (95% CI 9.7-14.6). Disease control was observed in 85% (95% CI 77-91%) of all patients. For twenty patients, surgical resection of secondary lesions became feasible post treatment and 17 were operated as per conditions of

the protocol and were considered resected "on study". Thirteen (77%) of patients resected "on study" were deemed free of tumour post-resection.

Safety results:

Treatment induced toxicity was moderate and manageable; few dose reductions were due to expected toxicity. Most cases of serious adverse events were due to the basic disease. Most common adverse events grade 3 and higher were, as expected, diarrhea, vomiting, fatigue, thromboembolic events, neutropenia. There were one case of cardiac arrest and one case of acute kidney failure, not related to treatment.

Nine patients deceased during treatment and within 30 days from the date of their last cetuximab administration, for causes deemed not related to the investigational drug. All events were reported as SAEs. Although no cardiac 5-FU related toxicity was reported, one of these patients deceased with cardio-respiratory arrest occurring on pre-existing atrial fibrillation and relationship to 5-FU cannot be excluded. Another patient deceased with circulatory failure of unknown origin. The other seven fatalities were considered due to the basic disease or intercurrent conditions. Details are provided in document "Everest 2 Deaths during treatment and within 30 days from treatment stop".

The toxicity observed in the study was as expected in this disease and treatment setting, both in frequency (except of mild skin toxicity) and intensity. Mild skin reactions occurred at a higher rate than expected in the first three weeks of treatment which determined a very low arm allocation to the dose escalation arm. Severity of the cetuximab related skin reactions during the whole duration of treatment was within expected limits. Severe skin tox occurred in 32 patients. Some grade 1-2 infusion related reactions occurred and two anaphylactic events (one grade 2 and one with angioedema grade 4) were observed in Arm B.

No SUSAR report was issued. No major safety concern derived from the study and no changes to the safety documents or the patient information materials derived from the observed toxicity.

The benefit of this treatment combination is well documented from sponsor's previous experience with the drugs and from literature. Furthermore, several patients with liver metastases initially deemed unresectable were able to undertake surgery with curative intent after treatment due to tumour downsizing, with improved outcomes. The clinical risk-benefit relationship for the combination is regarded as favourable.

Translational research results:

Hypothesis generating molecular studies are ongoing, limited by the small sample size and possible interactions of effects due to multiple interventions.

CONCLUSIONS

The Everest 2 study could not demonstrate that dose escalation of cetuximab in patients without early skin toxicity is a feasible strategy, as most patients had skin reactions in the first three weeks.

Consistent assessments and grading of skin toxicity are challenging in multicentric settings, especially when influencing treatment decisions. This may explain the low proportion of patients assigned to the dose escalation arm.

FOLFIRI in combination with cetuximab at standard and escalated dose levels had an acceptable safety profile.

PFS median times were long and consistent with other trials.

Response rates were good. Secondary resections could be performed in a relatively high number of patients with initially unresectable disease.

Patient selection by tumour molecular characteristics is needed for maximal benefit. Translational studies are ongoing and results will be published shortly.

A full discussion on clinical and pathological findings will be published shortly.

Trial conducted with financial support and medication from Merck BV, Belgium, affiliate of Merck KGaA, Darmstadt, Germany. Trial registration: EudraCT 2009-009992-36; NCT01251536.

Date of the report: June-2019