Non-randomized Phase IV trial of Cetuximab plus FOLFIRI in first-line metastatic colorectal cancer receiving a pre-defined skin care to avoid acneiform follicular exanthema

Clinical Study Report

Author [redacted]

Document Status	Final Version 2.0
Date of final version of the study report	29-May-2018
EudraCT register number	2010-019885-10

1. Title Page

Study Title	Non-randomized Phase IV trial of Cetuximab plus FOLFIRI in first-line metastatic colorectal cancer receiving a pre-defined skin care to avoid acneiform follicular exanthema
Study Title German	*Nicht-randomisierte Phase IV-Studie zur Wirksamkeit von FOLFIRI in Kombination mit Cetuximab in der Erstlinienbehandlung des metastasierten kolorektalen Karzinoms unter Einsatz einer regelhaften Hautpflege / -prophylaxe zur Vermeidung des akneiformen follikulären Exanthems*
Short Title	*Dermatux*
Protocol Code	*Dermatux*
EudraCT No	*2010-019885-10*
Name of test drug/product	*FOLFIRI in combination with Cetuximab (Erbitux®)*
Comparator	*Not applicable*
Dosage	*Cetuximab: 400 mg/m2 initial dose, afterwards 250 mg/m2*
Indication	*Metastatic colorectal cancer*
Design	*Non-randomized, prospective, national, multicenter*
Development phase	*Phase IV*
Sponsor	*University of Mainz, Germany*
Coordinating investigator	[redacted]
Author of report	[redacted]
Study initiation date	*13-Jan-2011*
Study completion date	*09-Jul-2017 (end of long-term follow up – last patient last visit)*
Version and date of report	*Final Version 2.0 dated 29-May-2018*

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

2. Synopsis

<table>
<tr><td>Name of Sponsor/Company:
University of Mainz</td><td rowspan="3">Volume: 1
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Cetuximab (Erbitux®)</td></tr>
<tr><td>Name of Active Ingredient:
Chimeric, monoclonal IgG1-antibody</td></tr>
<tr><td colspan="3">Title of study:
Non-randomized Phase IV trial of Cetuximab plus FOLFIRI in first-line metastatic colorectal cancer receiving a pre-defined skin care to avoid acneiform follicular exanthema</td></tr>
<tr><td colspan="3">Coordinating investigator:
[redacted]</td></tr>
<tr><td colspan="3">Study center(s):
Twenty-four centers were initiated in Germany, fifteen centers enrolled at least 1 patient into the study.</td></tr>
<tr><td colspan="3">Publication (reference):
The study protocol was already published by Schimanski et al. J Cancer Res Clin Oncol 2017, published online DOI 10.1007/s00432-017-2344-3.</td></tr>
<tr><td colspan="2">Studied period (years): 2011-2017
(date of first enrolment): 13-Jan-2011
(date of last completed): 09-Jul-2017</td><td>Phase of development:
IV</td></tr>
<tr><td colspan="3">Objectives:
Primary objective:
• 1 year Progression-free survival (PFS) rate
Secondary objectives:
• Rate of acneiform follicular exanthema (rash) grade ≥2 (NCI CTCAE v3.0) during specific, standard of care skin prophylaxis
• Time to onset of acneiform follicular exanthema (rash) ≥ grade 2
• Incidence of paronychia
• Incidence of skin fissures (hand and foot)
• Objective Response rate (ORR) according to RECIST 1.1
• Rate of secondary resections of liver metastases with curative approach
• Progression-free survival (PFS)
• Overall survival (OS)
• Assessment of safety and tolerability</td></tr>
<tr><td colspan="3">Methodology:
The Dermatux study was a national, multicenter, prospective, phase IV, first line trial in patients with metastatic colorectal carcinoma (mCRC) undergoing treatment with irinotecan, folic acid, 5-fluorocil (FOLFIRI) and with cetuximab and receiving a pre-defined dermal prophylaxis including vitamin K1 ointment and oral doxycycline.</td></tr>
</table>

Name of Sponsor/Company: University of Mainz	**Volume:** 1 **Page:**	(For National Authority Use Only)
Name of Finished Product: Cetuximab (Erbitux®)		
Name of Active Ingredient: Chimeric, monoclonal IgG1-antibody		

Number of patients	**planned:** 165 **screened:** 55	**enrolled:** 55 54 patients were treated	**analyzed efficacy:** 54 **analyzed safety:** 54

Diagnosis and main criteria for inclusion:

- Histologically verified adenocarcinoma of the colon or rectum
- Confirmed K-RAS wild type status (primary tumor or metastasis)
- Confirmed epidermal growth factor receptor (EGFR) expression (primary tumor or metastasis)
- UICC (Union Internationale Contre le Cancer) stage 4
- Eastern Cooperative Oncology group (ECOG) performance status 0-1
- Eligible to receive FOLFIRI chemotherapy in combination with cetuximab
- Signed patient's informed consent
- Age ≥ 18 years
- Estimated life expectancy > 3 months
- At least 1 tumor lesion had to be measurable according to RECIST criteria V1.1, and evaluation of tumor burden was performed ≤ 4 weeks before study entry
- Effective contraception for men and women of childbearing potential, e.g. hormone pill, hormone spiral, depot injection, hormone-releasing intrauterine device, abstinence. The partner of a participating woman has to use a condom or has to be surgically sterilized.
- Leucocytes ≥ 3x109/L with neutrophils ≥ 1.5x109/L, thrombocytes ≥ 100x109/L, hemoglobin ≥ 5.6 mmol/L (9 g/dL)
- Bilirubin in serum ≤ 1.5x upper limit of normal (ULN)
- Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) ≤ 2.5x ULN, in case of liver metastases ≤ 5x ULN
- Creatinine in serum ≤ 1.5x ULN
- Any surgery and biopsy needed to have been completed at least 4 weeks and 1 week before study entry, respectively, and wounds needed to be completely healed
- Patients had to be recovered from clinically relevant toxicities of previous therapies

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

Cetuximab (Erbitux®)

400 mg/m2 initial dose, 250 mg/m2 qw, intravenous (iv) infusion

Irinotecan 180 mg/m2 iv (d1), folic acid (FA) 400 mg/m2 iv (d1), 5-fluorouracil (5-FU) 400 mg/m2 bolus infusion (d1), 5-FU 2,400 mg/m2 continuous infusion (d1-2)

Reconval K1® ointment face/décolleté/ - daily in the evening

Doxycyclin 100 mg tablet po – daily in the morning and in the evening

Duration of treatment:

Maximum treatment time was 12 months

Name of Sponsor/Company: University of Mainz	**Volume:** 1 **Page:**	(For National Authority Use Only)
Name of Finished Product: Cetuximab (Erbitux®)		
Name of Active Ingredient: Chimeric, monoclonal IgG1-antibody		

Reference therapy, dose and mode of administration, batch number:
Not applicable

Criteria for evaluation:

Primary endpoint

- PFS rate after 1 year with PFS defined as time between registration and disease progression or death due to any cause

Secondary endpoints:

Skin-related parameters

- Onset of an acneiform follicular exanthema ≥grade 2 while receiving pre-defined skin care
- Time to onset of an acneiform follicular exanthema ≥grade 2 (calculated from day of receipt of first cetuximab dose until first onset of specific symptoms)
- Onset of paronychia (each paronychia during treatment with cetuximab is counted as 1 event)
- Rate of cetuximab-mediated skin fissures

Efficacy parameters

- Objective response rate (complete response [CR] or partial response [PR])
- Progression-free survival
- Overall survival

Safety

- Safety profile

Sample size:

The required sample size to reach the primary objective was determined to detect an increase in the 1-year PFS rate from 25% (“historical control”; van Cutsem et al, 2009a) to at least 35% in the Dermatux population with a two-sided significance level of 5% and a power of at least 80%. To show this, data of 155 patients are necessary. To account for possible drop-outs, it was planned to enroll 165 patients.

Statistical methods:

In contrast to the planned analysis, no formal statistical test was performed for the primary objective, because the recruitment was stopped after 55 patients leading to a marked reduction of power to establish an increase from 25 to 35%. Therefore, analyses of all endpoints were performed only descriptively.

Categorical data were analyzed using specified frequencies and percentages in the form of contingency tables. Continuous data were displayed using number of non-missing observations, mean, standard deviation (SD), 95% confidence limits of the mean, median, minimum and maximum. OS and PFS were estimated using the Kaplan-Meier method.

No interim analysis was performed.

Safety Analyses:

Adverse Events (AEs) were recorded according to the NCI Common Terminology Criteria v.3.0.

Vital signs were not considered as AEs and were only included in the safety analysis if they were associated with an AE. Deviations in laboratory results had to be assessed by the investigator and in case they were judged as being clinically relevant a diagnosis and a severity grade was assigned and those were included in the safety analysis.

Treatment emergent AE (TEAEs) were analyzed during treatment and until 30 days after treatment end.

Name of Sponsor/Company: University of Mainz	**Volume:** 1 **Page:**	(For National Authority Use Only)
Name of Finished Product: Cetuximab (Erbitux®)		
Name of Active Ingredient: Chimeric, monoclonal IgG1-antibody		

Efficacy analyses:

Response was evaluated as assessed by the investigator.

Best response and ORR as well as resectability of liver metastases (potentially curative) were presented using frequencies and percentages. For PFS and OS, the number of events as well as Kaplan Meier median together with 95% CI were provided. For PFS, 1-year rate with 95% CI was calculated (according to Klein and Moeschberger, 1997).

Analysis populations:

Patients with a major protocol deviation (K-RAS mutation or K-RAS testing not performed, treatment at study entry ≥ 2nd line) or patients that did not receive any study medication were excluded from the statistical analyses. For those patients only case reports were done.

Modified Intent-to-treat (mITT) population: This population was the primary population for evaluating the primary endpoint and consisted of all patients without a major protocol deviation as listed above. The mITT population consisted of 54 patients.

Per-protocol population (PP): In a 2nd analysis ("according to protocol") the Per-protocol (PP) set was analyzed. The Per-protocol set consisted of all patients who had received at least at least 3 cycles of the planned combination therapy including pre-defined skin care (Reconval K1® ointment and Doxycycline, as well as Dermatop® ointment, if applicable) according to the protocol. Patients were also eligible if treatment had to be stopped prematurely (within the first 3 cycles) due to early progression (including early death).

Summary - Conclusions:

Efficacy results:

The primary endpoint of this study was the 1-year PFS rate in patients with metastatic CRC receiving a combination of cetuximab plus FOLFIRI together with a pre-defined skin care.

The endpoints progression-free survival, overall survival, objective response rate, and rate of acneiform exanthema, paronychia, skin fissures and resectability of liver metastases were all analyzed in the mITT population (n=54) as well as in the PP population (n=46).

Primary efficacy endpoint:

The 1-year PFS rate for the mITT population was 25.9% (95%-CI 15.3% to 43.9%). Twelve patients were censored within 1 year after registration. The PFS rate was comparable in the PP population with 27.3% (95%-CI 16.2% to 46.1%), and 7 patients were censored after within 1 year.

Secondary efficacy endpoint:

The objective response rate was 63% in the mITT population, analysis of patient's outcome revealed a CR in 5.6% of patients and a PR in 57.4% of patients. Stable disease (14.8%) and PD for best response was observed in 11.1% of patients. The descriptive analysis of patient's outcome in the subgroups of exanthema grade 0-2 vs exanthema grade 3-4 revealed no relevant differences in in CR and PR rates (6.5% vs 0.0% and 58.7% vs 50.0%, respectively), as well as in the overall response rate (65.2% vs 50.0%). However, the rate of patients with SD was increased in grade 3-4 vs grade 0-2 exanthema (37.5% vs 10.9%).

In the mITT population 45 patients had liver metastases at inclusion. No resection of these metastases during course of the study was performed in 38 patients (84.4%) out of those 45 patients. In 7 patients (15.6%) a planned resection of liver metastases with curative intent was the reason behind therapy withdrawal. Resection of liver metastases was documented in 4 patients (8.9%).

The median PFS in the mITT population was 8.48 months (95%-CI 7.72 to 11.24 months). The grade of the exanthema had minor impact on PFS. Descriptive analysis of the median PFS revealed 8.6 months in patients with a grade 0-2 exanthema compared to 8.2 months in patients with a grade 3-4 exanthema.

Name of Sponsor/Company: University of Mainz	**Volume:** 1 **Page:**	(For National Authority Use Only)
Name of Finished Product: Cetuximab (Erbitux®)		
Name of Active Ingredient: Chimeric, monoclonal IgG1-antibody		

The median OS in the mITT population was 26.22 months (95%-CI 18.56 to 41.82 months). When considering OS related to the severity grade of the exanthema patients with a grade 2 exanthema survived for a median of 38.0 months, patients with an exanthema grade 3 survived for a median of 29.7 months, and patients with an exanthema grade 1 or no exanthema survived for a median of 24.3 months and 7.6 months, respectively.

An exploratory cox regression analysis was performed for OS focusing on several known prognostic markers. For ECOG performance status (ECOG 1 vs 0: HR=2.68, p=0.007), response to first-line therapy (No response vs response: HR=3.36, p=0.002) and liver limited disease (Not liver limited vs liver limited: HR=2.26, p=0.029) a relation to OS could be seen, while higher grade acneiform rash and CEA level did not show a trend towards better OS.

Data in the PP population for all parameters analyzed were similar to those observed in the mITT population.

Secondary endpoints: Skin-related parameters:

An acneiform follicular exanthema ≥grade 2 was observed in 23 patients (42.6%) out of 54 patients and the median duration until an exanthema was observed was 4.0 weeks in those 23 patients. The median time was longer in females compared to males (5.4 weeks vs 3.9 weeks).

A paronychia ≥grade 2 was observed in 12 patients (22.2%) out of 54 patients and the median duration until a paronychia ≥grade 2 was observed was 15.4 weeks in those 12 patients. The median time was longer in females compared to males (20.9 weeks vs 13.8 weeks).

Skin fissures ≥grade 2 were observed in 17 patients (31.5%) out of 54 patients. The median duration until skin fissures ≥grade 2 were observed was 19.9 weeks in those 17 patients. The median time was longer in females compared to male patients (23.4 weeks vs 14.9 weeks).

Safety results:

Exposure:

Patients received systemic therapy (cetuximab plus FOLFIRI) for a median duration of 20.5 weeks (or a median of 10 cycles). Skin prophylaxis was administered for a median of 139 days (19.86 weeks). Doxycycline was given for a median of 126 days (18.0 weeks), and Reconval K1® ointment was given for a median of 139 days (19.86 weeks).

Adverse events and NCI-CTCAE toxicities:

Overall, 54 patients (100.0%) experienced a total of 628 TEAEs after treatment with cetuximab and chemotherapy in this study. Of all 628 AEs, 509 AEs reported by 51 patients (94.4%) were graded as mild to moderate (grade 1-2), and 107 AEs occurring in 40 patients (74.1%) as severe to life-threatening or disabling (grade 3-4). Of all TEAEs 395 TEAEs in 53 patients (98.1%) were related to treatment with cetuximab and chemotherapy (any drug). From those, 344 related TEAEs in 50 patients (92.6%) were grade 1-2 and 48 related TEAEs in 27 patients (50.0%) were grade 3-4. None of the skin or subcutaneous tissue related disorders reported were grade 4.

167 TEAEs (27.2%) were related to irinotecan, 146 TEAEs (23.7%) were related to 5-FU, 34 TEAEs (5.5%) were related to folic acid, and 213 TEAEs (34.6%) were related to cetuximab.

There were 6 fatal TEAEs reported for 5 patients (9.3%). In total, 53 serious TEAEs (8.4%) occurred in 28 patients (51.9%). Eleven serious TEAEs in 7 patients (13.0%) were related to treatment with cetuximab and FOLFIRI. No SUSAR (suspected unexpected serious adverse reaction) or treatment-related deaths occurred in the study.

In general, the observed AE profile was typical for a combination therapy in patients with mCRC. There were 84 TEAEs leading to any treatment modification in this study, however, more TEAE led to modification of the chemotherapeutic agents (10.4% to 10.6% of all TEAEs) than to modification of cetuximab (8.5% of all AEs). Nine patients (16.6%) discontinued anti-EGFR treatment due to TEAE, 3 patients had to stop anti-EGFR treatment prematurely due to toxicity of cetuximab. Treatment of skin toxicities was necessary in 32 patients (59.3%).

Name of Sponsor/Company: University of Mainz	**Volume:** 1 **Page:**	(For National Authority Use Only)
Name of Finished Product: Cetuximab (Erbitux®)		
Name of Active Ingredient: Chimeric, monoclonal IgG1-antibody		

Other observations related to safety:

Some laboratory parameters, e.g. ALAT, ASAT and creatinine decreased slightly, and erythrocytes, leucocytes, thrombocytes, and neutrophils dropped throughout the study. In a few patients changes in hematological parameters could be observed that were assessed as being of clinical relevance and/or were at least CTC grade 3. Electrolytes remained stable and PTT increased. CEA and CA 19-9 concentrations decreased markedly during the course of the study. There were no obvious changes in other safety related parameters throughout the study, however, the ECOG performance status worsened in some patients but there were too many data missing towards the end of the study to draw general conclusions.

Conclusion:

Taken together, this was the first study reporting on different skin toxicities of cetuximab in detail. Although the study failed to reach its primary endpoint due to continuous slow recruitment rates together with increased dermal prophylaxis the use of pre-defined skin care pointed towards positive effects on skin toxicities in these patients. The data related to the secondary endpoints provided important insights, which will affect the treatment of patients with mCRC receiving cetuximab plus chemotherapy. Further randomized studies are warranted to confirm the findings presented here and to measure effects of the prophylactic vitamin K1-based skin treatment protocol on quality of life and effectiveness.

Date of report: 29-May-2018