2. Synopsis

<table>
<tr><td>Name of Sponsor/Company:

University of Heidelberg (Irmtraut Gürkan)</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier:

Volume:

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:

Hautveränderungen bei Patienten mit Kopf- und Halstumor unter kombinierter RadioImmuno-(chemo)-therapie mit Erbitux®

(Skin Changes in Head and Neck Cancer during Immuno-(Chemo-) and Radiotherapy with Erbitux®)

This clinical study report (CSR) is based on the final study protocol V2.0 dated 17-Jan-2011. There were no amendments to the protocol. The final study protocol was approved by the ethics committee (EC) and relevant competent authority (CA) on the dates shown in Table 2.1 below.</td></tr>
<tr><td colspan="3">Coordinating investigator:

Prof. Dr. Dr Jürgen Debus, Heidelberg, Germany</td></tr>
<tr><td colspan="3">Study center(s):

Forty centers in Germany (planned); 31 centers initiated; 20 centers enrolled patients.

Study centers are listed in Table 2.2 below.</td></tr>
<tr><td colspan="3">Publication (reference):

The study protocol was already published by Habl et al. BMC Cancer 2013, 13:345.</td></tr>
<tr><td colspan="2">Studied period (years):

(date of first enrolment): 14-Jun-2011

(date of last completed): 04-Nov-2015

Recruitment was stopped prematurely in July 2015. Due to persistently slow recruitment and increasing application of skin prophylaxis for patients undergoing radioimmunotherapy in the clinical routine, the expected planned number of patients could not be reached.</td><td>Phase of development:

IV</td></tr>
<tr><td colspan="3">Objectives:
Primary objective:
• Rate of radiation dermatitis Grade 3/4
Severity graded by the National Cancer Institute, Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.02</td></tr>
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Secondary objectives:

- Rate of radiation dermatitis Grade 1/2
- Rate of cetuximab-mediated acneiform rash Grade 1-4
- Rate of cetuximab-mediated rhagades Grade 1-4
- Rate of cetuximab-mediated nail changes Grade 1-4
- Objective response rate (ORR)
- Locoregional control (LRC)
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety profile
- Median dose density of radiation
- Safety profile of applied radiation protocol
- Quality of life (QoL)

Methodology:

The HICARE study is a national, multicenter, prospective phase IV study exploring the different types of skin reaction that occur in patients with locally advanced squamous cell carcinoma of head and neck (LASCCHN) undergoing radioimmuno(chemo)therapy with the Epithelial Growth Factor Receptor (EGFR) inhibitor cetuximab.

Number of patients	**planned**: 500 **screened**: 161	**enrolled**: 160 **completed**: 100	**analyzed efficacy**: 140 **analyzed safety**: 154

Diagnosis and main criteria for inclusion:

- Histological confirmed, locally advanced (stage III, IVA or IVB), non-metastatic squamous-cell carcinoma of the oral cavity, oro- or hypopharynx and larynx.
- Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 2
- ≥ 18 years of age
- Life expectancy of at least 6 months
- Adequate bone marrow, liver and renal function (according to Summary of Product Characteristics [SmPC] of cetuximab) based on laboratory assessments raised within 7 days prior to start of study treatment.
- Dated and signed informed consent before the start of specific protocol procedures
- Women of childbearing potential must have had a negative serum or urine beta-HCG pregnancy test within 7 days prior to the first administration of study treatment or must have a documented condition that prohibits pregnancy (e.g. post-menopausal, hysterectomy)
- Patients enrolled in this trial must be willing to use effective birth control measures during the course of the trial and the subsequent 2 months

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

Cetuximab (Erbitux®)

400 mg/m^2 initial dose, 250 mg/m^2 weekly for 6 to 7 weeks, intravenous (iv) infusion

Fractionated Radiotherapy (3D-conventional or IMRT) combined with cetuximab (Erbitux®): Total duration of treatment was 7 to 8 weeks corresponding to 30 to 35 fractions of RT

Duration of treatment:

7 to 8 weeks (including loading dose cetuximab)

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

Not applicable

Criteria for evaluation:

Primary endpoint

- Rate of radiation dermatitis NCI CTCAE grade 3 and 4 (v 4.02)

Secondary endpoints:

Skin-related parameters

- Rate of radiation dermatitis grade 1 and 2
- Rate of cetuximab-induced acneiform rash grade 1 to 4
- Rate of cetuximab-induced rhagades (all grades)
- Rate of cetuximab-mediated nail changes (all grades)

Efficacy parameters

- Objective response rate
- Locoregional control rate
- Progression-free survival
- Overall survival

Safety

- Safety profile
- Median dose density of radiation
- Safety profile of applied radiation protocol
- Quality of Life

Statistical methods:

All data were analyzed descriptively. Categorical data were analyzed using specified

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frequencies and percentages in the form of contingency tables. Continuous data were displayed using number of non-missing observations, average, standard deviation (SD), median, quartiles, minimum and maximum.

Safety Analyses: Determination of the primary variable, the rate of radiodermatitis grade 3 and 4, was performed based on the highest CTCAE severity grade during the collection period as assessed by the investigator (start of RT until the end of follow up 55 to 65 days after the last RT dose). This rate was reported together with the 95% confidence interval [CI]. In addition, the rate of radiodermatitis grade 3 and 4 was stratified by expression of acneiform rash (grade 0/1 versus grade 2 to 4) and subgroups were compared.

Efficacy analyses:

Response was evaluated as assessed by the investigator. Frequencies and percentages were calculated for response, locoregional control and metastasis-free survival at final visit (55 to 65 days after last radiotherapy) and first follow-up visit. Furthermore frequencies and percentages were presented for the best response and the objective response rate (i.e. percentage of patients with partial or complete remission for best response).

Determination of event times (progression-free, disease-specific and overall survival) was done according to non parametric Kaplan-Meier method. Number of events, quartiles and 12 month rates were displayed together with 95% CIs (calculated according to Klein and Moeschberger).

Analysis populations:

Modified Intent-to-treat (mITT) population: This was the primary population for evaluating all efficacy endpoints as well as patient characteristics. The mITT population consisted of 140 patients since patients that had an R0 resection prior to study treatment and patients that did not receive any cetuximab- or radiotherapy were excluded from the efficacy analysis.

Safety population (SAF): The safety population consisted of all patients who received at least 1 dose of study medication cetuximab and at least 1 fraction of radiotherapy. This population was the primary population for evaluating the rate of radiodermatitis, and the general safety profile.

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Summary - Conclusions:
Efficacy results:

Baseline characteristics: The study population consisted of a significantly higher number of male patients compared with female patients. Patients had a median age of 63.8 (SAF) and 66.2 (mITT) years and the majority of patients had no induction chemotherapy (93.5% and 94.3%, respectively). Most patients had undergone no surgeries (84.4%; 92.1%). The most affected site of the primary tumor was the oropharynx (in 107 and 101 patients), followed by hypopharynx (in 45 and 41 patients), larynx (in 18 and 15 patients), oral cavity (in 12 and 10 patients), and others. The time from primary diagnosis to date of consent was very variable (0.1 to 25.8 months).

Primary efficacy:

Not applicable

Secondary efficacy:

The median duration of PFS was 15.4 months and 47.9% of patients were free of signs of disease progression at the end of the observation period (median observation period was 20.0 months, 95%CI 15.4 months – 26.0 months). A total of 68.6% of patients were still alive at the individual study termination with a 12-month OS rate of 80.2%. Locoregional control, as reported by the investigators, was achieved in 76.4% of patients at the final visit (55 to 65 days after last radiotherapy, median time until final visit = 3.5 months) and in 47.9% at the 1st follow-up visit (median time until 1st FU = 9.4 months). A total of 78.6% of patients were alive and free of distant metastases at the final visit (55 to 65 days after last radiotherapy, median time until final visit = 3.5 months), this rate decreased to 53.6% at the 1st follow-up visit (median time until 1st FU = 9.4 months).

Safety results:

Exposure: The total dose of cetuximab administered to 154 patients ranged from 395.0 to 2661.1 mg/m^2 with a median of 1906.1 mg/m^2. Patients received cetuximab therapy for a median duration of 7.5 weeks ranging from 1.0 to 10.3 weeks.

Radiotherapy: The vast majority of patients received 1 fraction per day and a concomitant boost. A total dose of ≤ 72 Gy (median total dose of RT=69.8 Gy, range of 28 Gy to 78 Gy) was administered in 86% of patients.

Adverse events and NCI-CTCAE toxicities: Overall, 153 patients (99.4%) experienced a total of 1133 adverse events (AEs) during treatment with cetuximab and radiotherapy in this study. Of all 1133 AEs, 278 AEs occurring in 121 patients (78.6%) were graded as severe to life-threatening or disabling (grade 3-4), and 10 AEs reported in 9 patients (5.8%) were death-related (grade 5). Of the cetuximab-related AEs 172 AEs occurring

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in 97 patients (63.0%) were grade 3-4, and 2 AEs reported for 2 patients were grade 5. Of the radiotherapy-related AEs 189 AEs occurring in 107 patients (69.5%) were grade 3-4, and 1 AE reported for 1 patient was grade 5.

A total of 135 patients experienced a radiation dermatitis (all grades) in this study whereas 141 patients experienced a cetuximab-induced acneiform rash (all grades). Radiation dermatitis of grade 3/4 was seen in 56 patients (36.0%).

A total of 104 serious TEAEs were reported in 54 out of 154 patients (35.1%), of whom 33 patients (21.4%) reported cetuximab-related SAEs (n=47) and 30 patients (19.5%) reported radiotherapy-related SAEs (n=45)

Other observations related to safety: There were no obvious changes in global health status, hemoglobin values (median level at screening was 8.0 mmol/L, range 2.9 mmol/L – 10.6 mmol/L) and other safety related parameters (quantitative variables) throughout the study.

Conclusion:

The type and frequency of AEs reported by patients in this trial were consistent with the safety profile observed in other clinical trials investigating treatment with radioimmunotherapy [7, 8, 10]. Adverse events associated with treatment were manageable, and infrequently required discontinuation of therapy (14 out of 154 patients, 9.1%).

Efficacy data in this trial were comparable with the data in the phase III trial conducted by Bonner et al. Subgroup stratification by Hb-level revealed a pronounced impact on all endpoints. A higher Hb level at study entry positively influenced the outcome of all endpoints analyzed.

To gain further information and to make even better recommendations regarding treatment options a substudy will be performed with samples collected in this study to identify and evaluate biomarkers and surrogates correlating with clinical efficacy and outcome.

Date of report: 28-Oct-2016