Study Code: LEOPARD-II
EudraCT No.: 2010-023427-18

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Clinical Study Report

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DEFINITIVE RADIOCHEMOTHERAPY WITH 5-FU / CISPLATIN PLUS/MINUS CETUXIMAB IN UNRESECTABLE LOCALLY ADVANCED ESOPHAGEAL CANCER: A PHASE II STUDY

Study code:	LEOPARD-II
EudraCT:	2010-023427-18
Short title:	NA
Investigational substance:	Cetuximab
Reference substance:	Radiochemotherapy with 5-fluorouracil and cisplatin
Indication:	Unresectable esophageal cancer
Study phase:	II
Inclusion of first patient:	Sep09, 2011
End of treatment of last patient:	Dec08, 2016
Date of final report:	Feb20, 2019

Sponsor:
University Hospital Schleswig-Holstein
Campus Lübeck
Ratzeburger Allee 160
23538 Lübeck
Germany

Monitoring:
GSO mbH
Mittelweg 110
20149 Hamburg
Germany

Coordinating investigator:
Prof. Dr. Dirk Rades
University Hospital Schleswig-Holstein
Campus Lübeck
Department of Radiation Oncology
Ratzeburger Allee 160
23538 Lübeck
Germany

Study sites:
Universitätsklinikum Schleswig-Holstein, Lübeck, Germany
Klinikum der Universität München, Munich, Germany
Universitätsklinikum Heidelberg, Heidelberg, Germany
Klinikum der Stadt Wolfsburg, Wolfsburg, Germany
Universitätsklinikum Leipzig, Leipzig, Germany
Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany
Universitätsklinikum Hamburg-Eppendorf (UKE), Hamburg, Germany
Universitätsklinikum Tübingen (UKT), Tübingen, Germany
Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
Krankenhaus Dresden Friedrichstadt, Dresden, Germany
Klinikum Stuttgart – Katharinenhospital (KH), Stuttgart, Germany
Klinikum Magdeburg gemeinnützige GmbH, Magdeburg, Germany

GCP statement: This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.
Confidentiality statement: The information provided in this document is strictly confidential.

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Signatures

Title of the trial: DEFINITIVE RADIOCHEMOTHERAPY WITH 5-FU / CISPLATIN PLUS/MINUS CETUXIMAB IN UNRESECTABLE LOCALLY ADVANCED ESOPHAGEAL CANCER: A PHASE II STUDY

Trial substance: Cetuximab, 5-fluorouracil, cisplatin, radiation

Trial code: LEOPARD-II

The undersigned 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.

Sponsor Representative / Coordinating investigator / LKP in accordance with §40 AMG (German Drug Law):

15-04-2019
Date

Prof. Dr. Dirk Rades

GSO Representative:

16042019
Date

Dr. Anne L. Kranich

1   SYNOPSIS

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Trial title:

Definitive radiochemotherapy with 5-FU / cisplatin plus/minus cetuximab in unresectable locally advanced esophageal cancer

Study centres:

For a list of study sites, please refer to Appendix 16.1.4.

Trial duration: Inclusion of first patient: Sep09, 2011 End of treatment of last patient: Dec08, 2016	**Phase of development:** Phase II

Methodology:

Open-label, randomised, phase II study

Trial objectives:

The primary trial objective was to assess 2-year overall survival (OS) in patients treated with cetuximab plus radiochemotherapy compared to the 2-year OS in patients treated with radiochemotherapy alone. The experimental treatment would be rated active, i.e. worthy for further investigation, if the 2-year OS rate is found above 40%.

The secondary objectives were to compare the following parameters:

- 1-year OS
- 1-year and 2-year progression-free survival (PFS)
- 1-year and 2-year loco regional control (LC)
- 1-year and 2-year metastatic-free survival (MFS)
- Toxicity (NCI-CTCAE v4.0)
- Overall response rate (RECIST v1.1)
- Quality of Life (EORTC QLQ-C30 and QLQ-OES18)

In addition, the following parameters were to be assessed irrespective of a specific time point:

- OS
- PFS
- LC
- MFS

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Number of patients:

Initially planned: 134 patients – Due to the good experiences with respect to safety, the unexpectedly big difference in overall survival between the treatment arms after the last interim analysis on Jan29, 2016 and the slow recruitment, the study was terminated prematurely after randomisation of 74 patients.

Included in the final evaluation:

Number of patients	**Total**
Recruited	74
Evaluable regarding toxicity	68
Evaluable regarding efficacy	68

Diagnosis and key inclusion and exclusion criteria:

Inclusion criteria:

- Signed written informed consent

- Male or female between 18 and 75 years; patients > 75 years if KPS ≥ 80

- Histologically proven squamous cell carcinoma or adenocarcinoma of the esophagus, which is not curatively resectable*

*resectability has to be defined and documented by a surgeon prior to randomisation:
The tumor is considered unresectable due to:
T-stage, N-stage, performance status/nutritional status, co-morbidity (pulmonary function, other), tumor location upper third of the esophagus, relation to other organs/structures), other reasons.

- KPS ≥ 70

- Women of child-bearing potential had to have a negative pregnancy test

- Adequate cardiac, pulmonary, and ear function

- Adequate bone marrow function: leucocytes $\geq 3.0 \times 10^9$/L, neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, haemoglobin ≥ 10.0 g/dL

- Adequate liver function: Bilirubin ≤ 2.0 mg/dL, SGOT, SGPT, AP, γ-GT ≤ 3 x ULN

- Adequate renal function: serum creatinine ≤ 1.5 mg/dL, creatinine clearance ≥ 50 ml/min (calculated value according to Cockcroft-Gault equation)

- No known allergy against chimeric antibodies

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- Effective contraception for both male and female patients if the risk of conception existed

Exclusion criteria:

- Distant metastasis (M1b)
- Previous treatment of esophageal cancer
- Previous exposure to monoclonal antibodies and / or EGFR-targeted therapy
- Other previous malignancy with exception of a history of a previous curatively treated basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix
- Serious concomitant disease or medical condition
- $FEV_1 < 1.1$
- Clinically relevant coronary artery disease or a history of myocardial infarction within the last 12 months or left ventricular ejection fraction (LVEF) below the institutional range of normal
- Any active dermatological condition > Grade 1
- Contraindications to receive cisplatin, 5-FU or cetuximab
- Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to study screening
- Pregnancy or lactation
- Known active drug abuse/alcohol abuse
- Social situations limiting the compliance with the study requirements

Treatment duration:

The planned treatment duration per patient was 14 weeks.

The planned duration of radio-immuno-chemotherapy or radio-chemotherapy was 6.5 to 7 weeks.

Patients were withdrawn at any time during the study if they developed unacceptable toxicities or if they withdrew the consent to participate in the trial.

Ongoing adverse events related to study treatment were followed for 6 weeks (skin toxicities until outcome was known) after end of treatment.

Trial medication, dose and method of administration:

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Cetuximab: Supplied in single-use, ready-to-use vials, containing 5 mg/ml cetuximab, with a nominal fill volume of 50 mL (250 mg/50 mL).

Treatment Arm A (Radiochemotherapy + cetuximab):

- Cetuximab: Initial dose of 400 mg/m^2 (day 1), followed by weekly doses of 250 mg/m^2 for a total of 14 weeks, administered as intravenous infusion.
- 5-FU: 1000 mg/m^2/day administered as a continuous infusion on days 8-11 and 36-39 750 mg/m^2/day administered as a continuous infusion on days 71-74 and 99-102
- Cisplatin: 20 mg/m^2/day, administered as an intravenous bolus over 60 minutes on days 1-4 of each cycle (i.e. on days 8-11, 36-39, 71-74 and 99-102)
- Radiotherapy: 59.4 Gy (33 fractions of 1.8 Gy) were to be administered over 6.5-7 weeks (5 x 1.8 Gy per week) to the primary tumour and the involved lymph nodes. 50.4 Gy were to be administered to the loco-regional lymph nodes. If resectability had been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy was to be stopped at 45 Gy and patient would undergo surgery.

Treatment Arm B (Radiochemotherapy):

- 5-FU: 1000 mg/m^2/day administered as a continuous infusion on days 1-4 and 29-32 750 mg/m^2/day administered as a continuous infusion on days 64-67 and 92-95
- Cisplatin: 20 mg/m^2/day, administered as an intravenous bolus over 60 minutes on days 1-4 of each cycle (i.e. on days 1-4, 29-32, 64-67 and 92-95)
- Radiotherapy: 59.4 Gy (33 fractions of 1.8 Gy) were to be administered over 6.5-7 weeks (5 x 1.8 Gy per week) to the primary tumour and the involved lymph nodes. 50.4 Gy were to be administered to the loco-regional lymph nodes. If resectability had been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy was to be stopped at 45 Gy and patient would undergo surgery.

Evaluation criteria:

Primary endpoint:

- 2-year OS

Secondary endpoints:

- 1-year OS

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- 1-year and 2-year PFS
- 1-year and 2-year LC
- 1-year and 2-year MFS
- Overall response rate
- Toxicity (NCI-CTCAE v4.0)
- Quality of Life scores (EORTC QLQ-C30 and QLQ-OES18)

Statistical methods:

Treatment outcome:

The primary efficacy endpoint, 2-year OS, was analysed as the rate of patients alive at 2 years and compared to a pre-defined threshold proportion of 40% within each treatment arm, with a planned type I error level of 5%. No direct comparison between the arms had been planned for 2-year OS. The estimates for the 2-year OS rate were based on Kaplan-Meier methodology (KM)

The secondary endpoint OS (defined as time from randomisation until date of death or date last known to be alive in censored cases) was analysed using the Kaplan-Meier method (KM) and the univariate Cox proportional hazard method, where time to event/censoring was calculated as event/censoring date – randomisation date + 1. For OS the date of death was used as the event date. Additionally, number of events, median survival time based on KM analysis and an exploratory log-rank test comparing the two treatment arms were applied. Exploratory test results were considered significant if $p < 0.05$. The hazard ratio for treatment group comparison was calculated with the univariate Cox proportional hazard models.

The same methods and summaries as with the secondary efficacy endpoint OS were used for PFS, LC and MFS.

For PFS the event date was defined as the date of either radiologically proven progression, clinical progress or death due to progressive disease using the first occurrence of any of these. If the patient was still progression-free at the end of the follow-up or at time of death, the patient was censored at the last follow-up date (known to be alive).

For LC the event date was defined as the date of first finding on endoscopy, endoscopic ultrasound or computed tomography, of progressive primary tumour and/or regional lymph nodes. For MFS the event date was defined as the date of first occurrence of distant metastasis incl. distant lymph nodes. For both LC and MFS, patients with no events were censored at the last follow-up date (known to be alive).

The best overall response according to RECIST 1.1 was chosen for each patient out of all visits. Frequencies with percentages were presented for each category (CR, PR, SD, PD) by

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treatment group. The difference between the treatments in incidence of responders was compared with a Chi-square test.

All tests except for the primary endpoint analysis were exploratory.

OS was evaluated with the KM-method and FM curves for subgroups defined by the following prognostic factors: age (≤ 60 vs. > 60 years), Karnofsky performance status (100- 80% vs. 70%), tumour location (upper third vs. middle third vs. lower third), histology (squamous cell carcinoma vs. adenocarcinoma), histologic grade (G1-2 vs. G3), T-stage (T2-3 vs. T4, according to endoscopic ultrasound and CT), N-stage (N0 vs. N+), and haemoglobin before radiotherapy (< 12 vs. 12-14 vs. > 14 g/dl). Differences between the KM curves were evaluated with exploratory log-rank tests. Additionally, potential prognostic factors found to be in a univariate analysis were to be evaluated in a multivariable analysis together with treatment effect, performed with a Cox proportional hazard model.

Toxicity:

All adverse events occurring after signature of informed consent until the end of study were tabulated using NCI-CTCAE v4.0 by CTC category and AE Term as event and patient counts with percentage of patients within the group. P-Values were calculated for all and severe AE terms/CTC categories more common than 5% in either of the groups with the Fisher's exact test.

Interim analysis: Three interim analyses have been performed during the course of the trial:

1. Sep20, 2013: Twenty patients were analysed in the interim analysis (9 patients in Arm A, 11 patients in Arm B). Patients treated with cetuximab + radiochemotherapy showed a trend towards a higher response rate compared to patients treated with radiochemotherapy only (p=0.051). The objective response rate (ORR) in Arm A was 67% (95% CI [30-90]) compared to 27% in Arm B (95% CI [8-61]). No significant difference in overall survival (OS) until this point of time was observed and no analysis of 2-year OS rate was included. The median OS was 10.2 months in arm A (95% CI [7, 6]) and 11.7 months in arm B (95% CI [3, 6]) with a mean follow-up of 7.8 months and range of those surviving 3.3 to 19.5 months. The 1-year survival rate was 44% in Arm A and 35% in Arm B.

   In general, treatment was well tolerated and most adverse events (AEs) were of mild to moderate intensity. The most frequently observed AEs were gastrointestinal disorders, skin and subcutaneous tissue disorders and impaired haematological, liver and renal parameters.

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2. Mar06, 2015 (safety analysis): Safety results were similar to those in the first interim analysis. 46 out of 49 patients had experienced at least one AE. Most AEs were of a gastrointestinal nature. The most frequent AE was nausea (45% of patients in Arm A and 58% of patients in Arm B), followed by esophagitis (30% and 31%), dysphagia (22% and 35%), constipation (17% and 31%), diarrhea (30% and 15%), and vomiting (13% and 23%). Other frequently observed AEs included leukopenia (52% and 27%), thrombocytopenia (22% and 23%), fatigue (27% and 58%), hypokalemia (43% and 35%), hypomagnesemia (43% and 12%) and anemia (39% and 35%). As expected, acneiform rash occurred only in Arm A (39%).

    A total of 76 SAEs were reported until the date of the report. Three of them resulted in death. 7 SAEs were considered related to cetuximab, 10 to background radiation therapy, 42 to background chemotherapy, 7 to the underlying disease, and 4 to pre-existing conditions. Otherwise, the possible causes of the SAEs were unknown or "other".

3. Jan29, 2016: 69 patients had been included in the study at this date (32 patients in Arm A, 37 patients in Arm B). Of these 69 patients, information regarding surgery was available for 57 patients. Out of these, 3 patients were screening failures and 2 patients had withdrawn consent. Out of the remaining 52 patients, 32 patients (62%) did not undergo surgery (16 patients in each arm). Surgery after re-evaluation (after cycle 2) was performed in 19 patients (37%) and one patient (2%) underwent surgery after completion of 4 cycles.

    The other 17 patients either were still on treatment at the time of the interim analysis or no information regarding surgery was available.

    Sixty patients were included in the safety analysis. Thereof, 58 patients experienced at least one AE. 26% of the total AEs were Grade 3-5. Similar to the previous interim analyses many AEs were of a metabolic or nutritional nature (74% in Arm A and 71% in Arm B) or gastrointestinal nature (71% in Arm A and 63% in Arm B). At the date of the analysis a total of 109 SAEs had been reported in 42 patients. Six of them resulted in death. 9 SAEs were considered related to cetuximab, 13 to background radiation therapy, 56 to background chemotherapy, 15 to the underlying disease and 4 to pre-existing conditions. Otherwise, the possible causes of the SAEs were unknown or "other".

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Summary:

Demographic data and baseline data:

Six of the 74 patients randomised never received protocol treatment (1 withdrawn consent, 3 exclusion criterion failures, 1 investigator decision and for 1 patient, no data were available). Demographic data and baseline characteristics were analysed from the 68 patients evaluable for safety and efficacy. Fifty-two patients (22 patients [68.8%] in Arm A and 30 patients [83.3%]) in Arm B) were male. 16 patients (10 patients [31.3%] in Arm A and 6 patients [16.7%] in Arm B) were female. The median age was 65 years (Arm A: 65 years, Arm B: 64 years) ranging from 44 to 80 years. All patients were Caucasian.

Fifty-five patients (80.9%) had a squamous cell carcinoma, 13 patients (19.1%) had an adenocarcinoma. The majority of patients had a tumour of grade 2 (34 patients, 50.0%) and grade 3 (21 patients, 30.9%) with a similar distribution in both treatment arms.
The major T-stage was T3 (40 patients, 58.8%), the major N-stage was N1 (28 patients, 41.2%). Almost all patients had an M-stage of 0 (66 patients, 97.1%), one patient had M1a-stage disease (Arm B) and one patient had Mx-stage disease (Arm A).

The main reasons for unresectability were T-stage (26 patients, 52.9%) and N-stage (27 patients, 39.7%, [multiple answers possible]). In 14 patients (20.6%) the tumour was considered unresectable owing to the tumour location in the upper third of the esophagus.

19 patients (27.9%) had a Karnofsky Performance Status of 100% at screening, 32 patients (47.1%) of 90%, 14 patients (20.6%) of 80%, and 3 patients (4.4%) of 70%.

Efficacy results:

Efficacy endpoints:

The primary endpoint of 2-year OS was 71% in Arm A (95% CI: 55%; 87%) and 53% in Arm B (95% CI: 36%; 71%) based on Kaplan-Meier estimation. Since the two-sided 95% Kaplan-Meier-CI for the 2-year OS rate in Arm A excludes the 40% rate of the null hypothesis, the null hypothesis could be rejected and the combination of cetuximab plus standard radiochemotherapy can be considered a promising treatment.

The median overall survival was 49.1 months in Arm A and 24.1 months in Arm B (total median OS: 38.37 months). The exploratory log-rank test comparing the two treatment groups did not detect a significant difference in OS with p-value of p=0.1470. The 1-year OS rate was 74% in Arm A (95% CI: 59%; 90%) and 70% in Arm B (95% CI: 54%; 86%). The hazard ratio for

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cetuximab vs. standard therapy was 0.60 (95% CI: 0.30; 1.21). The results showed a consistent, but not statistically significant trend to improved survival with the addition of cetuximab to the regimen.

Analysis of PFS, LC and MFS also tended to an advantage of cetuximab plus standard radiochemotherapy over standard radiochemotherapy alone. The hazard ratios were in favour for cetuximab treatment for all parameters – OS: 0.60 (95% CI 0.30-1.21); PFS: 0.51 (95% CI 0.25-1.04); LC: 0.43 (95% CI 0.13-1.40); MFS: 0.43 (95% CI 0.17-1.05) – but were not significant.

The median PFS was 17.6 months in Arm B and 27.2 months in the overall population. In Arm A, the median PFS was not reached. The log-rank test's p-value for the difference between the treatment groups was 0.0600. The 2-year PFS rate was 56% (95% CI: 37%; 75%) in Arm A and 44% (95% CI: 26%; 62%) in Arm B. The 1-year PFS rate was 64% (95% CI: 47%; 82%) in Arm A and 58% (95% CI: 40%; 75%) in Arm B. The hazard ratio for cetuximab vs. standard therapy was 0.51 (95% CI 0.25-1.04).

The median LC time was not reached in any group nor in the overall population. The log-rank test's p-value for the difference between the treatment groups was 0.1505. The 2-year LC rate was 84% (95% CI: 70%; 99%) in Arm A and 72% (95% CI: 55%; 89%) in Arm B. The 1-year LC rate was 89% (95% CI: 77%; 101%) in Arm A and 81% (95% CI: 67%; 95%) in Arm B. The hazard ratio for cetuximab vs. standard therapy was 0.43 (95% CI 0.13-1.40).

The median MFS was 31.3 months in Arm B; it was not reached in Arm A and the overall population. The log-rank test comparing MFS between the treatment groups did not detect a significant difference (p = 0.0568). The 2-year MFS rate was 74% (95% CI: 57%; 91%) in Arm A and 54% (95% CI: 36%; 73%) in Arm B. The 1-year MFS rate was 79% (95% CI: 64%; 94%) in Arm A and 70% (95% CI: 53%; 86%) in Arm B. The hazard ratio for cetuximab vs. standard therapy was 0.43 (95% CI 0.17-1.05).

The overall response rate (CR+PR) was higher in Arm A compared to Arm B (81.3% vs. 69.4%). However, this difference was not statistically significant (p = 0.2618, Chi-square test). A CR was achieved by 81.3% of patients in Arm A (all responders) and 41.7% of patients in Arm B; this difference appeared to be statistically significant (p = 0.0014, Chi-square test).

Toxicity:
All 68 patients who had received at least one dose of study medication experienced at least one adverse event (AE). Forty-five patients (66.2%) experienced serious AEs (SAEs), thereof 21 patients in Arm A (65.6%) and 24 patients (66.7%) in Arm B. Fifty-three patients (77.9%) experienced at least one severe AE (defined as CTC grade 3-5), thereof 26 patients (81.3%) in Arm A and 27 patients (75.0%) in Arm B.

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The most frequently observed clinical AEs in Arms A and B, respectively, were nausea (experienced by 59.4% and 55.6% of patients), fatigue (28.1% and 50.0%)), esophagitis (34.4% and 38.9%), dysphagia (28.1% and 25.0%), constipation (18.1% and 30.6%), vomiting (18.8% and 19.4%), lung infection (9.4% and 25.0%), diarrhea (21.9% and 13.9%), oral mucositis (25.0% and 11.1%), weight loss (28.1% and 8.3%), cough (15.6% and 19.4%), and acneiform rash (24.4% and 0%).

The most frequently observed AEs related to laboratory values were hypokalemia (50.0% and 33.3%), anemia (40.6% and 36.1%), leukopenia (50.0% and 22.2%), thrombocytopenia (34.4% and 19.4%), hypomagnesemia (40.6% and 8.3%), and hypocalcemia (28.1% and 5.6%).

For the majority of AEs occurring in ≥ 10 patients the occurrence was similar in both treatment arms. A higher occurrence in Arm A (all grades) was observed for the following AEs: Leukopenia, hypomagnesemia, hypocalcemia, acneiform rash, radiation dermatitis, maculo-papular rash, and allergic reactions.

The majority of AEs was of mild or moderate severity. The most frequent grade 3-5 AEs were lung infection, leukopenia, anemia, esophagitis (11 patients each, 16.2%), and dysphagia (7 patients, 10.3%).

A total of 33 patients (48.5%) died during the course of the study. Two patients in Arm B died during the treatment phase, one from progression of disease, and for one patient, the reason of death could not be specified. About half the deaths were due to disease progression (17 patients). None of the deaths during the treatment phase was associated with study treatment. In the cetuximab Arm, a total of 13 patients (40.6%) died, thereof 6 patients (18.8%) from disease progression. In Arm B, 20 patients (55.6%) died, thereof 11 patients (30.6%) died from disease progression. There was no difference between the treatment arms.

A total of 129 serious adverse events (SAEs) was reported. Forty-five patients (66.2%) experienced at least one SAE. Overall, the most frequently reported clinical SAEs were lung infection (12 patients, 17.6%), esophagitis (11 patients, 16.2%) and thromboembolic events (4 patients, 5.9%).

Altogether, the addition of cetuximab to the chosen standard radiochemotherapy was feasible and did not lead to a significantly higher occurrence of either severe AEs except for allergic reactions. The experienced adverse events were consistent with the known safety profiles of cetuximab, 5-FU, cisplatin and radiotherapy as well as with the severity of the underlying disease. No unexpected risks occurred.

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4 ABBREVIATIONS

5-FU	5-fluorouracil
ADR	adverse drug reaction
AMG	Arzneimittelgesetz (German Drug Law)
ANC	absolute neutrophil count
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
ß-HCG	beta human chorionic gonadotrophin
BSA	body surface area
CEA	carcinoembryonic antigen value
CIOMS	Council for International Organizations of Medical Sciences
CR	complete response
CRF	case report form
CT	computed tomography
DNA	deoxyribonucleic acid
DLT	dose limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
FPI	first patient in
FAS	full analysis set
G-CSF	granulocyte colony stimulating factor
GCP	good clinical practice
GFR	glomerular filtration rate
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	good manufacturing practice
Gy	Gray
γ-GT	gamma glutamyl transferase

HR	hazard ratio
HAHA	human anti-humanized antibody
Hb	Haemoglobin
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IRB	Institutional Review Board
ITT	intention to treat
i.v.	intravenous
LC	locoregional control
LDH	lactate dehydrogenase
LKP	Leiter der klinischen Prüfung
LP	last patient
LPI	last patient in
LVEF	left ventricular ejection fraction
MAb	monoclonal antibody
MFS	metastases-free survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTC	National Cancer Institute Common Toxicity Criteria
pCR	pathological complete response
PD	progressive disease
PK	pharmacokinetics
PPE	palmar-plantar erythrodysesthesia (hand and foot syndrome)
pPR	pathological partial response
PR	partial response
Q3, Q4	quartile 3, quartile 4
QoL	quality of life
SAE	serious adverse event
SD	stable disease
SGOT	aspartate aminotransferase
SGPT	alanine aminotransferase
SmPC	summary of product characteristics
SUSAR	serious unexpected suspected adverse reaction
TNM	tumor classification index (tumor, nodes, metastasis)
TME	total mesorectal excision
UICC	International Union against Cancer
ULN	upper limit of normal
WHO	World Health Organization

5 ETHICS AND AUTHORITIES

5.1 Independent Ethics Committee

Final approval of the IEC was obtained for the following documents:

Document	Date of approval by IEC
Protocol v1.7, Jul26, 2011	Aug22, 2011
Protocol v2.0, Aug25, 2011	Sep09, 2011
Protocol v3.0, Oct16, 2016	Dec22, 2016
Patient information incl. informed consent v1.1, Jul26, 2011	Aug22, 2011
Patient information incl. informed consent translational research v1.1, Jul26, 2011	Aug22, 2011
Patient information incl. informed consent v2.0, Aug06, 2012	Oct10, 2012
Addendum to patient information v1.1, Jul26, 2011	Oct10, 2012

A list of the IECs involved is presented in Appendix 0.

5.2 Ethical conduct of the study

The study was conducted in conformity with the locally legally valid requirements, the German Drug Law (AMG 1976 and amendments), the principles for the proper conduct of clinical trials for medical products (Federal Gazette no. 243, dated Dec30, 1987), the ICH Harmonised Tripartite Guideline for Good Clinical Practice E6(R2) (2016), and the "Ethical principles for medical research involving human subjects" of the 18th World Medical Association General Assembly in Helsinki (1964), and amended by the 29th, 35th, 41st, 48th, 52nd, 53rd, and 55th World Medical Association General Assemblies (Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Seoul 2008, and Fortaleza 2013), the Note of Clarification on Paragraph 29 added by the World Medical Association General Assembly, Washington 2002, and the Note of Clarification on Paragraph 30 added by the World Medical Association General Assembly, Tokyo 2004 – as applicable in the respective countries.

In conformity with ICH guidelines and in accordance with applicable national laws (§40 AMG [section 1, clause 8] and §3 AMG), patients participating in the study were covered by an insurance policy that was taken out by the sponsor.

Country	Insurance company	Address	Policy number	Max. amount insured/patient
Germany	Allianz Versicherungs-AG	Großer Burstah 3 20457 Hamburg	AS-9100160845	500.000 €

The following national regulatory authorities were informed about the conduct of the study:

Country	National regulatory authority	Date of authorisation
Germany	Paul-Ehrlich-Institut (PEI)	Aug24, 2011
	Paul-Ehrlich-Straße 51-59	
	63225 Langen	

The applicable local regulatory authorities were informed about the participation of a centre in the conduct of the study according to §67 para. 1 AMG.

5.3 Patient information and informed consent

Before being enrolled in the clinical trial, each patient was informed that participation in the trial was voluntary and that he/she could withdraw from the study at any time without giving any reasons and without having to fear any detrimental effects on his/her medical care.

The patient was informed about the study medication and the possible side effects. At the same time, the purpose, significance, and scope of the study were explained to him/her. The explanation also included informing the patient about the insurance protection and the obligations of the insured.

The patient had sufficient time and opportunity to clarify any unresolved questions. Furthermore, the patient was given a copy of the Patient Information Form, containing all the important information in written form (in the local language) and a copy of the signed informed consent. A sample patient information/informed consent form is included in the protocol in Appendix 16.1.1.

The patient's consent had to be obtained in writing before the start of the study. By signing the informed consent form, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator, and to answer the questions asked during the course of the trial. The investigator kept the signed patient informed consent form in the designated place in the investigator's file.

By giving consent, the patient also agreed to the storage of his/her medical data in the context of the trial and its forwarding to third parties in pseudonymised form for checking by the sponsor. He/she also consented to the forwarding of his/her personal data for review by the supervisory authorities or to persons authorised by the sponsor to check the proper conduct of the clinical trial.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The number of patients who were enrolled at each study site is shown in Table 1.

Table 1: Study sites and recruitment

Centre	Location	No. of patients recruited	Start of treatment
01	Lübeck	30	Sep20, 2011

Centre	Location	No. of patients recruited	Start of treatment
02	Munich	4	Jan04, 2012
03	Heidelberg	8	Oct22, 2012
07	Wolfsburg	3	Dec17, 2012
09	Leipzig	1	Jul16, 2015
10	Mainz	21	Jun25, 2012
11	Hamburg	2	Aug20, 2012
13	Tübingen	3	Sep03, 2014
14	Erlangen	1	Patient not treated
19	Magdeburg	1	Patient not treated

A list of sites is attached in Appendix 0.

LKP in accordance with §40 AMG/ Coordinating Investigators

Prof. Dr. Dirk Rades
University Hospital Schleswig-Holstein
Campus Lübeck
Department of Radiation Oncology
Ratzeburger Allee 160
23538 Lübeck
Germany

Sponsor

University Hospital Schleswig-Holstein
Campus Lübeck
Ratzeburger Allee 160
23538 Lübeck
Germany

Study coordination
GSO mbH
Mittelweg 110
20149 Hamburg
Germany

CRO responsible for monitoring in Germany

GSO mbH
Mittelweg 110
20149 Hamburg
Germany

Statistics (Safety and efficacy analysis)

Oy 4Pharma Ltd.
ElectroCity
Tykistökatu 4D
20520 Turku
Finland

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7   INTRODUCTION

Esophageal cancer is a highly aggressive neoplasm which is fatal in the great majority of patients[1]. On a global basis, cancer of the esophagus is the sixth leading cause of cancer death worldwide. In fact, gastric and esophageal cancers together accounted for nearly 1.3 million new cases and 980,000 deaths worldwide in 2000 - more than lung, breast, or colorectal cancer[2].

With advances in surgical techniques and treatment, the prognosis of esophageal cancer has slowly improved over the past decades. However, with a 5-year overall survival rate of approximately 14%, at the time of development of the LEOPARD-II protocol, survival was poor, even in comparison with the dismal survival rates (4%) from the 1970s[3].

Underlying reasons for this disappointingly low survival rate are above all the difficulties in cancer detection at an advanced stage, with over 50% of patients with unresectable disease or distant metastasis at presentation and the limited survival achieved with palliative chemotherapy alone for patients with metastatic or unresectable disease[4].

Clearly, additional strategies are needed to improve the systemic treatment options for esophageal cancer.

The optimal treatment of locally advanced esophageal cancer, a potentially curable disease, is controversial. Through several non-randomized cooperative group trials, concurrent cisplatin-based chemoradiation or surgery alone represent acceptable standards of care for patients with resectable tumors.

Metastatic or unresectable esophageal cancer is found at presentation in more than 50% of patients and is considered incurable. At the time of protocol development, chemotherapy was palliative, improving quality of life and dysphagia in 60%–80% of patients[5-7]. Typical clinical and radiographic responses lasted for fewer than 4 months, with a median overall survival time of 8–10 months.

Combination chemotherapies have been demonstrated to be superior to best supportive care and chemotherapy given as a single agent, with occasional patients achieving complete responses (0%–11%)[5-11]. However, even with the combination regimens, the median survival time remained less than 10 months.

An improved understanding of the molecular pathogenesis of cancer has facilitated the development of novel agents designed to target critical pathways involved in cancer development and progression. Epidermal growth factor receptor (EGFR) plays a crucial role in tumour growth. EGFR-dependent signaling is involved in cell proliferation, apoptosis, angiogenesis, and metastatic spread.

The overexpression of EGFR has repeatedly been shown to predict poor prognosis in both esophageal squamous cell carcinoma and gastro esophageal junction adenocarcinoma[12-15]. EGFR blockade through monoclonal antibodies (Cetuximab, Matuzumab and Panitumumab) and

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tyrosine kinase inhibitors (gefitinib, erlotinib) has translated into promising evidence of clinical benefit in clinical trials[16].

Cetuximab is a targeted therapeutic agent, a chimeric IgG1 monoclonal antibody that specifically binds to the EGFR with high affinity, internalising the receptor and preventing the ligands EGF and TGF-α from interacting with the receptors and thus effectively blocking ligand-induced EGFR phosphorylation. In addition, cetuximab had been found to potentiate the effects of chemotherapy and radiotherapy in experimental systems. The dose of cetuximab (initial dose 400 mg/m^2 and subsequent weekly doses of 250 mg/m^2) has been found to be generally safe and effective in several studies in major tumor types expressing the EGFR. These included colorectal cancer and squamous cell carcinoma of the head and neck, with cetuximab given either in combination studies with chemotherapy and radiotherapy or as monotherapy.

In two phase I studies prior to LEOPARD-II, EGFR-directed antibodies had shown activity in patients with esophageal cancer. In the phase I study of the humanized EGFR mAb EMD72000, one patient with metastatic, pretreated squamous cell carcinoma had had a durable, 6-month partial response[17].

In addition, a phase I trial with ABX-EGF, a fully human IgG2 EGFR mAb, had reported stable disease for 7 months in one esophageal cancer patient[18]. Preclinical and these early clinical studies suggested potential activity and minimal toxicities with EGFR antibodies for esophageal cancer.

Furthermore, Lorenzen et al.[19] had reported a randomised phase II of cisplatin + 5-FU (CF) compared to cisplatin + 5-FU + cetuximab (CET-CF) (n=62). Cetuximab did not increase grade 3/4 toxicity, except for rash (6% versus 0%) and diarrhea (16% versus 0%). The overall response rates were 19% and 13% for the CET–CF and CF arms respectively, and the disease control rates were 75% and 57%, respectively. The median progression free survival was 5.9 and 3.6 months and median overall survival 9.5 and 5.5 months for CET–CF and CF, respectively.

With respect to the combination of Cetuximab with radiotherapy, preclinical studies had shown, that Cetuximab enhanced the radiosensitivity of EGFR expressing tumour cells in vitro and in tumour xenografts[20,21] and the repopulation of epithelial tumour cells after exposure to radiation was related to the activation and expression of EGFR[22,23]. Cetuximab also enhanced the efficacy of docetaxel chemoradiotherapy in human adenocarcinoma xenografts[24].

Rationale for the LEOPARD-II study

Esophageal cancer is a highly aggressive tumor and one of the most frequent malignant diseases worldwide.

Treatment options are various and range from chemotherapy to radiotherapy and several surgical techniques. Nevertheless, the overall survival rates for this disease remain poor.

During the last years before protocol development the combination of cetuximab with standard chemotherapy or radiotherapy had mainly been investigated in clinical trials focusing on colorectal and/or head and neck cancer. The results obtained from these studies had been very encouraging and led to the initiation of active clinical research in esophageal cancer patients with antibody inhibition of the EGFR.

The first data in this indication were encouraging showing that cetuximab could safely be added to chemoradiation for esophageal cancer patients with first hints of efficacy.

Based on the experiences with cetuximab in colorectal cancer and in combination with radiotherapy in head and neck cancer, the aim of the LEOPARD-II study was to evaluate the feasibility of a combined treatment of cetuximab with continuous infusional 5-FU, cisplatin and radiotherapy in patients with esophageal cancer and to assess if the overall survival rates could be increased by addition of an EGFR-targeted therapy.

Risk-benefit assessment

The clinical data available at protocol development suggested that cetuximab in combination with a standard radiochemotherapy should be well tolerated and aggravations of 5-FU-related or radiation related toxicities were not expected. However, in one study in head and neck cancer with high-dose radiation and cisplatin combined with cetuximab severe toxicities had been observed[25].

Nonetheless, a phase III study of the Radiation Therapy Oncology Group (RTOG 0522) comparing the same dosing-schedule of cetuximab with cisplatin and concomitant high-dose radiation vs. the standard combination without cetuximab had closed recruitment shortly before start of LEOPARD-II without reporting safety issues. As determined in the Phase I study (LEOPARD Phase I) a dose of 1000 mg/m^2 of continuous infusional 5-FU was considered safe in combination with cisplatin, radiotherapy, and cetuximab.

In head and neck cancer, the combination of cetuximab with radiotherapy alone was safe and resulted in only minimal increase in the overall toxicity profile associated with radiation therapy, especially regarding skin reactions.

Given the possible benefits of the treatment regarding increased response rate and survival, the conduct of the study was regarded as justifiable and there was no indication that patients were exposed to an increased risk associated with study participation. If therapy-related toxicities occurred during the study, detailed instructions for dose modifications of cetuximab and 5-FU were given in the protocol.

8 STUDY OBJECTIVES

The primary objective of the study was to assess the 2-year overall survival (OS).

The secondary objectives of the study were to assess the following parameters:

- 1-year OS
- 1-year and 2-year progression-free survival (PFS)
- 1-year and 2-year loco-regional control (LC)
- 1-year and 2-year metastases-free survival (MFS)
- Toxicity (NCI-CTC v4.0)
- Overall response rate (RECIST Version 1.1)
- Quality of Life scores (EORTC QLQ-C30 and QLQ-OES18)

In addition, the following parameters were to be assessed irrespective of a specific time point:

- OS
- PFS
- LC
- MFS

9 INVESTIGATIONAL PLAN

9.1 Overall study design and plan – description

This was an open-label, randomised Phase II-study to evaluate immuno-radiochemotherapy in patients with unresectable esophageal cancer.

Initially, 134 patients were planned. Due to slow recruitment, the study was discontinued after enrolment of 74 patients on Dec31, 2016.

Eligible patients had a diagnosis of histologically confirmed locally advanced initially unresectable esophageal cancer.

Resectability was to be defined and documented by a surgeon prior to randomisation: The tumour was considered unresectable based on:

- T-stage
- N-stage
- Performance status/Nutritional status
- Comorbidity:
    - Pulmonary function
    - Other
- Tumor location:
    - Upper third of the esophagus

- o   Relation to other organs/structures
- Other reasons that were to be defined in the CRF.

Patients were randomised into two treatment arms (Arm A and B) and treated with or without cetuximab according to randomisation.

Patients in Arm A received cetuximab with concurrent radiochemotherapy as follows:

- Cetuximab initial dose of 400 mg/m^2 (day 1), followed by weekly doses of 250 mg/m^2 for a total of 14 weeks.
- 5-FU: 1000 mg/m^2/day* administered as continuous infusion over 4 days at the beginning of 4 week cycles 1 and 2, i.e. on days 8-11 and 36-39.

  750 mg/m^2/day administered as continuous infusion over 4 days at the beginning of 4 week cycles 3 and 4, i.e. on days 71-74 and 99-102. Note: The time period between cycles 2 and 3 was 5 weeks.
- Cisplatin (20 mg/m^2/day) administered as intravenous bolus over 60 minutes on days 1-4 at the beginning of each cycle, i.e. on days 8-11, 36-39, 71-74 and 99-102.
- Radiotherapy: 59.4 Gy (33 fractions of 1.8 Gy) were to be administered over 6.5 - 7 weeks (5 x 1.8 Gy per week) to the primary tumour and the involved lymph nodes. 50,4 Gy were to be administered to the loco-regional lymph nodes (mediastinum). If resectability had been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy was stopped at 45 Gy and the patient underwent surgery.

*Safe dose level had been identified in the earlier phase I-study (LEOPARD Phase I)

Patients in Arm B were treated with radiochemotherapy as follows without receiving cetuximab:

- 5-FU: 1000 mg/m^2/day* administered as continuous infusion over 4 days at the beginning of 4 week cycles 1 and 2, i.e. on days 1-4 and 29-32.

  750 mg/m^2/day administered as continuous infusion over 4 days at the beginning of 4 week cycles 3 and 4, i.e. on days 64-67 and 92-95. Note: The time period between cycles 2 and 3 was 5 weeks.
- Cisplatin (20 mg/m^2/day) administered as intravenous bolus over 60 minutes on days 1-4 at the beginning of each course, i.e. on days 1-4, 29-32, 64-67 and 92-95.
- Radiotherapy: 59.4 Gy (33 fractions of 1.8 Gy) were to be administered over 6.5 - 7 weeks (5 x 1.8 Gy per week) to the primary tumor and the involved lymph nodes. 50,4 Gy were to be administered to the loco-regional lymph nodes (mediastinum). If resectability had

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been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy was stopped at 45 Gy and patient underwent surgery.

Figure 1: Study Design Flow Chart
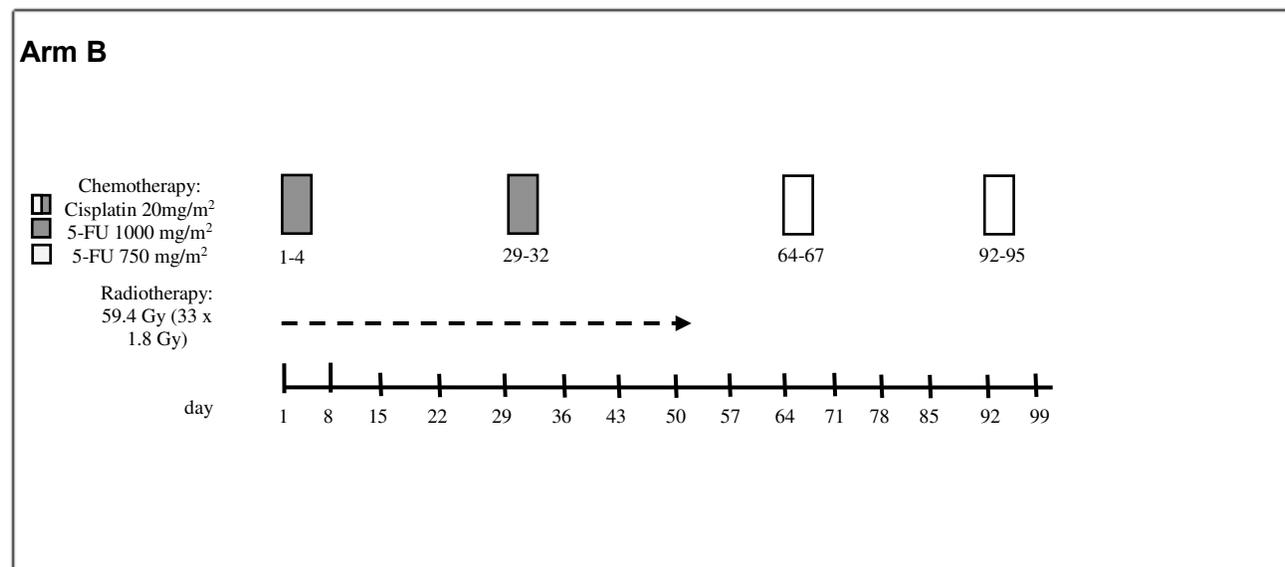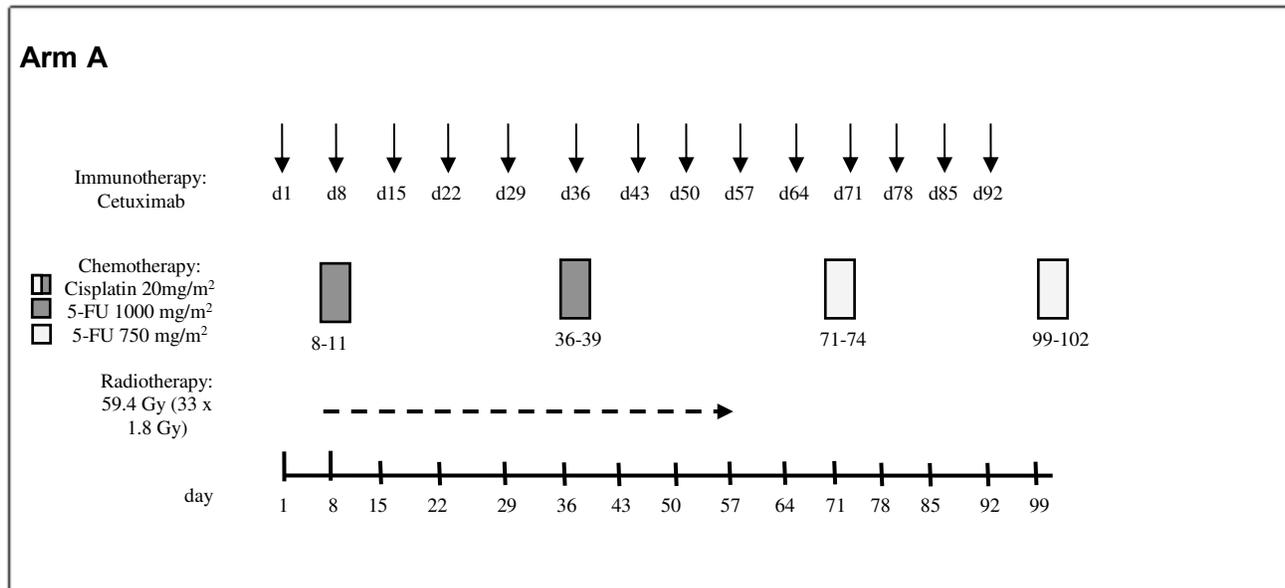
At the end of study treatment or at the time of premature withdrawal for any reason the patient was to have an end of treatment evaluation.

The assessments performed in this study are summarised in the schedule of assessments in section 9.5.1.

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9.2 Discussion of study design, including the choice of control groups

This was an open-label, randomised, multi-center phase II study.

The trial was designed as a randomised phase II study which aimed at estimating the therapeutic efficacy of the experimental targeted regimen including the EGFR antibody. The OS rate after 2 years was chosen as primary efficacy endpoint. The objective was to show that the 2-year OS was above a certain, predefined threshold.

The estimation of the efficacy rate of the experimental cetuximab regimen was based on an exploratory pilot study, since immediately embarking on a large scale comparative efficacy trial would not have been acceptable from the point of view of resources. Moreover, this would have induced ethical objections, as it did not seem to be justifiable to expose a large number of patients to an experimental approach without any exploratory indications of an improved risk-benefit ratio.

In this situation, a randomized phase II trial with a standard treatment control group proves to be an appropriate research design in order to achieve a valid efficacy estimation. This type of cancer study design is propagated since the early 1980s, especially by representatives of the National Cancer Institute[26]. The key idea of randomising in phase II of treatment development offers the opportunity to reduce some of the result variability which is typically encountered in phase II trials, especially caused by patient selection phenomena and investigator bias. Thus, with a randomised control group at hand, differences obtained for the two treatments will more likely represent real differences in efficacy rather than differences in patient selection, clinical evaluation, and other factors, since these factors will be handled in similar fashion for both arms of the study. The purpose of randomised phase II designs is not a formal, rigorous comparison of two or more treatment arms, but rather a reduction in certain sources of variability that afflict conventional phase II trials and their comparison across studies. Moreover, this design offers the additional advantage that the trial may immediately be expanded into a phase III trial including the patients already randomised, if the results of the experimental group(s) are considered to be promising.

The clinical data available at the time of protocol development suggested that cetuximab in combination with a standard radiochemotherapy should be well tolerated and aggravations of 5-FU related or radiation-related toxicities were not expected. Radiochemotherapy containing 5-FU and cisplatin belong to the most effective radiochemotherapy regimens achieving an OS rate of 36% to 40% after 2 years[27-29]. In our phase I study "LEOPARD Phase I", we established a dose of 1000 mg/m² of continuous infusional 5-FU in combination with cisplatin, radiotherapy and cetuximab as safe and feasible.

9.3 Selection of study population

Patients with locally advanced unresectable esophageal cancer were eligible for this study if all of the following criteria were fulfilled and the patients had provided written informed consent. There

was no preferred enrolment of men or women within this study. However, pregnant or breast-feeding women were excluded from participation.

9.3.1 Inclusion criteria

Patients who <u>met all of the following criteria</u> could be enrolled into the study:

- Signed written informed consent

- Male or female between 18 and 75 years; patients > 75 years if KPS ≥ 80

- Histologically proven squamous cell carcinoma or adenocarcinoma of the esophagus, which was not curatively resectable*

*resectability had to be defined and by a surgeon prior to randomisation:

The tumor was considered unresectable due to:

T-stage, N-stage, performance status/nutritional status, co-morbidity (pulmonary function, other), tumor location upper third of the esophagus, relation to other organs/structures), other reasons.

- KPS ≥ 70

- Women of child-bearing potential had to have a negative pregnancy test

- Adequate cardiac, pulmonary, and ear function

- Adequate bone marrow function: leucocytes $\geq$ 3.0 x 10^9/L, neutrophils $\geq$ 1.5 x 10^9/L, platelets $\geq$ 100 x 10^9/L, haemoglobin $\geq$ 10.0 g/dL

- Adequate liver function: Bilirubin $\leq$ 2.0 mg/dL, SGOT, SGPT, AP, γ-GT $\leq$ 3 x ULN

- Adequate renal function: serum creatinine $\leq$ 1.5 mg/dL, creatinine clearance $\geq$ 50 ml/min (calculated value according to Cockcroft-Gault equation)

- No known allergy against chimeric antibodies.

- Effective contraception for both male and female patients if the risk of conception existed

9.3.2 Exclusion criteria

Patients who met any of the following criteria were not allowed to be enrolled into the study:

- Distant metastasis (M1b)

- Previous treatment of esophageal cancer

- Previous exposure to monoclonal antibodies and / or EGFR-targeted therapy

- Other previous malignancy with exception of a history of a previous curatively treated basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix

- Serious concomitant disease or medical condition

- FEV_1 < 1.1

- Clinically relevant coronary artery disease or a history of myocardial infarction within the last 12 months or left ventricular ejection fraction (LVEF) below the institutional range of normal

- Any active dermatological condition > Grade 1

- Contraindications to receive cisplatin, 5-FU or cetuximab

- Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to study screening

- Pregnancy or lactation

- Known active drug abuse/alcohol abuse

- Social situations limiting the compliance with the study requirements

9.3.3   Removal of patients from therapy or assessment

Patients were free to discontinue the study at any time without giving their reason(s).

The patient had to be withdrawn from study treatment in the event of any of the following:

- Withdrawal of the patient's consent

- Occurrence of an exclusion criterion which was clinically relevant and affected the patient's safety

- Occurrence of AEs, if discontinuation was desired or considered necessary by the patient and/or investigator

- Occurrence of pregnancy during treatment

- Lack of subject compliance

- A delay of treatment with cetuximab for more than 2 consecutive weeks

- Occurrence of any grade 4 toxicities related to cetuximab

- Occurrence of $\geq$ grade 3 allergic/hypersensitivity reaction related to cetuximab

- Occurrence of disease progression

If there was a medical reason for withdrawal, the patient was to remain under the supervision of the investigator until the AEs had been resolved or declined to baseline values.

If a patient had failed to attend scheduled assessments in the study, the investigator had to determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment by a patient, the investigations scheduled for the last visit should have been performed, if possible. In any case, the CRF section entitled "End of Treatment" had to be completed.

9.4   Treatments

9.4.1   Treatments administered

Patients in Arm A received cetuximab with concurrent radiochemotherapy and patients in Arm B were treated with radiochemotherapy without receiving cetuximab as displayed in section 9.1.

The Investigational Medicinal Product (IMP) in this study was cetuximab.

Commercially available 5-FU and cisplatin were used.

Cetuximab had to be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring was required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment had to be ensured.

For the initial dose, the recommended infusion period was 120 minutes. For subsequent weekly doses, the recommended infusion period was 60 minutes.

The maximum infusion rate was 10 mg/min (i.e., 2 mL/min of the 5 mg/mL solution, or, after dilution of 1 part cetuximab 5 mg/mL in 4 parts 0.9%-NaCl solution (1:5 dilution) 10 mL/min = 600 mL/h).

Prior to the first infusion, patients had to receive premedication with an antihistamine and glucocorticoid. This premedication was recommended prior to all subsequent infusions. Vital signs were to be checked pre-, mid-, post- and one hour post-infusion.

Cetuximab was administered once a week for a total of 14 weeks. The initial dose was 400 mg cetuximab per m² body surface area. The subsequent weekly doses were 250 mg/m² each.

Cetuximab should always be administered prior to cisplatin and 5-FU. There had to be at least one hour between the end of the cetuximab infusion and the beginning of the chemotherapy infusions.

5-FU was to be administered as a continuous intravenous infusion on days 1-4 at the beginning of each cycle.

Cisplatin was to be administered after saline hydration as intravenous bolus infusion on days 1-4 at the beginning of each cycle. The saline hyperhydration was to be given according to the investigational centre's routine.

All subjects had to receive adequate anti-emetic therapy prior to the administration of cisplatin. It was recommended that a $5HT_3$ antagonist (e.g. Granisetron) and dexamethasone 8mg i.v. were administered prior to each cycle of treatment.

9.4.2 Identity of investigational product(s)

The trial medication was characterised as follows:

Investigational product: Cetuximab	
Manufacturer:	Merck KGaA, Darmstadt, Germany
Trade name:	Erbitux® 5 mg/mL solution for infusion
Mode of administration:	Intravenous infusion

Storage instructions:	Store under refrigeration at +2 to +8°C. Do not expose to direct sunlight or heat. Do not freeze.

Infusion sets or syringes made of polyethylene, polyurethane, polyolefine thermoplastic, polyamide glass microfibre, polypropylene and polyvinyl chloride have been tested for compatibility with cetuximab, and were recommended for use.

The IMP was labelled according to §5 GCP-Ordinance. Infusions were prepared according to instructions given in the protocol in section 5.1.1 and the SmPC of cetuximab.

For a list of patients receiving the investigational product from specific batches, please refer to Appendix 0.

9.4.3   Method of assigning patients to treatment groups

Randomisation was performed centrally by GSO mbH. The notification was carried out by fax with a standardised randomisation form.

To achieve uniform distribution within both treatment arms the patients were stratified with respect to the Karnofsky performance status (100%-80% vs. 70%), the tumor stage (T1-3 N0-1 vs. T4 and/or N2 and/or M1a) and the type of carcinoma (adenocarcinoma vs. squamous cell carcinoma).

All patients were assigned a unique 6-digit identification number during randomisation. The first 2 digits of this number indicated the center number. The last 4 digits were consecutively assigned to the patients at each center. For example, patient number 01-0001 corresponds to the first patient enrolled at center number 01 and patient number 02-0001 corresponds to the first patient enrolled at center number 02.

Stratification at randomisation was done according to:

- Histology (SCC vs. adenocarcinoma)
- KPS (100%-80% vs. 70%)
- Stage (T1-3 N0-1 vs. T4 and/or N2 and/or M1a)

9.4.4   Selection of doses in the study

Treatment was administered as displayed in section 9.1.

The dose of cetuximab, initial dose of 400 mg/m² and subsequent weekly doses of 250 mg/m², has been found to be generally safe and effective in several studies in major tumour types expressing EGFR. These included colorectal cancer, squamous cell carcinoma of the head and neck and non-small cell lung cancer, with cetuximab either given in combination studies with chemotherapy and radiotherapy or as monotherapy (see summary of product characteristics Erbitux®).

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Cisplatin and 5-FU were administered according to label.

Radiotherapy was administered over 6.5 - 7 weeks, in 33 fractions of 1.8 Gy up to total dose of 59.4 Gy. 50.4 Gy was to be administered to the loco-regional lymph nodes. If resectability had been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy was to be stopped at 45 Gy and the patient should undergo surgery.

Radiotherapy started on the first day of the chemotherapy following cetuximab infusion and prior to the 5-FU and cisplatin infusions. A total of 59.4 Gy (at the reference point according to ICRU 62) was to be delivered in daily fractions of 1.8 Gy for 6.5 - 7 consecutive weeks (5 fractions/week). Irradiation was to be performed using high energetic photons, preferably a linear accelerator with photon energies of at least 6 MV. The 95% isodose should have covered the target volume.

Isocentric 3- or 4- field techniques with individual absorbers were to be used. To adequately perform planning a treatment simulator and computerized 3-D-treatment planning had to be used. The CT-slices should have been contiguous and not thicker than 10 mm, preferably 5 mm with clip labelling. Optimal patient positioning to reduce normal tissue damage - if necessary including the use of a belly board was required to be performed by the protocol.

9.4.5   Selection and timing of dose for each patient

9.4.5.1   Cetuximab

Patients were to receive 14 weekly infusions with cetuximab. If a patient had to receive 5-FU and cisplatin at the same day, they should have been administered after a 1-hour observation period post cetuximab infusion.

For all patients, the dosage and administration procedure for cetuximab was as follows:

Initial dose:

The total **initial dose** (first infusion) was **400 mg/m² (80 mL/m² ready-to-use solution)** and was administered over a period of 120 minutes (maximum infusion rate of 10 mg/min, corresponding to 2 mL/min ready-to-use solution). Patients must have been pre-treated with an antihistamine as well as a glucocorticoid. The patient should have been observed during infusion and for one hour afterwards. Vital signs were to be checked pre-, mid-, post- and one hour post-infusion. A sterile 0.9% NaCl solution was to be used to flush the line at the end of infusion.

Further infusions:

The **weekly dose** (all further infusions) was **250 mg/m² (= 50 mL/m² ready-to-use solution)** and was to be administered over a period of 60 minutes (maximum infusion rate of 10 mg/min, corresponding to 2 mL/min ready-to-use solution). It was recommended that the patient was pre-treated with an antihistamine as well as a glucocorticoid prior to each infusion. The patient was to

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be observed during infusion and for one hour afterwards. Vital signs were to be checked pre-, mid, post- and one hour post-infusion. A sterile 0.9% NaCl solution was to be used to flush the line at the end of infusion.

9.4.5.1.1 Skin toxicities

If a patient experienced a grade 3 skin toxicity (as defined in the US National Cancer Institute's - Common Toxicity Criteria [NCI-CTC], Version 4.0), cetuximab therapy could have been delayed for up to two consecutive infusions without changing the dose level. For grade 1 or 2 acne-like rash treatment with topical antibiotics (e.g. benzoylperoxide, erythromycin) or systemic antibiotics (e.g. oral tetracyclines such as doxycycline 100 mg od) should have been considered. Patients with grade ≥ 3 reactions should have been referred to the dermatologist for advice and management. If pruritus occurred an oral antihistamine was advised. In case of dry skin the use of emollient creams was recommended. Fissures may occur in dry skin and topical dressings were considered helpful. If the toxicity resolved to grade 2 or less by the following treatment period, treatment might have been resumed. With the second and third occurrences of grade 3 skin toxicity, cetuximab therapy could again be delayed for up to two consecutive weeks with concomitant dose reductions to 200 mg/m^2 and 150 mg/m^2, respectively. Cetuximab dose reductions were permanent. Patient should have discontinued cetuximab if more than two consecutive infusions were withheld or a fourth occurrence of a grade 3 skin toxicity occurred despite appropriate dose reduction (see Figure 2).

However, if in the opinion of the investigator the discontinuation of cetuximab was considered necessary, the subject should have been withdrawn immediately.

The dose of cetuximab was to be adjusted for cetuximab-related grade 3 skin toxicities only. Cetuximab therapy was not to be withheld for chemotherapy related toxicities. Therefore, in the event that the next infusion of chemotherapy was delayed, the patient was to receive cetuximab as previously planned.

Figure 2: Treatment adjustment in the event of grade 3 skin toxicity considered to be related to cetuximab
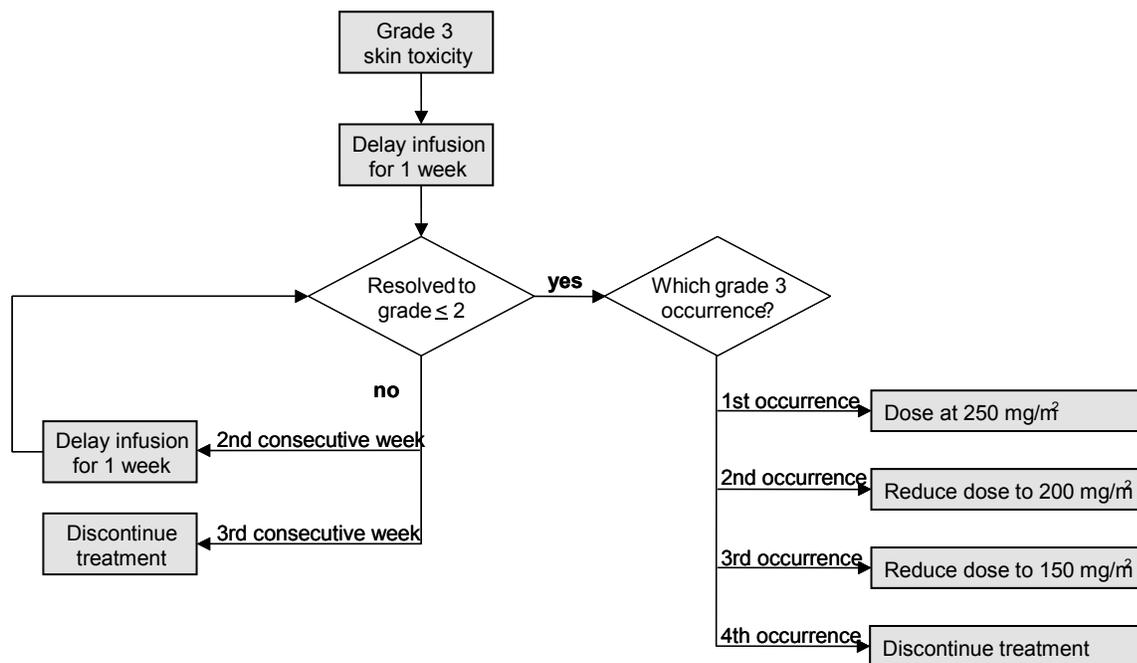
9.4.5.1.2 Allergic/hypersensitivity reactions

In each case of allergic/hypersensitivity reaction, the investigator should implement treatment measures according to the best available medical practice. Based on previous experience with cetuximab allergic/hypersensitivity reactions, the treatment guidelines as described in Table 2 were applicable.

Table 2: Treatment adjustment in the event of cetuximab caused allergic/hypersensitivity reactions

CTC Grade Allergic/ Hypersensitivity Reaction	Treatment
Grade 1	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 4 hours.
Grade 2	Stop cetuximab infusion. Administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4	Stop the cetuximab infusion immediately and disconnect infusion tubing from the subject.

	Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. **Subjects must be withdrawn immediately from the treatment and must not receive any further cetuximab treatment**.

Re-treatment following allergic/hypersensitivity reactions:

Once a cetuximab infusion rate had been decreased due to an allergic/hypersensitivity reaction, it had to remain decreased for all subsequent infusions. If the patient had a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should have been stopped and the patient should have been removed from the study. If a patient experienced a Grade 3 or 4-allergic/hypersensitivity reactions at any time, cetuximab was to be discontinued.

9.4.5.1.3 Other reasons for cetuximab discontinuation

If a subject developed an intercurrent illness (i.e., infection) that, in the opinion of the investigator mandated interruption of cetuximab therapy, that intercurrent illness must have been resolved within a time frame such that no more than two consecutive infusions were withheld. After the interruption of treatment, the patient should have continued with a cetuximab dose of 250 mg/m^2 at subsequent visits or the last dose before the interruption if there had been previous dose reductions.

If therapy had to be withheld for a longer period of time, the patient had to be removed from the study treatment. In special cases, the investigator could request that the patient continued to receive cetuximab (the investigator had to ask permission from the Investigator-Sponsor).

9.4.5.2 5-Fluorouracil

Toxicities solely related to chemotherapy do not lead to a dose modification or interruption of cetuximab and vice versa.

Dose modifications and treatment alterations for 5-FU

The dose of 5-FU was to be modified, if the following toxicities (Table 3) were observed during the radiochemotherapy on the planned day of 5-FU infusion.

Once a 5-FU dose modification had occurred, the dosage was not allowed to be re-escalated for this patient. If therapy was delayed for longer than 2 weeks, the patient had to be withdrawn from the study.

If on the day of planned 5-FU infusion one of the following toxicities occurred, a dose modification according to the following scheme was to be performed:

Table 3: Dose modification for 5-FU in case of toxicities on the day of planned 5-FU infusion

Toxicity	CTC - Grade	Continue with Chemotherapy	Dose modification
Neutropenia	ANC $\geq$ 1.5 x 10^9/L	Yes	No
	ANC < 1.5 x 10^9/L	Delay until ANC $\geq$ 1.5 x 10^9/L	No
	ANC < 0.5 x 10^9/L	Delay until ANC $\geq$ 1.5 x 10^9/L	Yes 5-FU 75% of original dose
Thrombocytopenia	Platelets $\geq$ 100 x 10^9/L	Yes	No
	Platelets < 100 x 10^9/L	Delay until platelets $\geq$ 100 x 10^9/L	No
	Platelets < 25 x 10^9/L	Delay until platelets $\geq$ 100 x 10^9/L	Yes 5-FU 75% of original dose
Diarrhea	Grade 0-1	Yes	No
	Grade 2	Delay until resolved to grade < 2	No
	Grade 3	Delay until resolved to grade < 2	1st occurrence: No 2nd occurrence: Yes 5-FU 75% of original dose
	Grade 4	withdrawal	withdrawal
Mucositis/Stomatitis	Grade $\geq$ 1	Delay until resolved	Yes 5-FU 75% of original dose
Skin (except irradiated region and cetuximab-related skin toxicities)	Grade $\geq$ 2	Delay until grade 0-1	Yes 5-FU 75% of original dose
Further non-hematological toxicities (except nausea/vomiting and alopecia)	Grade 0-1	Yes	No
	Grade 2-3	Delay until grade 0-1	Yes 5-FU 75% of original dose
	Grade 4	withdrawal	withdrawal

If at any time during the radiochemotherapy one of the following toxicities occurred, a dose modification of 5-FU at the next planned infusion was to be performed according to the following scheme:

Table 4: Dose modification of 5-FU in case of toxicities during radiochemotherapy

Toxicity	CTC-Grade	Dose modification
Neutropenia	ANC < 0.5 x 10^9/L	5-FU 75% of original dose
Thrombocytopenia	Platelets < 50 x10^9/l	5-FU 75% of original dose
Diarrhea	$\geq$ Grad 3 ($\geq$ stools/day or incontinence)	5-FU 75% of original dose
Nausea/vomiting	$\geq$ Grad 3	5-FU 75% of original dose

9.4.5.3 Cisplatin

Dose modifications and treatment alterations for cisplatin

Table 5: Dose modification regarding the cisplatin-induced renal toxicity prior to every new cycle

Creatinine value	Dose modification
$\leq$ 1.5 mg/dl	no dose modification
> 1.5 mg/dl	Delay until creatinine is < 1.5 mg/dl, then restart with 50% of original dose

Additionally the following criteria had to be fulfilled prior to every chemotherapy cycle:

- Neutrophils ≥ 1,5 x 10^9/L

- Thrombocytes ≥ 100 x 10^9/L

- Diarrhea NCI-CTC Version 4.0 Grade < 2

If these parameters were not appropriate at the scheduled time point of the new cycle, cisplatin administration had to be delayed until the criteria above were fulfilled.

If cisplatin was delayed for less than two weeks, the therapy had to be continued at the previous dosage.

If cisplatin was delayed for more than two weeks, the administered dose was to be 75% of the original value.

If at any time during the radiochemotherapy one of the following toxicities occurred, a dose modification of cisplatin at the next planned infusion had to be performed according to the following scheme:

Table 6: Dose modification for cisplatin in case of toxicities during radiochemotherapy

Toxicity	CTC-Grade	Dose modification
Neutropenia	ANC < 0.5 x 10^9/L	Cisplatin 75% of original dose

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Toxicity	CTC-Grade	Dose modification
Thrombocytopenia	Platelets < 25 x10^9/l	Cisplatin 75% of original dose
Further non-hematological toxicities (except nausea and vomiting**)**	Grade 3 Grade 4	Cisplatin 75% of original dose Discontinuation of chemotherapy

9.4.5.4 Radiotherapy

Adverse reactions and dose modifications of radiotherapy

Expected acute adverse reactions of the radiotherapy are esophagitis and dysphagia. These reactions may be aggravated by the concurrent chemotherapy. Treatment should have been symptomatic. Generally, these acute adverse reactions abate within two to four weeks following completion of radiotherapy. In severe cases, the treatment could be interrupted for up to one week, if deemed necessary be the responsible radio-oncologist. If radiotherapy had to be stopped due to adverse reactions, the sponsor had to be informed. Rare severe events of radiotherapy are e.g. skin reactions, pneumonitis, arrhythmia.

Interruption or termination of radiotherapy due to adverse reactions should have been based on the following recommendations:

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Table 7: Interruption of radiotherapy in case of gastrointestinal toxicity

Toxicity grade	Esophagitis/dysphagia	Radiotherapy
0	None	Continue
1	Mild dysphagia, but can eat regular diet	Continue
2	Dysphagia requiring predominantly liquid, pureed or soft diet	Continue
3	Dysphagia, requiring feeding tube, IV hydration or hyperalimentation	Interruption of radiotherapy for a maximum of 7 days. If the esophagitis/dysphagia does not resolve, the radiotherapy should be stopped.
4	Complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation	Stop radiotherapy

9.4.6 Blinding

Not applicable.

9.4.7 Prior and concomitant therapy

All concomitant medication or medication administered within 4 weeks prior to study start and during the study had to be recorded in the CRF, including the specification of duration of the treatment.

Additionally, any therapeutic, or surgical procedures performed during the study period were to be recorded in the CRF, including the date, indication, description of the procedures, and any clinical findings.

Any change in the permitted concomitant medication taken at the beginning of the clinical study had to be recorded in the CRF, noting the type of medication, duration, and indication.

Additional concurrent chemotherapy or radiation therapy was not allowed to be administered. Sedatives, antibiotics, analgesics, antihistamines, steroids, Granulocyte-Colony-Stimulating Factor (G-CSF), erythropoietin or other medications as well as red blood cells, platelets or fresh frozen plasma transfusions were allowed to be given to assist in the management of pain, infection, and other complications of the malignancy.

Patients had to be premedicated with an antihistamine and a glucocorticoid prior to receiving the initial dose of cetuximab. Premedication with an antihistamine and a glucocorticoid was recommended prior to further subsequent weekly doses.

Anything which may interfere with the immune systems of the patient should preferably have been avoided except the indicated study regimen and necessary supportive treatment.

9.4.8   Treatment compliance

Since the intravenous infusion was administered in a hospital or in an outpatient setting, compliance could easily be supervised. Cetuximab, cisplatin and 5-FU were to be administered either by the investigator or under his direct supervision.

The date and the exact amount of cetuximab given at each infusion was to be documented in the CRF.

As a routine precaution, patients enrolled in this study were to be observed from the start of the infusion until at least one hour after the end of the infusion in an area with resuscitation equipment and emergency agents (epinephrine, prednisolone equivalents etc.) available. In the event that the treatment had to be interrupted during infusion, the clinical staff should have made an estimate of the percentage of dose received by the patient and documented it in the CRF. Any reason for non-compliance should have been documented as well. Insufficient compliance was defined as a patient missing more than two infusions of cetuximab without medical reason. In the event of insufficient compliance, discontinuation of study treatment for this patient was to be considered in mutual agreement between the investigator and the Investigator-Sponsor.

9.5   Efficacy and safety variables

9.5.1   Efficacy and safety measurements assessed and flow chart

Assessment of tumour response was evaluated applying RECIST 1.1 criteria[30].

Only patients with measurable disease could be enrolled into this study. Measurable disease requires the presence of at least one measurable lesion. Imaging, CT- or MRI-scan, of chest and abdomen had to be performed at baseline (within 28 days before start of treatment) for eligibility and also to establish a baseline tumour assessment.

The lesions were to be assessed with imaging with the same method as at baseline during treatment at week 4-4.5, and at the end of treatment to monitor progression of disease. Furthermore, at the end of treatment visit, the investigator had to exclude symptomatic deterioration suggestive of progression of disease (e.g. a decrease in Karnofsky performance status, metastases). If progression of disease was suspected for any reason during the treatment phase, radiological confirmation was necessary and a new scan had to be performed unless a scan taken no more than 14 days earlier was available. For patients without progression of disease by the end of treatment, tumor assessments were repeated every 3 months during post-treatment follow-up.

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Resectability of the primary tumour and the lymph nodes was to be assessed by a surgeon after 4-4.5 weeks of treatment.

Overall response was defined according to the RECIST criteria Version 1.1 based on the assessments for target lesions, non-target lesions as well as considering the occurrence of new lesions.

In patients undergoing surgery, residual tumour classification (R-classification) was to be performed by the pathologist using the resected tumour. The pathologist had to determine if residual tumour was present at the resection lines. The definitive R-classification considers clinical and pathological information and includes the following categories:

R0 no residual tumour

R1 microscopic residual tumour

R2a macroscopic residual tumour, microscopically not confirmed

R2b macroscopic residual tumour, microscopically confirmed

Patients were to be carefully monitored for adverse events at the sites. This monitoring included clinical laboratory tests. Adverse events were to be assessed on a cycle basis, and the highest grade according to CTCAE was to be recorded. Adverse events were to be assessed in terms of seriousness, severity, and relationship to the study drug.

The schedule of visits and procedures is displayed in

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Table 8. A more detailed description of the cycle and procedures are provided with the Clinical Study Protocol (Appendix 16.1.1).

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Table 8: Schedule of Assessments

Evaluation	Screening Day -28 to 0	Screening Day -7 to 0	weekly	every 4 weeks	after 4-4.5 weeks	End of Treatment	Follow-Up (every 3 months)[8]
Written informed consent	X						
Medical history	X						
Clinical staging (endoscopy incl. biopsy)	X				X	X	
Endoscopic ultrasound	X				X	X	X
Tumour assessment (CT chest, CT abdomen)	X				X	X	X
(Re)-evaluation by a surgeon with respect to resectability	X				X		
ECG and LVEF	X						
FEV$_1$	X						
Height		X					
Weight		X	X				
Vital signs (blood pressure, pulse) [1]		X	X			X	
Karnofsky-Performance Status		X		X		X	
Hematology [2]		X	X			X	
Clinical chemistry [3]		X		X		X	
Pregnancy test [4]		X					
Serum Sample for EGFR and ligands determination[5]		X			X	X	
Tissue Immunohistochemistry[5]	X					X	
DC-MRT [6]			X				
Quality of Life [7]		X			X	X	
Clinical signs and symptoms			continuing				X
Treatment outcome							X

1: vital signs weekly during radio-immunochemotherapy: prior, during and after each cetuximab infusion

2: Hematology included: leucocytes, neutrophils, platelets, erythrocytes, haemoglobin

3: Clinical chemistry included: sodium, potassium, calcium, magnesium, creatinine, bilirubine, SGOT, SGPT, LDH, alkaline phosphatase, γ-GT

4: Serum or urine β-HCG in patients of child-bearing potential

5: Serum Sample (10ml), an additional whole blood sample (10 ml) at screening, Frozen tissue or paraffin-embedded tissue for immunohistochemistry from previous operations/biopsies or biopsies obtained at screening or after week 4-4.5 and end of treatment (optional, if patient agreed to participate in translational study)

6: DC-MRT: at day 7 (+/-2) or day 14 (+/-2) of the first cycle (in selected centers)

7: Quality of Life was assessed using the EORTC QLQ-30 questionnaire and the esophagus-specific EORTC QLQ-OES18 module

8: The first follow-up assessment were to be performed 3 months after the end of treatment assessment. Follow-up assessments should terminate 2 years after the last patient had completed end of treatment (incl. biopsy, if patient agreed to participate in translational study).

9.5.2   Appropriateness of measurements

The efficacy and safety tests used in this clinical trial are standard tests in oncological clinical trials.

9.5.3   Efficacy variables

For quantification of efficacy the primary efficacy variable was the 2-year overall survival (OS).

Secondary efficacy variables included 1-year OS, 1-year and 2-year progression-free survival (PFS), 1-year and 2-year loco-regional control (LC), 1-year and 2-year metastatic-free survival (MFS), overall response rate according to RECIST v1.1, toxicity according to NCI-CTC v4.0, and quality of life by EORTC QLQ-C30 and QLQ-OES18.

The following parameters were to be assessed irrespective of a specific timepoint: OS, PFS, LC and MFS

9.5.4   Drug concentration measurements

NA

9.6   Data quality assurance

The evaluation criteria were consistent for all sites. Each site had to provide its laboratory normal values. Each laboratory was validated with routine intra-laboratory tests. Toxicity was assessed using the evaluation criteria from NCI-CTCAE Version 4.0, while efficacy was assessed using RECIST standards.

The main objective was to obtain those data required by the study protocol in a complete, accurate, legible and timely fashion.

9.6.1   Monitoring

The trial started with an initiation visit, where a CRA representing the sponsor introduced the study to the investigational site personnel.

During the trial, a CRA representing the sponsor had regular contact with the investigational site to provide information and support the investigator(s).

During monitoring visits the CRAs had to:

• Help resolve any problems.

• Examine all CRFs for omission of data, compliance and possible AEs.

• Discuss inconsistencies in the trial data.

• Ensure that all trial materials were correctly stored and dispensed.

• Check adherence to the obligations of the investigator.

• Review consent forms, in particular the date of consent and signature.

• Perform Source Data Verification as described below.

In line with ICH GCP guidelines monitoring included verification of data entered in the CRFs against original patient records. This verification was performed by direct access to the original

patient records and the monitoring organisation guaranteed that patient confidentiality was respected at all times. Participation in this study was taken as agreement to permit direct source data verification. Data generated at the pre-screening visit were verified against source data only in case the patient entered the study.

In addition the representatives of the Clinical Quality Assurance of monitoring organisations, and of national regulatory authorities, were permitted to inspect the study documents (study protocol, case report forms, study medication, original medical records/files). All patient data were to be treated confidentially.

In the course of the clinical study, the CRFs were to be forwarded to the data management organisation after completion of the individual sections (e.g. visits) of the study.

The study protocol, each step of the data-recording procedure, and the handling of the data as well as the study report was to be subject to a Clinical Quality Assurance. Audits could be conducted to assure the validity of the study data.

9.6.2 Audits

Regulatory authorities might request access to all source documents, CRF, and other trial documentation. Direct access to these documents has to be guaranteed by the investigator who has to provide support for these activities at any time.

9.7 Statistical methods planned in the protocol and determination of sample size

9.7.1 Statistical and analytical plans

Statistical analysis, tables and patient data listings were to be performed with SAS® version 9.3 or higher for Windows (SAS Institute Inc., Cary, NC, USA).

Primary efficacy variable:

The primary efficacy endpoint, 2-year OS, was analysed as the rate of patients alive at 2 years and compared to a pre-defined threshold proportion of 40% within each treatment arm, with a planned type I error level of 5%. No direct comparison between the arms had been planned for 2-year OS. The estimates for the 2-year OS rate were based on Kaplan-Meier methodology (KM).

Time to event/censoring was to be calculated as event/censoring date – randomisation date + 1. For OS the date of death was to be used as the event date. In case the date of death was missing even though the patient had died, the last date alive was to be used. In case the patient was still alive at the end of the follow-up period, the patient was to be censored at the last date known to be alive.

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For the primary hypothesis of 2-year survival, the survival rate with 95% confidence interval was to be calculated for the 2-year timepoint using the proc lifetest timelist option. The inference for the primary hypothesis was to be done based on the 95% confidence interval.

The 1-year survival rates were estimated using the same method.

Secondary efficacy variables:

The same method and summaries as for the secondary endpoint of OS were to be used for progression-free survival (PFS), loco-regional control (LC) and metastases-free survival (MFS).

For PFS, the event date was defined as the date of either radiologically proven progress, clinical progression of death due to progressive disease using the first occurrence of any of these. In case the patient was still progression-free at the end of the follow-up or at time of death, the patient was to be censored at the last follow-up date (known to be alive).

For LC the event date was defined as the date of first finding of recurrent or progressive primary tumour and/or regional lymph nodes on endoscopy, endoscopic ultrasound or computed tomography. On data level, this meant the first occurrence of either disease progression or recurrence in target lesions (primary tumour, involved regional lymph nodes), progression in non-target lesions (if primary tumour or regional lymph nodes were initially classified as non-target lesions).

For MFS the event date was defined as the date of first occurrence of distant metastasis incl. distant lymph nodes. On data level, this meant the first occurrence of new non-target lesions that were not primary tumour or regional lymph nodes.

For both LC and MFS, patients with no event were to be censored at the last follow-up date (known to be alive).

For PFS, LC and MFS the first occurrence of the respective events was used excluding any tumour assessments made under a subsequent line of therapy.

Additionally, number of events, median survival time from the KM analysis and an exploratory log-rank test comparing the treatment arms was to be presented. The hazard ratio for treatment group comparison was calculated with the univariate Cox proportional hazard model.

The best overall response (RECIST) was chosen for each patient out of all valid tumour assessments before start of next-line therapy (CR being the best and PD the worst). Frequencies with percentages were to be given for each category (CR, PR, SD, PD) by treatment group. The data were to be presented as the dichotomous endpoint of objective response (OR), for which patients with best overall response of CR or PR were considered as responders, and those with best overall response of SD or PD as non-responders. The difference between OR rates in the two treatment arms was to be compared with a Chi-square test. In case the cell frequencies such as number of responders or non-responders in either one of the treatment groups was 5 or lower, a Fisher's exact test was to be used for the comparison instead, which is a more suitable method with low expected frequencies.

Additional analyses:

OS, PFS, LC and MFS were also examined in subgroups defined by potential prognostic factors, such as: age (≤60 vs. >60 years), Karnofsky performance status (100%-80% vs. 70%), tumour location (upper third vs. middle third vs. lower third), histology (squamous cell carcinoma vs. adenocarcinoma), histologic grade (G1-2 vs. G3), T-stage (T2-3 vs. T4, according to endoscopic ultrasound and computed tomography), N-Stage (N0 vs. N+), and haemoglobin before radiotherapy (<12 vs. 12-14 vs. > 14 g/dl).

Kaplan-Meier curves were plotted for these subgroups and exploratory log-rank tests were performed to detect differences in these endpoints for the various subgroups and results were considered significant if $P < 0.05$.

Potential prognostic factors were examined in a univariate Cox proportional hazards analysis and those found to be significant in a univariate analysis were to be evaluated in a subsequent multivariable Cox proportional hazards analysis.

Toxicity:

All AEs occurring after signature of informed consent until the end of study were to be captured, documented and reported. AEs were to be tabulated using NCI-CTC v4.0 by CTC category and AE term as event and patient counts with percentage of patients within the group. Also, summaries by severity (worst CTC grade) were to be given, and a separate table for severe events (grade 3-5) were to be done. P-Values were calculated for all and for severe AE terms/CTC categories more common than 5% in either of the groups with the Fisher's exact test.

Causality of AEs was to be summarized separately by relationship to cetuximab. Additionally, listings of AEs leading to discontinuation of cetuximab, radiotherapy or chemotherapy were to be provided.

AEs classified as SAE were to be listed separately. Deaths together with the reason for death and the possible relation to study treatment was to be summarized.

Safety analyses:

For vital signs (supine systolic/diastolic blood pressure, heart rate) descriptive statistics were to be calculated by chemotherapy cycle, visit and treatment group. Physical examination results (height, weight and body surface area) were to be tabulated similarly.

The Karnofsky Performance Status was to be summarised both with descriptive statistics and as percentage and number of patients within each Karnofsky category by visit and treatment.

Quality of Life (QoL) was to be assessed through EORTC QLQ-C30 and QLQ-OES18 questionnaires. For QLQ-C30, the scoring of the global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning) and

symptom scales (fatigue, nausea and vomiting, pain, dyspnea, loss of appetite, constipation, diarrhea, financial difficulties) were to be calculated based on the instructions in EORTC QLQ-C30 Scoring Manual[35]. The scores were to be scaled to 0-100, higher scores representing higher level of QoL, higher level of functioning, or higher level of symptomatology/problems depending on the item. In case more than half of the items were missing for a scale, the score was to be set missing. For cases with less than half of missing items per scale the score was to be calculated by using the mean of the available items.

For QLQ-OES18 the symptom scales (eating, reflux, pain, trouble swallowing saliva, choked when swallowing, dry mouth, trouble with taste, trouble with coughing, trouble talking) and the functional scale (dysphagia) were to be assessed following the same instructions.

For all scales descriptive statistics by visit and treatment group were to be reported.

Design and assumptions:

At the time of protocol development in 2010, the most effective radiochemotherapy regimens, containing 5-FU and cisplatin, achieved an overall survival (OS) rate of 36% to 40% after two years[27-29]. Thus, a 40% OS rate at 2 years was assumed as the baseline efficacy level for the present trial.

- Explorative randomised phase II study with 2 parallel groups.

- Primary endpoint: Overall survival rate after 2 years. Survival time was to be calculated from time of randomisation until death for any reason, or until last date known to be alive, whichever occurred first. In patients without death, the last date known to be alive was to be considered as censored survival time.

- The respective experimental therapy arm would be rated as insufficiently active, if the observed OS rate at 2 years was 40 % or lower, as this corresponds to the standard treatment efficacy.

- On the other hand, the experimental therapy would be considered to be a promising candidate for further development (e.g. in a phase III trial), if the true OS rate at 2 years amounted to 45% or more.

9.7.2 Determination of sample size

This phase II study was an explorative randomised study with 2 parallel groups. Using a standard single-stage phase II design by FLEMING (1981), n = 62 patients evaluable for efficacy were calculated to be recruited. As a similar number of patients was to be recruited to the standard arm, a total number of 124 patients was required. The standard treatment control group served to reduce some of the result variability which is typically encountered in single-arm phase II trials, especially caused by patient selection phenomena and investigator bias. To cover potential drop outs 67 patients per arm were to be recruited.

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The probability to accept the experimental therapy as promising (> 45% 2-year OS rate) with respect to efficacy, in spite of a true 2-year OS rate of ≤ 40% was 5% (type I error).

The probability to reject the experimental therapy as not sufficiently efficient (≤ 40%), although the true 2-year OS rate is promising (> 45%) was 20% (type II error, corresponding to a power of 80%).

With the amendment to protocol v3.0 dated Oct06, 2016, the last patient was planned to be randomised on Dec31, 2016 at the latest, which was 2.5 years later than originally planned. Based on number of patients randomised until end of July 2016 and who had received study treatment (n=66) at this timepoint it was expected that the total number of patients in the Full Analysis Set (FAS) would be between 72 and 78 patients, while the number of patients in the per protocol population was expected to be between 66 and 72 patients.

The final conclusion of the phase II trial would depend on the definite 2-year OS rate (and its confidence interval), the respective findings in the 5-FU/cisplatin reference arm, as well as the information on type, frequency and severity of toxicities.

After the amendment the 2-year overall survival rates were to be estimated using Kaplan-Meier methods and the difference between treatment groups regarding 2-year OS curves was to be compared using the log-rank test. In addition, univariate Cox proportional hazard methods were to be used to estimate the corresponding hazard ratio (HR) and 95% confidence intervals for HR.

Based on the expected number of patients randomised until end of 2016, the following difference (hazard ratios) can be detected between the two treatment arms with 80% power and at a two-sided significance level of 0.05, assuming that the 2-years OS probability is between 30 and 40%, and number of lost-to-follow-ups is about 5% during the 2 years.

Table 9: Hazard ratios and necessary numbers of events

Sample size	2-year OS probability		Necessary number of events	Hazard ratio
	CT only	CT plus Cetuximab		
2 x 33	30%	63.14%	34	0.3820
	35%	68.38%	31	0.3621
	40%	73.19%	28	0.3407
2 x 36	30%	61.73%	38	0.4007
	35%	67.02%	35	0.3812
	40%	71.90%	31	0.3601
2 x 39	30%	60.48%	42	0.4177
	35%	65.81%	38	0.3986
	40%	70.74%	34	0.3778

9.8 Changes in the conduct of the study or planned analysis

During the course of the study, the protocol was amended twice:

Amendment 1, Protocol v2.0, Aug25, 2011: The conduct of the study was not changed compared to the initially approved v1.7 dated Jul26, 2011. Some corrections were done and specifications were detailed. Some changes were made due to initial deficiency letters by the Ethics Committee and the competent authority.

A substantial change was the introduction of a data safety monitoring board (DSMB) and an adaptation of the planned chemotherapy to reduce toxicity. The sponsor had decided with respect to a publication by Minsky et al. (2002)[34] to continue with administration of chemotherapy in 4 cycles, but to reduce the dose of 5-FU to 750 mg/m² in cycle 3 and 4. Additionally, the interval between cycles 2 and 3 was defined as 5 instead of 4 weeks.

This amendment was approved before the first patient had been included, so all patients had been treated according to this treatment scheme.

Amendment 2, Protocol v3, Oct06, 2016: The amendment contained an additional interim analysis at the time of the planned end of the therapy phase in Q1 2017, a change in the planned duration of the study, a change in the planned number of patients and, correspondingly, the adaptation of the statistical analysis.

Due to the good experiences during the last years of the trial with respect to safety, the unexpectedly high difference in overall survival between the treatment groups and the slow recruitment, the sponsor decided to terminate the study prematurely.

If recruitment would continue to be as slow as it was during the first years, the study would have been prolonged for a further 5 years to reach the initially planned number of 134 patients. It was also unlikely that the recruitment rate would increase as the possibilities for surgical treatment had improved. Operability of the tumour was the most frequently named reason for non-inclusion.

With the amendment, the sample size calculation was updated (see also Section 9.7.2). It was planned that the last patient was to be randomised on Dec31, 2016 at the latest, which was 2.5 years later than originally planned. Based on the number of patients randomised until the end of July 2016 and who had received study treatment (n=66) it was expected that the total number of patients in the Full Analysis Set (FAS) was between 72 and 78 patients, while the number of patients in the Per Protocol Population was expected to be between 66 and 72 patients.

Premature termination:
Recruitment was terminated prematurely on Dec31, 2016 after randomisation of 74 patients.

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The last patient was included on Nov03, 2016. The end of trial was declared to the competent authority and ethics committees on Sep04, 2018. With the early termination, the follow-up period of 2 years was not completed.

No patients received treatment at the time of the early de-registration. No patient had a medical harm or a risk by the early termination, as the usual standard of care continued to exist. Only data collection and forwarding to the sponsor did not take place anymore after de-registration.

Changes to the planned statistical analysis:

According to protocol, the Chi-square test was to be applied for the comparison of toxicity of both treatment groups. Since the cell counts in many of the comparisons were less than 5, p-values were calculated using Fisher's exact test.

When designing the protocol a subgroup analysis by tumour length (< 7cm vs. ≥ 7cm) according to endoscopy was planned. As determination of the tumour length by CT is more precise than by endoscopy, and as tumour length is covered by disease stage which was included in the subgroup analysis, it was decided that no subgroup analysis by tumour length was performed. Due to the low number of patients, no additional prognostic factors should be analysed.

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10 STUDY PATIENTS

10.1 Disposition of patients

Between September 2011 and November 2016, a total of 74 patients were randomised into the clinical trial at 10 sites. 35 patients were randomised into Arm A (radiochemotherapy + cetuximab) and 39 patients were randomised into Arm B (radiochemotherapy alone).

Table 10: Number of patients randomised per site

Site number	Number of patients recruited n (%[1])	Number of patients: Arm A n (%[1])	Number of patients: Arm B n (%[1])
01	30 (40.5)	14 (40.0)	16 (41.0)
02	4 (5.4)	1 (2.9)	3 (7.7)
03	8 (10.8)	6 (17.1)	2 (5.1)
07	3 (4.1)	1 (2.9)	2 (5.1)
09	1 (1.4)	0	1 (2.6)
10	21 (28.4)	9 (25.7)	12 (30.8)
11	2 (2.7)	2 (5.7)	0
13	3 (4.1)	0	3 (7.7)
14	1 (1.4)	1 (2.9)	0
19	1 (1.4)	1 (2.9)	0
Total	**74**	**35**	**39**

[1] Percentages are based on the total number of patients in each column.

Six patients (8.1%) did not receive study treatment:

- One patient in Arm A withdrew consent before start of treatment (patient 020004).

- In one patient in Arm A an exclusion criterion occurred after randomisation; the patient had a pre-existing polyneuropathy (patient 010014).

- In one patient in Arm A an exclusion criterion occurred (M1) (patient 100002).

- For one patient in Arm B it was decided to administer another therapy regimen after randomisation (patient 130002).

- One patient in Arm B received radiation therapy too early to start within the clinical trial (patient 100007).

- No data are available from one patient randomised into Arm B (patient 030008).

Table 11: Reason for End of Treatment (EOT)

Reason for EOT	Total (N=68)[3] n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Treatment completed according to protocol	**25 (36.8)**	**14 (43.8)**	**11 (30.6)**
Treatment phase prematurely discontinued	**42 (61.8)**	**18 (56.3)**	**24 (66.7)**
Resectability achieved	22 (32.4)	7 (21.9)	15 (41.7)
Progression of disease	4 (5.9)	2 (6.3)	2 (5.6)
Grade 4 toxicity related to cetuximab	1 (1.5)	1 (3.1)	0
≥ Grade 3 allergic/hypersensitivity reaction related to cetuximab	3 (4.4)	3 (9.4)	0
Other adverse event[1]	9 (13.2)	5 (15.6)	4 (11.1)
Withdrawal of consent	0	0	0
Death	2 (2.9)	0	2 (5.6)
Other[2]	1 (1.5)	0	1 (2.8)
Unknown	**1 (2.9)**	**0**	**1 (2.8)**

[1] Other adverse events (AEs) included pneumonia, several severe complications, leucopenia, heart attack, oedema, chest pain, impaired tubular function, and a general bad state. For one patient, the AE leading to treatment discontinuation is unknown.

[2] Other reason for premature end of treatment was the occurrence of pneumonia and worsening of ECOG in one patient.

3 Patients not receiving treatment (010014, 020004, 030008, 100002, 100007, 130002) were not included in the table.

10.2 Protocol deviations

10.2.1.1 Inclusion and exclusion criteria

- In patient 010001 (Arm A) exclusion criterion no. 4 – other previous malignancy – was violated. The patient had had a melanoma in 2001. Eligibility was confirmed by the sponsor. Also the patient was included despite documented alcohol abuse (exclusion criterion no. 12 – known active drug abuse/alcohol abuse) and no LVEF measurement was done for screening (exclusion criterion no. 7 – Clinically relevant coronary artery disease [...] left ventricular ejection faction [LVEF] below the institutional range of normal).

- In patient 010003 (Arm A) FEV_1 measurement was not done during screening, so exclusion criterion no. 6 – $FEV_1 < 1.1$ – could not be evaluated.

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- In patient 010007 (Arm B) inclusion criteria no. 7 – adequate bone marrow function – and 8 – adequate liver function - could not be evaluated. Neutrophils and alkaline phosphatase were not determined at baseline.

- In patient 010008 (Arm B) exclusion criterion no. 9 – contraindications to receive cisplatin, 5-FU or cetuximab - was violated. The patient suffered from renal failure grade 1. The patient received full treatment.

- In patient 010014 (Arm A) exclusion criterion no. 9 – contraindications to receive cisplatin, 5-FU or cetuximab - was violated. The patient received two cycles of chemotherapy, both without cisplatin.

- In patients 010015 (Arm A), 010017 (Arm B), 010018 (Arm A), and 010019 (Arm B) exclusion criterion no. 6 – $FEV_1 < 1.1$ – was violated. Eligibility was confirmed by the sponsor.

- In patients 010016 (Arm B), 010018 (Arm A) and 010019 (Arm B) FEV_1 was not measured at screening, so exclusion criterion no. 6 could not be evaluated.

- In patient 010020 (Arm B) exclusion criterion no. 1 – distant metastasis (M1) – was violated. The deviation was discovered after EOT (at re-evaluation by the radiologist).

- In patient 010021 (Arm B) exclusion criterion no. 4 – other previous malignancy – was violated. Eligibility was confirmed by the sponsor, as the oropharynx cancer had been successfully treated (CR) and was under control. The oropharyngeal cancer was not considered prognostically relevant with respect to the LEOPARD-II study.

- In patient 010025 (Arm A) inclusion criterion no. 8 – adequate liver function – was violated. The γ-GT value was 3x above the normal value. It was decided by the sponsor that the patient can remain in the study after the deviation was detected during a monitoring visit.

- In patient 030002 (Arm A) inclusion criterion no. 8 – adequate liver function – and exclusion criterion no. 4 – other previous malignancy – were violated. Eligibility was confirmed by the sponsor. The patient had a high γ-GT value at study entry and had suffered from malignant melanoma 12 years ago.

- In patient 070001 (Arm B) exclusion criterion no. 4 – other previous malignancy – was violated. The patient had a prostate carcinoma operation in 2007. Eligibility was confirmed by the sponsor as a local prostate carcinoma has a good prognosis and treatment does not interfere with treatment for esophageal cancer. Also the patient was included although neutrophil count and bilirubin were not measured before randomisation (inclusion criteria no. 7 and 8).

- In patient 100002 (Arm A) inclusion criterion no. 8 – adequate liver function – was violated. Eligibility was confirmed by the sponsor, as the bilirubin value was elevated due to a suspected Gilbert's disease which was considered a not relevant morbidity. Also exclusion criterion no. 1 – distant metastasis (M1) – was violated.

- In patient 100006 (Arm B), no ECG at screening was done. Inclusion criterion no. 6 – adequate cardiac, pulmonary and ear function – could not be evaluated.
- In patient 100008 (Arm B) inclusion criterion no. 6 – adequate cardiac, pulmonary and ear function – and exclusion criterion no. 6 – $FEV_1 < 1.1$ – were violated, FEV_1 and LVEF were not measured.
- In patient 100011 (Arm B) exclusion criterion no. 1 – distant metastasis (M1) – was violated. Eligibility was confirmed by the sponsor. The patient had supraclavicular lymph nodes.
- In patient 100014 (Arm B) exclusion criterion no. 4 – other previous malignancy – was violated. The previous malignancy was considered not clinically or prognostically meaningful.
- In patient 110001 (Arm A) exclusion criterion no. 1 – distant metastasis (M1) – was violated. The tumour was initially assessed as M0.

10.2.1.2 Randomisation, treatment allocation and blinding

- Patient 010008 (Arm B) signed the ICF one day after start of treatment.
- For patient 100004 (Arm B) no ICF was signed for the translational research project, but samples were taken.
- Patient 140001 (Arm A) was not treated with study medication, but with the commercially available product.

10.2.1.3 Compliance with time windows

- In patient 020004 (Arm A) gastroscopy incl. biopsy was performed 30 days prior to randomisation. Eligibility was confirmed by the sponsor.
- In patient 100007 (Arm B) radiation started before randomisation and the patient did not receive chemotherapy. The patient was withdrawn from the study.

10.2.1.4 Treatment compliance

- In patients 010004 (Arm B) and 010006 (Arm A) tumour assessment was not done according to RECIST 1.1, but by endoscopy.
- In patient 020002 (Arm B) cycle 3 was administered one week too early.
- Patient 030007 (Arm A) had progressive disease after cycle 1, but treatment was continued.

10.2.1.5 Non-permitted concomitant medication

No major protocol deviation with respect to non-permitted concomitant medication were observed.

10.2.1.6 Demographic and baseline characteristics

No major protocol deviation with respect to demographic and baseline characteristics were observed.

11 EFFICACY EVALUATION

11.1 Data sets analysed

Safety Analysis Set

The safety population included all patients who had received at least one dose of trial medication or radiotherapy and for whom at least one post-baseline safety measurement was available.

Six out of 74 randomised patients did not receive any study treatment and were excluded from the safety analysis set. For all patients receiving study medication, at least one post-baseline safety assessment was available, so the safety analysis set consisted of 68 patients.

Full Analysis Set

The Full Analysis Set included all patients who had received at least one dose of trial medication or radiotherapy and for whom at least one post-baseline efficacy measurement was available.

Six out of 74 randomised patients did not receive study treatment and were excluded from the full analysis set. For all patients receiving study medication, at least one post-baseline efficacy measurement was available, so the full analysis set consisted of 68 patients. Post-baseline efficacy measurement was defined as post-baseline tumour assessment and/or availability of survival data, as the primary efficacy endpoint was 2-years overall survival.

Per Protocol Set

This population included all patients with at least six weeks of trial medication plus all patients who discontinued the study prematurely due to lack of efficacy, death or toxicity.

All 68 patients had either received study medication for at least six weeks, had achieved resectability after 4-4.5 weeks, or discontinued study treatment due to progression of disease (lack of efficacy), death, or toxicity/adverse events. So, the per protocol set also consisted of 68 patients.

All safety analyses were performed on the safety analysis set. All efficacy analyses were performed on the full analysis set. The per protocol set contained the same patients as the FAS.

11.2 Demographic and other baseline characteristics

The Full Analysis Set (FAS) consisting of 68 patients was analysed regarding demographic and baseline characteristics. 52 patients (22 patients [68.8%] in Arm A and 30 patients [83.3%]) in Arm B) were male. 16 patients (10 patients [31.3%] in Arm A and 6 patients [16.7%] in Arm B) were

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female. The median age was 65 years (Arm A: 65 years, Arm B: 64 years) ranging from 44 to 80 years. All patients were Caucasian.

Table 12: Demographics (Full Analysis Set)

		Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Age	Mean	64	64	64
	SD	7.94	9.35	6.57
	Median	65	65	64
	Min, max	44, 80	44, 80	49, 79
Gender	Male	52 (76.5)	22 (68.8)	30 (83.3)
	Female	16 (23.5)	10 (31.3)	6 (16.7)
Ethnic origin	Caucasian	68 (100.0)	32 (100.0)	36 (100.0)

Fifty-five patients (80.9%) had a squamous cell carcinoma, 13 patients (19.1%) had an adenocarcinoma. The majority of patients had a tumour of grade 2 (34 patients, 50.0%) and grade 3 (21 patients, 30.9%) with a similar distribution in both treatment arms. In 24 patients (35.3%), the tumour was located in the lower esophagus, in 21 patients (30.9%) in the middle esophagus, in 15 patients (22.1%) in the upper esophagus, in 6 patients there was more than one location and for 2 patients the location was unknown.

The major T-stage was T3 (40 patients, 58.8%), the major N-stage was N1 (28 patients, 41.2%). Almost all patients had an M-stage of 0 (66 patients, 97.1%), one patient had M1a-stage disease (Arm B). For one patient in Arm A, the M-stage was initially evaluated as M0, but later on, pulmonary metastases were detected that were possibly already existent at screening. The M-stage at screening was evaluated as Mx.

The main reasons for unresectability were T-stage (26 patients, 52.9%) and N-stage (27 patients, 39.7%, multiple answers possible). In 14 patients (20.6%) the tumour was considered unresectable due to the tumour location in the upper third of the esophagus. Further details on tumour characteristics at baseline are listed in Table 13.

Table 13: Tumour characteristics at baseline (Full Analysis Set)

		Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Tumour type	Squamous cell carcinoma	55 (80.9)	27 (84.4)	28 (77.8)
	Adenocarcinoma	13 (19.1)	5 (15.6)	8 (22.2)
Tumour grade	1	1 (1.5)	0	1 (2.8)
	2	34 (50.0)	16 (50.0)	18 (50.0)
	3	21 (30.9)	11 (34.4)	10 (27.8)
	Unknown	12 (17.6)	5 (15.6	7 (19.4)

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		Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Tumour localisation (esophagus)	Lower	24 (35.3)	9 (28.1)	15 (41.7)
	lower and middle	4 (5.9)	1 (3.1)	3 (8.3)
	Middle	21 (30.9)	13 (40.6)	8 (22.2)
	upper and middle	2 (2.9)	0	2 (5.6)
	upper	15 (22.1)	9 (28.1)	6 (16.7)
	unknown	2 (2.9)	0	2 (5.6)
TNM status at start of study	T1	2 (2.9)	1 (3.1)	1 (2.8)
	T2	2 (2.9)	2 (6.3)	0
	T3	40 (58.8)	20 (62.5)	20 (55.6)
	T4	21 (30.9)	8 (25.0)	13 (36.1)
	Tx	3 (4.4)	1 (3.1)	2 (5.6)
	N0	15 (22.1)	7 (21.9)	8 (22.2)
	N1	28 (41.2)	14 (43.8)	14 (38.9)
	N2	14 (20.6)	7 (21.9)	7 (19.4)
	N3	6 (8.8)	3 (9.4)	3 (8.3)
	Nx	2 (2.9)	0	2 (5.6)
	N+	2 (2.9)	1 (3.1)	1 (2.8)
	N missing	1 (1.5)	0	1 (2.8)
	M0	66 (97.1)	31 (96.9)	35 (97.2)
	M1	0	0	0
	M1a	1 (1.5)	0	1 (2.8)
	Mx	1 (1.5)	1 (3.1)	0
Reason for unresectability (multiple answers)	T-stage	36 (52.9)	14 (43.8)	22 (61.1)
	N-stage	27 (39.7)	13 (40.6)	14 (38.9)
	Performance/nutritional status	2 (2.9)	1 (3.1)	1 (2.8)
	Pulmonary function	1 (1.5)	(3.1)	0
	Tumour location upper third of esophagus	14 (20.6)	7 (21.9)	7 (19.4)
	Tumour relation to other organs/structures	6 (8.8)	4 (12.5)	2 (5.6)
	Other reason	9 (13.2)[1]	4 (12.5)	5 (13.9)
	Unknown	2 (2.9)	1 (3.1)	1 (2.8)

[1] Other reasons for unresectability were current/heavy smoker (3 patients), co-morbidity, patient's wish, patient's denial of surgery, cervical anastomosis needed at surgery, age, and unclear pulmonary lesions.

19 patients (27.9%) had a Karnofsky Performance Status of 100% at screening, 32 patients (47.1%) of 90%, 14 patients (20.6%) of 80%, and 3 patients (4.4%) of 70%. For further relevant screening assessments as well as relevant diseases other than esophageal cancer, please refer to section 14.1.

11.3 Measurements of treatment compliance

Since all treatment components were administered at the hospital, compliance could be easily supervised. All drugs were administered either by the investigator or another qualified member of the study team.

11.4 Efficacy results and tabulation of individual patient data

11.4.1 Analysis of efficacy

11.4.1.1 Primary endpoint: 2-year overall survival (OS)

The primary endpoint of 2-year OS was 71% in Arm A (95% CI: 55%; 87%) and 53% in Arm B (95% CI: 36%; 71%) based on Kaplan-Meier estimation. Since the two-sided 95% Kaplan-Meier-CI for the 2-year OS rate in Arm A excludes the 40% rate of the null hypothesis, the null hypothesis could be rejected and the combination of cetuximab plus standard radiochemotherapy can be considered a promising treatment.

11.4.1.2 Secondary endpoints

11.4.1.2.1 Overall survival (OS)

A total of 13 events (40.6% of patients) occurred in Arm A, and a total of 20 events (55.6% of patients) occurred in Arm B. The median overall survival was 49.1 months in Arm A and 24.1 months in Arm B (total median OS: 38.4 months). The exploratory log-rank test for the difference between the treatment groups had a p-value of 0.1470 (statistically not significant).

The 1-year OS rate was 74% in Arm A (95% CI: 59%; 90%) and 70% in Arm B (95% CI: 54%; 86%).

The hazard ratio for cetuximab vs. standard therapy was 0.60 (95% CI: 0.30; 1.21).

The results show a consistent, but not statistically significant trend to improved survival with the addition of cetuximab to the regimen.

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14.2 Efficacy data
Figure 14.2.1.1 Kaplan-Meier curves for Overall survival (PP)
By treatment group
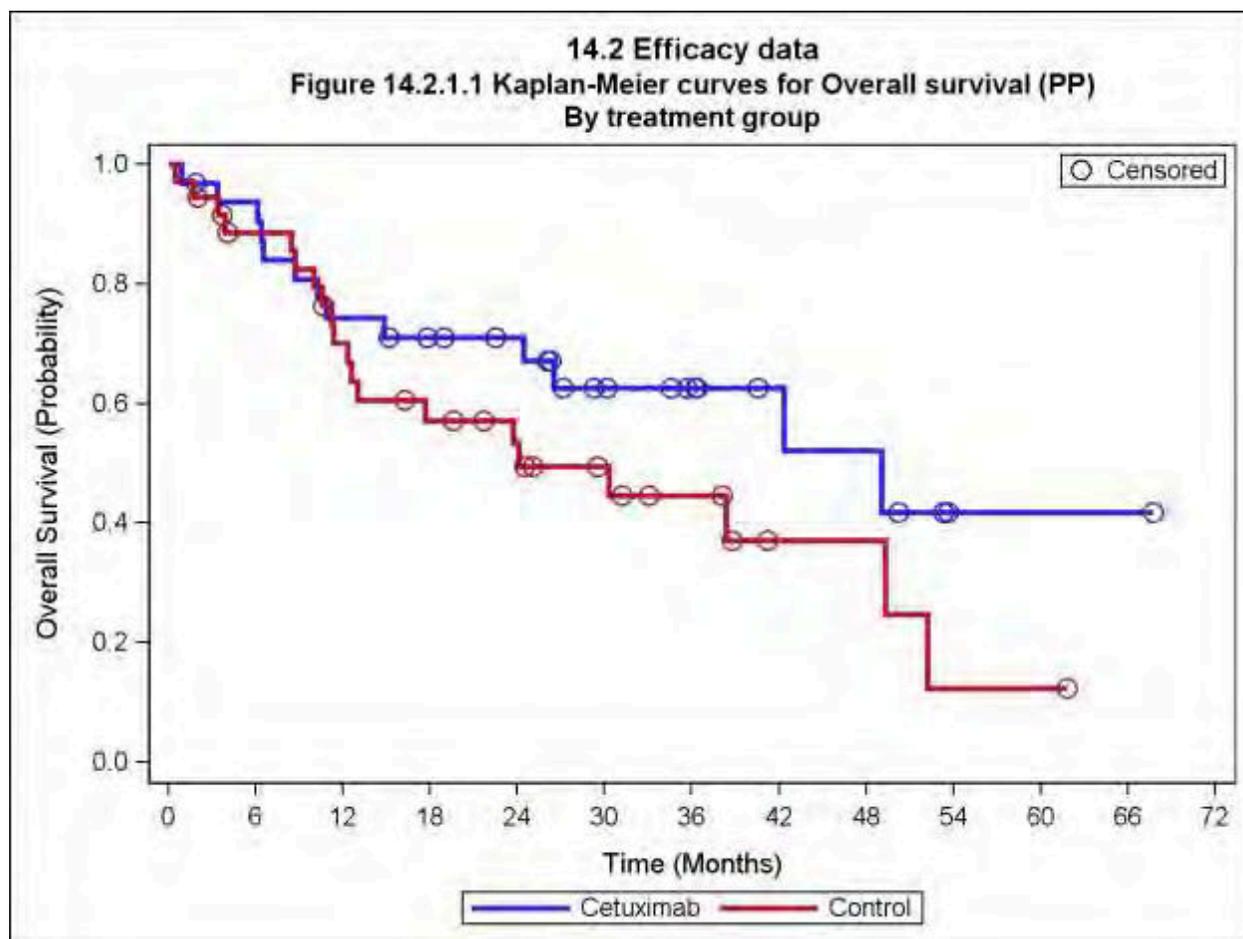
Figure 3: Kaplan-Meier curve for Overall Survival by treatment group (Full Analysis/Per Protocol Set)

For further details and the KM curve for OS in the overall population, please refer to Section 14.2.

11.4.1.2.2 Progression-free survival (PFS)

For PFS the event was defined as the date of radiologically proven progression, clinical progression or death due to progressive disease using the first occurrence of these.

In Arm A, 12 events occurred (37.5% of patients), and in Arm B, 22 events occurred (61.1% of patients). The median PFS was 17.6 months in Arm B and 27.2 months in the overall population. In Arm A, the median PFS was not estimable due to censored cases of patients who died from other reasons that progressive disease. The log-rank test's p-value for the difference between the treatment groups was 0.0600.

The 2-year PFS rate was 56% in Arm A (with a 95% CI of 37%; 75%) and 44% in Arm B (95% CI: 26%; 62%).

The 1-year PFS rate was 64% in Arm A (95% CI: 47%; 82%) and 58% in Arm B (95% CI: 40%; 75%).

The hazard ratio for cetuximab vs. standard therapy was 0.51 (95% CI: 0.25; 1.04).
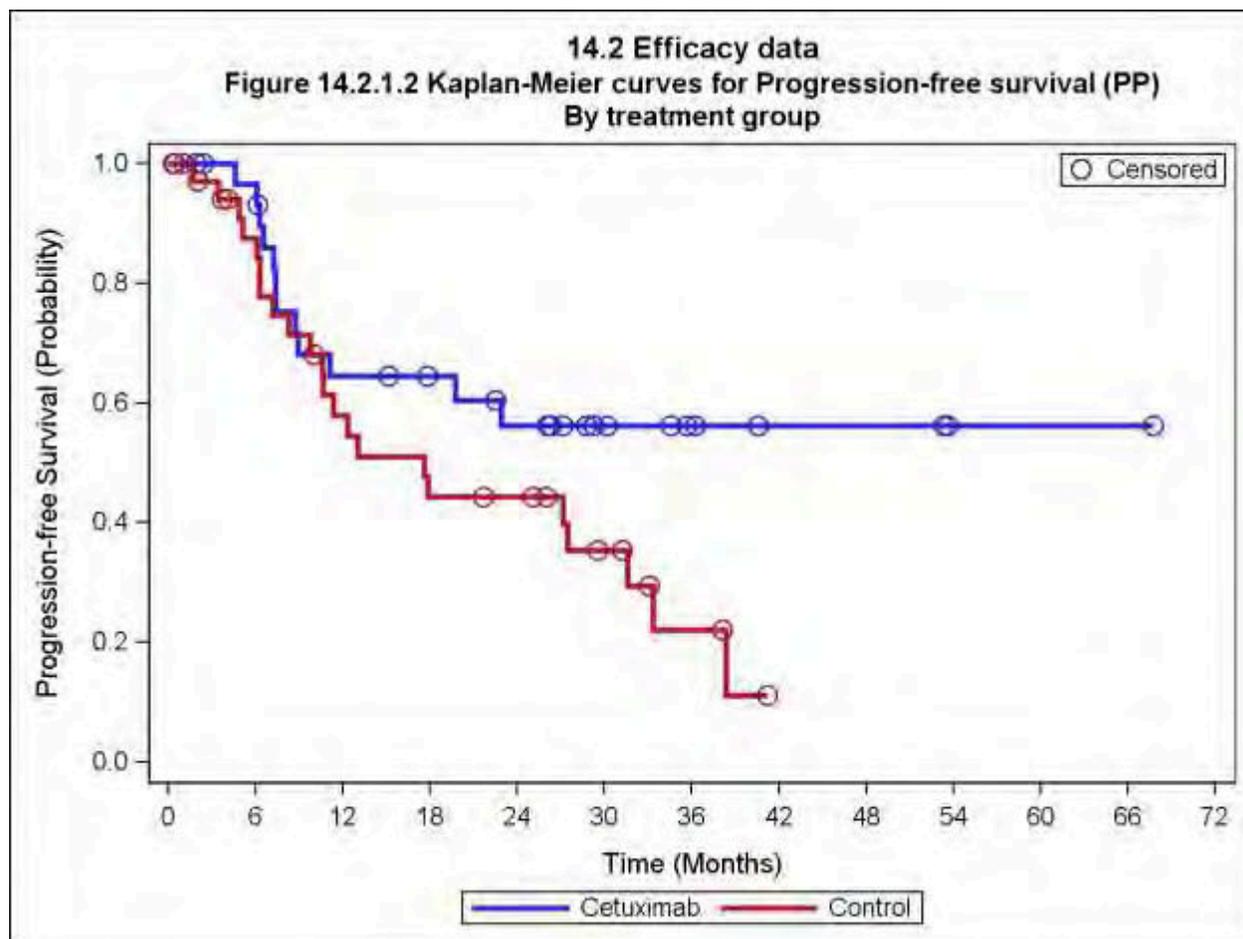
Figure 4: Kaplan-Meier curve for Progression-Free Survival by treatment group (Full Analysis/Per Protocol Set)

For further details and the KM curve for PFS in the overall population, please refer to Section 14.2.

11.4.1.2.3 Loco-regional control (LC)

For LC the event date was defined as the date of first finding of progressive primary tumour and/or regional lymph nodes on endoscopy, endoscopic ultrasound or computed tomography. Patients with no events were censored at the last follow-up date (known to be alive).

In Arm A, 4 events occurred (12.5% of patients), in Arm B, 9 events occurred (15.0% of patients). The median LC time was not reached in any group nor in the overall population. The p-value of the exploratory log-rank test for the difference between the treatment groups was 0.1505.

The 2-year LC rate was 84% in Arm A (with a 95% CI of 70%; 99%) and 72% in Arm B (95% CI: 55%; 89%).

The 1-year LC rate was 89% in Arm A (95% CI: 77%; 101%) and 81% in Arm B (95% CI: 67%; 95%).

The hazard ratio for cetuximab vs. standard therapy was 0.43 (95% CI: 0.13; 1.40).
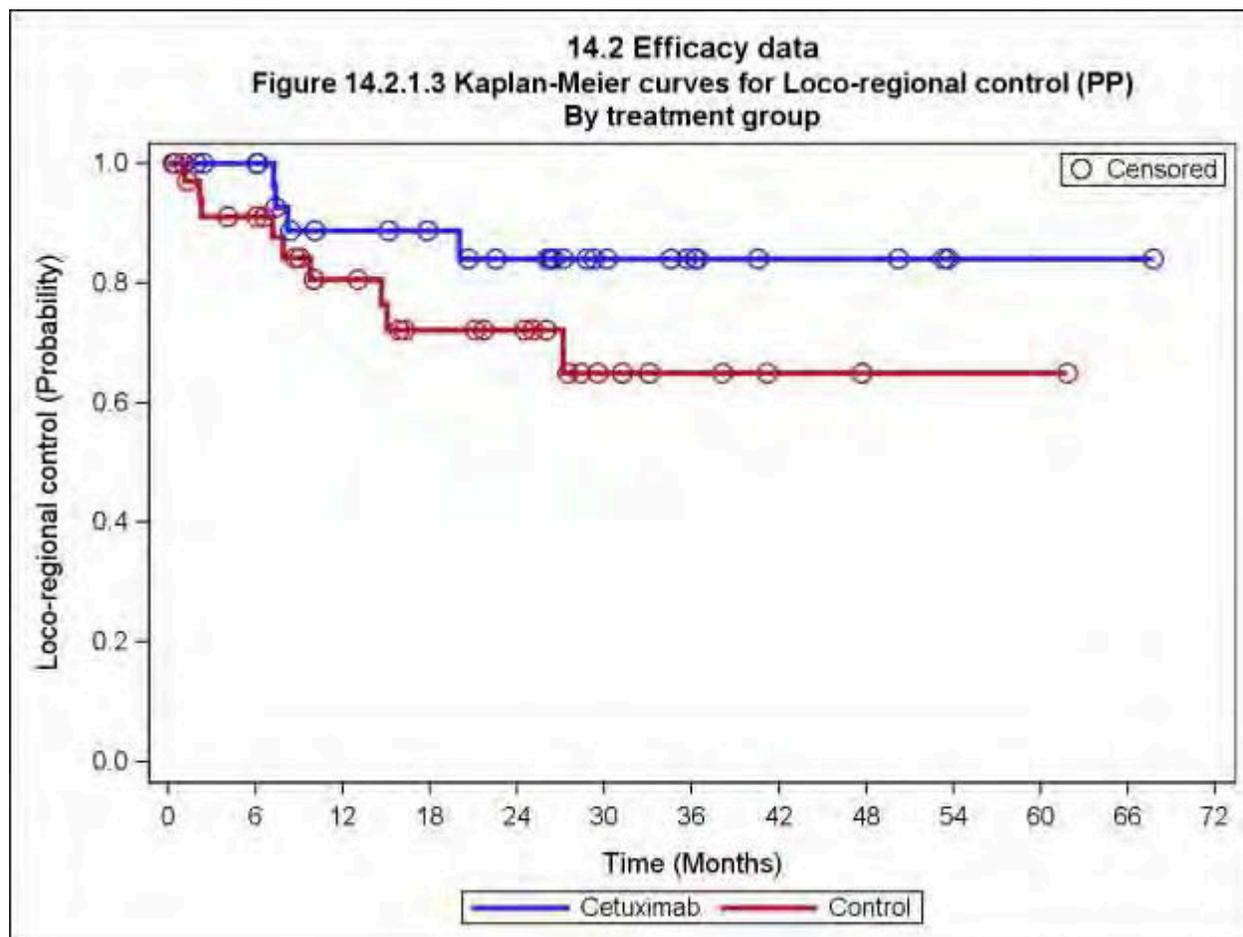
Figure 5: Kaplan-Meier curve for Loco-regional Control by treatment group (Full Analysis/Per Protocol Set)

For further details and the KM curve for LC in the overall population, please refer to Section 14.2.

11.4.1.2.4 Metastases-free survival (MFS)

For MFS the event date was defined as the date of first occurrence of distant metastasis incl. distant lymph nodes. Patients with no events were censored at the last follow-up date (known to be alive).

In Arm A, 7 events occurred (21.9% of patients), in Arm B, 15 events occurred (32.4% of patients). The median MFS was 31.3 months in Arm B; it was not reached in Arm A and the overall population during the observation period. The p-value of the exploratory log-rank test for the difference between the treatment groups was 0.0568).

The 2-year MFS rate was 74% in Arm A (with a 95% CI of 57%; 91%) and 54% in Arm B (95% CI: 36%; 73%).

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The 1-year MFS rate was 79% in Arm A (95% CI: 64%; 94%) and 70% in Arm B (95% CI: 53%; 86%).

The hazard ratio for cetuximab vs. standard therapy was 0.43 (95% CI: 0.17; 1.05).
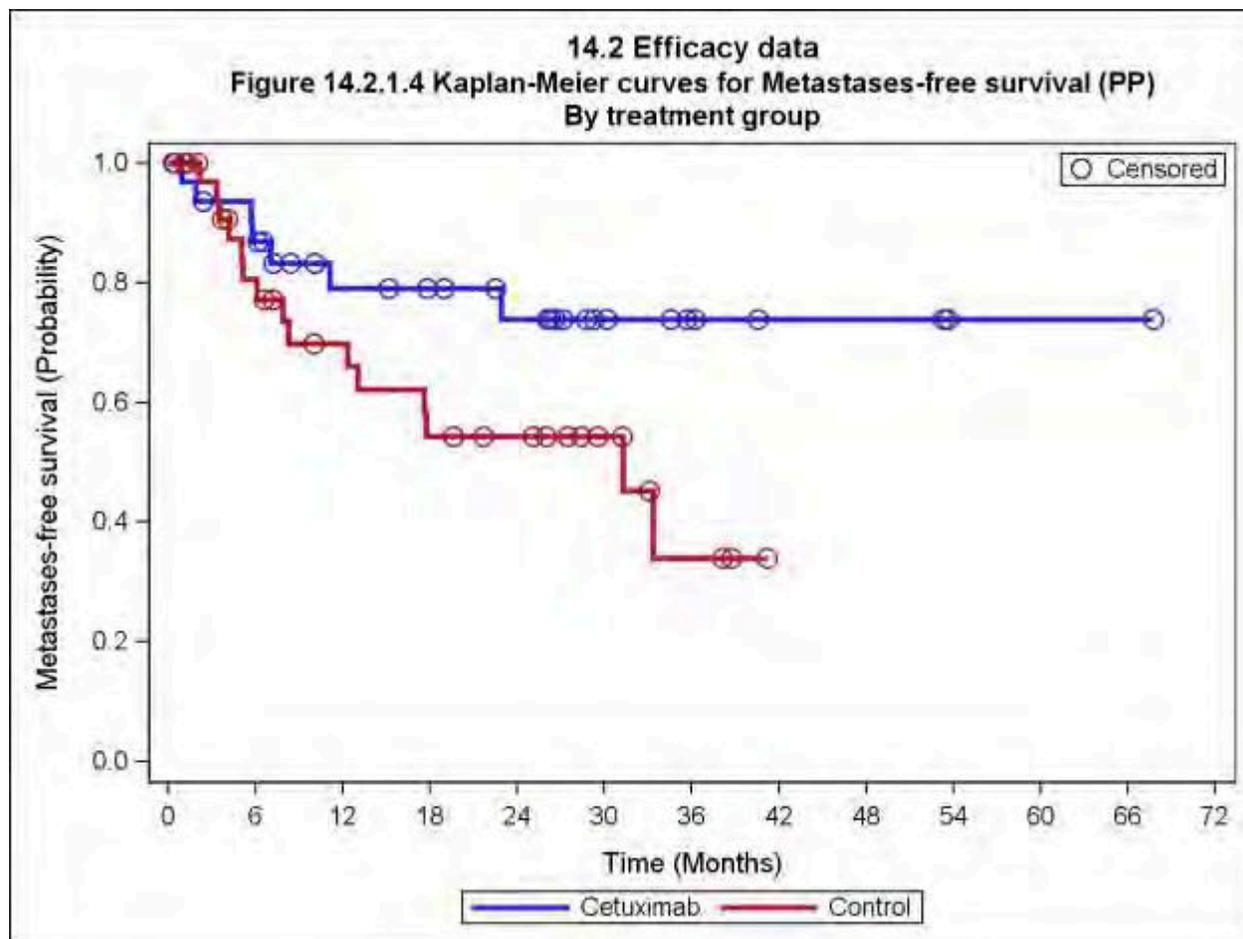
Figure 6: Kaplan-Meier curve for Metastasis-Free Survival by treatment group (Full Analysis/Per Protocol Set)

For further details and the KM curve for MFS in the overall population, please refer to Section 14.2.

11.4.1.2.5 Overall best response

26 out of 32 of patients in Arm A (81.3%) and 15 out of 36 patients in Arm B (41.7%) reached a Complete Response (CR). Furthermore, 10 patients in Arm B (27.8%) reached a Partial Response (PR) as best response. The overall response rate thus was 81.3% in Arm A and 69.4% in Arm B. The exploratory chi-square test for difference between the treatment arms was not statistically significant (p = 0.2618). Considering the total population, 75.0% of patients were responders.

81.3% of patients in Arm A and 41.7% of patients in Arm B achieved a CR. The Chi-square test comparing CR vs. non-CR revealed a significant difference (p = 0.0014).

There were 6 non-responders in Arm A (18.8%), whereby 4 patients (12.5%) had stable disease (SD) as best response and 1 patient (3.1%) had progressive disease (PD). For one patient, the evaluation was missing. In Arm B, 11 patients (30.6%) were non-responders: 4 patients each (11.1%) had SD and PD, and for 3 patients (8.3%) the evaluation was missing.

11.4.1.3 Analysis of prognostic factors
All tables and Kaplan-Meier curves for overall survival by prognostic factor groups are presented in Section 14.2.

11.4.1.3.1 Overall survival by age
The overall survival of patients aged ≤ 60 years (22 patients) was compared to the OS of patients older than 60 years (46 patients).

The median survival for the younger patients was 42.4 months and 38.4 months for the patients older than 60 years. In the first group 9 events occurred (40.9% of patients), in the second group, 24 events occurred (52.2% of patients). The difference was statistically not significant (p = 0.6830, based on an exploratory log-rank test).

The 2-year OS rate was 65% (95% CI: 45%; 86%) for the younger patients and 61% (95% CI: 46%; 75%) for the older patients.

The 1-year OS rate was 65% (95% CI: 45%; 86%) for the younger patients, but 75% (95% CI: 62%; 88%) for the patients older than 60 years.

The hazard ratio was 0.85 (95% CI: 0.40; 1.84) for patients aged ≤ 60 years vs. patients aged > 60 years.

11.4.1.3.2 Overall survival by Karnofsky performance status
We compared patients with a Karnofsky performance status (KPS) of 100%-80% vs. patients with a KPS of 70%.

Sixty-five patients had a KPS of 100-80%. In this group, the median OS was 42.4 months, 31 events (47.7% of patients) occurred. Three patients had a KPS of 70%, and the median OS in this group was 38.4 months. Two events (66.7% of patients) occurred. The p-value of the exploratory log-rank test comparing the two groups was 0.6120.

The 2-year OS rate was 62% (95% CI: 49%, 74%) in the group of patients with a KPS of 100-80% and 67% (95% CI: 13%; 120%) in the group of patients with a KPS of 70%.

The 1-year OS rate was 72% (95% CI: 61%; 84%) for patients with a KPS of 100-80% and 67% (95% CI: 13%; 120%) for patients with a KPS of 70%.

The hazard ratio was 0.69 (95% CI: 0.16; 2.92) for KPS 100-80% vs. KPS of 70%.

11.4.1.3.3 Overall survival by tumour location
In 24 patients the tumour was located in the lower third of the esophagus, in 21 patients, the tumour was located in the middle third of the esophagus, and in 15 patients, the tumour was

located in the upper third of the esophagus. Patients with missing tumour location (2 patients) were categorised to the lower third group, patients with both lower and middle (4 patients) to the middle third group, and patients with both middle and upper (2 patients) to the upper third group. Therefore, for the purposes of analysis the lower third group consisted of 26 patients, the middle third group of 25 patients, and the upper third group of 17 patients.

In the group of patients with the tumour in the lower third of the esophagus, 11 events (42.3% of patients) occurred, the median OS was 30.3 months. In the group of patients with the tumour in the middle third of the esophagus, 13 events (52.0% of patients) occurred and the median OS was 42.4 months. In the group of patients with the tumour in the upper third of the esophagus, a total of 9 events (52.9% of patients) occurred, and the median OS was 24.1 months. The p-value of the exploratory log-rank test for the difference between the tumour location groups was 0.9388.

The 2-year OS rate was 65% (95% CI: 45%; 84%) for patients with the tumour in the lower third, 63% (95% CI: 44%; 82%) for patients with the tumour in the middle third, and 57% (95% CI: 32%; 81%) for patients with the tumour in the upper third of the esophagus.

The 1-year OS was 79% (95% CI: 62%; 95%) for patients with the tumour in the lower third, 72% (95% CI: 54%; 90%) for patients with the tumour in the middle third, and 63% (95% CI: 39%; 87%) for patients with the tumour in the upper third of the esophagus.

The hazard ratios were 0.99 (95% CI: 0.44; 2.24) for the lower third vs. middle third, 0.87 (95% CI: 0.36; 2.11) for the lower third vs. upper third, and 0.87 (95% CI: 0.37; 2.05) for the middle third vs. upper third.

11.4.1.3.4 Overall survival by histology

Thirteen patients had an adenocarcinoma (AC) and 55 patients had a squamous cell carcinoma (SCC).

Amongst the patients with AC, 8 events (61.5% of patients) occurred, the median OS was 30.3 months. Amongst the patients with SCC, 25 events (45.5% of patients) occurred, the median OS was 49.1 months. The difference was statistically not significant based on an exploratory log-rank test (p = 0.7791).

The 2-year OS rate was 68% (95% CI: 43%; 94%) in the AC group and 61% (95% CI: 47%; 74%) in the SCC group. The 1-year OS rate was 85% (95% CI: 65%; 104%) in the AC group and 69% (95% CI: 56%; 82%) in the SCC group. The hazard ratio was 1.12 (95% CI: 0.50; 2.49) for AC vs. SCC.

11.4.1.3.5 Overall survival by histologic grade

Thirty-five patients had a tumour of grade 1 (G1) or G2, and 21 patients had a tumour of G3. Patients with missing histologic grading information (12 patients) were categorized to Grade 1-2 group, so the G1-2 group consisted of 47 patients.

In the G1-2 group, 20 events occurred (42.6% of patients), and the median OS was 42.4 months. In the G3 group, 13 events (61.9% of patients) occurred, and the median OS was 24.4 months. The p-value of the exploratory log-rank test for the difference between the histologic grade groups was 0.2060.

The 2-year OS rate was 66% (95% CI: 52%; 80%) in the G1-2 group and 53% (95% CI: 31%; 76%) in the G3 group. The 1-year OS rate was 73% (95% CI: 60%; 86%) in the G1-2 group and 70% (95% CI: 50%; 90%) in the G3 group. The hazard ratio was 0.64 (95% CI: 0.31; 1.29) for Grade 1-2 vs. Grade 3.

11.4.1.3.6 Overall survival by T-stage

Two patients had a T1 tumour, 2 patients had a T2 tumour, 40 patients had a T3 tumour, and 21 patients had a T4 tumour. For 3 patients the T-stage was unknown. We compared patients with T-stage 2-3 vs. T-stage 4. The patient with T-stage 1 and the patients with unknown T-stage were categorized into the T2-3 group which then consisted of 47 patients.

In the T2-3 group, 22 events occurred (46.8% of patients), and the median OS was 42.4 months. In the T4 group, 11 events occurred (52.4%) and the median OS was 24.4 months. The p-value of the exploratory log-rank test for the difference between the T-stage groups was 0.7914.

The 2-year OS rate was 66% (95% CI: 53%; 80%) for the T2-3 group and 52% (95% CI: 30%; 75%) for the T4 group. The 1-year OS rate was 76% (95% CI: 63%; 88%) for the T2-3 group and 63% (95% CI: 42%; 85%) for the T4 group. The hazard ratio was 1.10 (95% CI: 0.53; 2.31) for T-stage 2-3 vs. T-stage 4.

11.4.1.3.7 Overall survival by N-stage

15 patients had an N-stage of 0, 28 patients had an N-stage of 1, 14 patients had an N-stage of 2, and 6 patients had an N-stage of 3. We analysed patients with N0 vs. patients with N1-N3 (N+). One patient with missing N-stage was categorized to the N0 group, and patients with N-stage x (2 patients) and patients with N-stage + (2 patients) to the N+ group. Therefore, the N0 group consisted of 16 patients, and the N+ group of 52 patients.

In the N0 group, 8 events occurred (50.0% of patients). The median OS in this group was 38.4 months. In the N+ group 25 events occurred (48.1% of patients), and the median OS was 42.4 months. The p-value of the exploratory log-rank test for the difference between the N-stage groups was 0.7736.

The 2-year OS was 67% (95% CI: 42%; 91%) for patients in the N0 group and 60% (95% CI: 46%; 74%) for patients in the N+ group. The 1-year OS was 81% (95% CI: 62%; 100%) for patients in the N0 group and 69% (95% CI: 56%; 82%) for patients in the N+ group. The hazard ratio for N0-stage vs. N+ stage was 1.12 (95% CI: 0.51; 2.50).

11.4.1.3.8 Overall survival by haemoglobin before radiotherapy

We categorised the patients according their haemoglobin (Hb) values at screening: 10 patients had Hb < 12 g/dl, 32 patients had Hb 12-14 g/dl, and 26 patients had Hb > 14 g/dl at screening.

In the group of patients with Hb < 12 g/dl, 8 events (80.0% of patients) occurred. The median OS was 11.3 months. In the group of patients with Hb 12-14 g/dl, 16 events (50.0% of patients) occurred, and the median OS was 49.1 months. In the group of patients with Hb > 14 g/dl, 9 events (34.6% of patients) occurred, and the median OS was 52.2 months. The p-value of the exploratory log-rank test for the difference between the treatment groups was 0.0449. However, no statement can be made on significance due to the exploratory nature of the tests and as no alpha adjustment was done.

The 2-year OS was 46% (95% CI: 13%; 78%) for patients with Hb < 12 g/dl, 59% (95% CI: 42%; 76%) for patients with Hb 12-14 g/dl, and 73% (95% CI: 54%; 91%) for patients with Hb > 14 g/dl. The 1-year OS rate was 46% (95% CI: 13%; 78%) for patients with Hb < 12 g/dl, 69% (95% CI: 53%; 85%) for patients with Hb 12-14 g/dl, and 87% (95% CI: 74%; 101%) for patients with Hb > 14 g/dl.

The hazard ratio for Hb < 12 g/dl vs. 12-14 g/dl was 1.68 (95% CI: 0.70; 4.01), the hazard ratio for Hb < 12 g/dl vs. > 14 g/dl was 3.20 (95% CI: 1.23; 8.33), and the hazard ratio for Hb 12-14 g/dl vs. > 14 g/dl was 1.91 (95% CI: 0.82; 4.42).

Since the log rank test for the difference in OS between the haemoglobin groups revealed a p-value < 0.05, we performed a multivariable Cox proportional hazard analysis. In the group of patients with Hb < 12 g/dl at screening (10 patients), the hazard ratio was 0.15 (95% CI: 0.03; 0.79) for cetuximab vs. standard radiochemotherapy. In the group of patients with Hb 12-14 g/dl (32 patients), the hazard ratio was 1.07 (95% CI: 0.40; 2.88) for cetuximab vs. standard therapy, and in the group of patients with Hb > 14 g/dl (26 patients), the hazard ratio was 0.32 (95% CI: 0.07; 1.57) for cetuximab vs. standard therapy.

11.4.2 Statistical/analytical issues

No statistical or analytical issues occurred during the analysis of efficacy data.

11.4.3 Tabulation of individual response data

Individual response data for each patient are displayed in Appendix 16.2.2.4.

11.4.4 Efficacy conclusions

We had the null hypothesis H_0 that cetuximab as part of the treatment resulted in a 2-year OS of 40% or less, and the alternative hypothesis H_1 that cetuximab as part of the treatment resulted in a 2-year OS ≥ 45%. The decision for rejection of H_0 was to be made based on the 95% CI of the

survival rate at 2 years. The null hypothesis was to be rejected in case the lower limit of the 95% CI was > 40%. In case the lower limit of the 95% CI was > 45%, cetuximab as part of the treatment should be considered as a promising treatment.

In our study, the 2-year OS rate in Arm A was 71% with a 95% CI [55%; 87%]. Therefore, the null hypothesis was rejected and the addition of cetuximab to standard radiochemotherapy can be considered a promising treatment.

No formal comparison between the treatment arms was planned in the study.

There was a trend to a longer PFS and MFS for an advantage of cetuximab plus standard radiochemotherapy over standard radiochemotherapy alone. For LC, no signals for an advantage of either of the groups were detected. Also the overall response rate was higher in Arm A compared to Arm B (81.3% vs. 69.4%). This difference was not statistically significant (p = 0.2618). In an exploratory analysis, 81.3% of patients in Arm A and 41.7% of patients in Arm B achieved a CR.

The following prognostic factors for overall survival were analysed in a univariate analysis: Age, Karnofsky performance status (KPS) at screening, tumour location, histology, histologic grade, T stage, N stage and haemoglobin before radiotherapy. Additionally, Hgb was analysed in a multivariate Cox proportional hazard analysis together with the treatment.

There was a trend towards a longer OS for patients with Hgb ≥ 12 g/dl compared to patients with Hgb < 12 g/dl (49.05 and 52.21 months for patients with Hgb 12-14 g/dl and > 14 g/dl vs. 11.34 months for patients with Hgb < 12 g/dl). The 1- and 2-year survival was best in patients with Hgb > 14 g/dl. The hazard ratios showed a favour for cetuximab vs. standard therapy in the Hgb < 12 g/dl group (0.15, 95% CI 0.03-0.79), while the results were inconclusive in the other two groups.

The age of the patient, tumour location and the histologic grade appeared to have no prognostic value. Hazard ratios were 1.10 for T-stage 2-3 vs. T-stage 4 and 1.12 for N-stage 0 vs. N-stage + with wide 95% CIs in both cases. Thus, also T-stage and N-stage did not show prognostic value in these analysis

Also no difference was observed for patients with KPS of 100-80% and patients with a KPS of 70%. However, in this analysis, we had a strong imbalance between the subgroups, as there were only 3 patients with a KPS of 70%, so this was not a robust analysis.

In the analysis of patients with adenocarcinoma (AC) vs. patients with squamous cell carcinoma (SCC) we had an imbalance, as there were only 13 patients with AC, but 55 patients with SCC. The median OS was higher in patients with SCC (49.1 vs. 31.3 months), but in the analysis of the 1- and 2-year OS rates the 95% CIs showed wide overlaps. Therefore, histology appeared to have no significant impact on OS.

12 SAFETY EVALUATION

12.1 Extent of exposure

Cetuximab

A total of 32 patients was randomised into Arm A and received cetuximab. Except for one patient, who received 200 mg/m² cetuximab for organisational reasons, all patients received a loading dose of 400 mg/m². The median cetuximab dose for cycle 1 was 741.6 mg (range 320 – 1016 mg). In total, 4 of the 32 patients in Arm A (12.5%) experienced allergic/hypersensitivity reactions and subsequently discontinued cetuximab (patients 030006, 070003, 140001, 190001). Only patient 070003 received further chemotherapy, the other patients were removed from study treatment and had their end of treatment visit.

From cycle 2 onwards, 250 mg/m² cetuximab was to be administered weekly. In cycle 2, 28 patients (87.5%) were still on treatment. No dose reductions were observed. The number of patients receiving cetuximab reduced to 14 (43.8%) as of day 78 (12th administration). Seven patients in Arm A (21.9%) achieved resectability at 4-4.5 weeks after start of treatment and underwent surgery, so were not further treated with cetuximab. Further reasons for premature treatment of cetuximab were toxicity from chemotherapy, cetuximab-induced pneumonitis, skin toxicity and SAEs.

The median dose of cetuximab essentially remained constant between day 8 and day 92 (14 administrations) and all administered doses ranged between 383 mg and 635 mg. Details on exposure to cetuximab are displayed in Section 14.3 (Table 14.3.7.1).

Chemotherapy

Cisplatin and 5-FU were administered on four consecutive days in each 4-weeks cycle (note: the interval between cycles 2 and 3 was 5 weeks). The starting dose of cisplatin was 20 mg/m²/day, administered as an intravenous bolus. The planned starting dose of 5-FU was 1000 mg/m²/day, administered as a continuous infusion over 4 days in cycles 1 and 2; in cycles 3 and 4 the dose of 5-FU was 750 mg/m²/day.

Three patients in Arm A did not start chemotherapy, as they did not continue study treatment after the first cetuximab administration due to allergic/hypersensitivity reactions to cetuximab. The fourth patient who had discontinued cetuximab after the first application due to an allergic reaction received chemotherapy (patient 070003). In cycle 3, 27 patients were still on cisplatin, and 25 patients were still on 5-FU therapy.

Dose reductions and delays occurred in each cycle in several patients; no major differences between the treatment arms with respect to frequency and reason for reduction/delay occurred. The main reason for dose reduction was toxicity. The main reasons for dose delays were organisational reasons and toxicity.

The median dose of cisplatin showed no major differences between the treatment groups. The minimum single dose was 23.6 mg, the maximum single dose was 176 mg. The median total cycle doses in Arm A were 37.7 mg (cycle 1), 37.0 mg (cycle 2), 36.4 mg (cycle 3), and 35.5 mg (cycle 4). In Arm B, the median total cycle doses were 37.0 mg (cycle 1), 36.95 mg (cycle 2), 37.2 mg (cycle 3), and 38.4 mg (cycle 4).

In cycle 3, three patients (2 patients in Arm A and 1 patient in Arm B) received several doses of carboplatin instead of cisplatin due to nephrotoxicity of cisplatin.

The median dose of 5-FU also showed no major differences between the treatment groups. The minimum single dose was 825 mg, the maximum single dose was 2500 mg. The median total cycle doses in Arm A were 1887 mg (cycle 1), 1830 mg (cycle 2), 1275 mg (cycle 3), and 1333 mg (cycle 4). In Arm B, the median total cycle doses were 1850 mg (cycle 1), 1851 mg (cycle 2), 1421 mg (cycle 3), and 1440 mg (cycle 4).

Details on exposure to cisplatin and 5-FU are displayed in Section 14.3 (Tables 14.3.7.2 and 14.3.7.3).

Radiotherapy

65 out of 68 patients received radiotherapy. The three patients who did not receive radiotherapy were three of the patients from Arm A with allergic/hypersensitivity reactions to cetuximab. Of those 65 patients, 25 patients (8 patients [25.0%] in Arm A and 17 patients [26.2%] in Arm B) achieved resectability and radiotherapy was stopped after 45 Gy. 30 patients (18 patients [56.3%] in Arm A and 12 patients [33.3%] in Arm B) received the full dose of 59.4 Gy according to protocol. For further details, please refer to Section 14.3 (Table 14.3.7.4).

12.2 Adverse events (AEs)

12.2.1 Brief summary of adverse events

All 68 patients who had received at least one dose of study medication experienced at least one adverse event (AE).

Forty-five patients (66.2%) experienced serious AEs (SAEs), thereof 21 patients in Arm A (65.6%) and 24 patients (66.7%) in Arm B.

Fifty-three patients (77.9%) experienced at least one severe AE (defined as CTC grade 3-5), thereof 26 patients (81.3%) in Arm A and 27 patients (75.0%) in Arm B.

In Arm A, 27 patients (84.4%) experienced cetuximab-related AEs defined as AEs classified as possibly, probably, or certainly/definitely related to cetuximab. Those are 84.4% of patients in Arm A.

Fifty-eight patients (85.3%) experienced chemotherapy-related AEs, defined as AEs classified as possibly, probably, or certainly/definitely related to chemotherapy, thereof 26 patients (81.3%) in Arm A and 32 patients (88.9%) in Arm B.

Fifty patients (73.5%) experienced at least one radiotherapy-related AE, defined as an AE classified as possibly, probably, or certainly/definitely related to radiotherapy, thereof 23 patients (71.9%) in Arm A and 27 patients (75.0%) in Arm B.

In 8 patients in Arm A (25.0%) an AE led to discontinuation of cetuximab. This corresponds to 25.0% of patients in Arm A.

In 16 patients (23.5%) an AE led to discontinuation of chemotherapy. Of those 16 patients, 7 were treated in Arm A (21.9%) and 9 were treated in Arm B (25.0%).

In 2 patients (2.9%) an AE led to discontinuation of radiotherapy. Both patients were in Arm B (5.6%).

In 1 patient (1.5%) an AE led to death. The patient was treated in Arm B (2.8%).

Further details are presented in Table 14.3.1.1.

12.2.2 Display of adverse events

The most frequently observed clinical AEs were nausea (experienced by 39 patients, 57.4%), fatigue (27 patients, 39.7%), esophagitis (25 patients, 36.8%), dysphagia (18 patients, 26.5%), constipation (17 patients, 25.0%), vomiting (13 patients, 19.1%), lung infection, diarrhea, mucositis oral, weight loss, cough (12 patients each, 17.6%), acneiform rash (11 patients, 34.4% of patients in Arm A), radiation dermatitis and edema (10 patients each, 14.7%).

The most frequently observed AEs related to laboratory values were hypokalemia (28 patients, 41.2%), anemia (26 patients, 38.2%), leukopenia (24 patients, 35.3%), thrombocytopenia (18 patients, 26.5%), hypomagnesemia (16 patients, 23.5%), and hypocalcemia (11 patients, 16.2%).

For the majority of AEs occurring in ≥ 10 patients the occurrence was similar in both treatment arms. A higher occurrence of more than 10% in Arm A was observed for the following AEs: Hypokalemia (50.0% of patients in Arm A vs. 33.3% of patients in Arm B, p = 0.2186), leukopenia (50.0% vs. 22.2%, p = 0.0228), thrombocytopenia (34.4% vs. 19.4%, p = 0.1816), hypomagnesemia (40.6% vs. 8.3%, p = 0.0033), mucositis oral (25.0% vs. 11.1%, p = 0.2031), weight loss (28.1% vs. 8.3%, p = 0.0539), hypocalcemia (28.1% vs. 5.6%, p = 0.0188), acneiform rash (34.4% vs. 0%, p < 0.0001), radiation dermatitis (28.1% vs. 2.8%, p = 0.0046), maculo-papular rash (21.9% vs. 2.8%, p = 0.0219), and allergic reaction (12.5% vs. 0%, p = 0.0442). The difference was clinically significant for acneiform rash, hypomagnesemia, weight loss, radiation dermatitis, maculopapular rash, hypocalcemia, leukopenia, thrombocytopenia and allergic reaction.

A higher occurrence of more than 10% in Arm B was observed for fatigue (28.1% of patients in Arm A vs. 50.0% of patients in Arm B, p = 0.0846), constipation (18.8% vs. 30.6%, p = 0.4006), and lung infection (9.4% vs. 25.0%, p = 0.1180).

Further details on AEs occurring in more than 5% of patients are displayed in Table 14.

Table 14: Adverse events occurred in > 5% of patients (Safety Analysis Set)

AE Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)	Fisher's exact p-value
Nausea	39 (57.4)	19 (59.4)	20 (55.6)	0.8091
Hypokalemia	28 (41.2)	16 (50.0)	12 (33.3)	0.2186
Fatigue	27 (39.7)	9 (28.1)	18 (50.0)	0.0846
Anemia	26 (38.2)	13 (40.6)	13 (36.1)	0.8042
Esophagitis	25 (36.8)	11 (34.4)	14 (38.9)	0.8028
White blood cell decreased	24 (35.3)	16 (50.0)	8 (22.2)	0.0228
Dysphagia	18 (26.5)	9 (28.1)	9 (25.0)	0.7901
Platelet count decreased	18 (26.5)	11 (34.4)	7 (19.4)	0.1816
Constipation	17 (25.0)	6 (18.8)	11 (30.6)	0.4006
Hypomagnesemia	16 (23.5)	13 (40.6)	3 (8.3)	0.0033
Vomiting	13 (19.1)	6 (18.8)	7 (19.4)	1.0000
Lung infection	12 (17.6)	3 (9.4)	9 (25.0)	0.1180
Diarrhea	12 (17.6)	7 (21.9)	5 (13.9)	0.5268
Mucositis oral	12 (17.6)	8 (25.0)	4 (11.1)	0.2031
Weight loss	12 (17.6)	9 (28.1)	3 (8.3)	0.0539
Cough	12 (17.6)	5 (15.6)	7 (19.4)	0.7576
Hypocalcemia	11 (16.2)	9 (28.1)	2 (5.6)	0.0188
Acneiform rash	11 (16.2)	11 (34.4)	0	< 0.0001
Radiation dermatitis	10 (14.7)	9 (28.1)	1 (2.8)	0.0046
Edema	10 (14.7)	6 (18.8)	4 (11.1)	0.4980
Neutrophil count decreased	9 (13.2)	5 (15.6)	4 (11.1)	0.7249
Dizziness	8 (11.8)	5 (15.6)	3 (8.3)	0.4605
Dyspnea	8 (11.8)	3 (9.4)	5 (13.9)	0.7134
Rash maculopapular	8 (11.8)	7 (21.9)	1 (2.8)	0.0219
Pain	7 (10.3)	5 (15.6)	2 (5.6)	0.2409
Insomnia	7 (10.3)	2 (6.3)	5 (13.9)	0.4338
Alopecia	7 (10.3)	4 (12.5)	3 (8.3)	0.6986
Pleural effusion	6 (8.8)	1 (3.1)	5 (13.9)	0.2025
GGT increased	6 (8.8)	3 (9.4)	3 (8.3)	1.0000
Infection (without further specification)	5 (7.4)	3 (9.4)	2 (5.6)	0.6603
Paresthesia	5 (7.4)	1 (3.1)	4 (11.1)	0.3605
Thromboembolic event	5 (7.4)	2 (6.3)	3 (8.3)	1.0000
Allergic reaction	4 (5.9)	4 (12.5)	0	0.0442
Dehydration	4 (5.9)	2 (6.3)	2 (5.6)	1.0000
Stoma site infection	4 (5.9)	3 (9.4)	1 (2.8)	0.3357
Hyponatremia	4 (5.9)	1 (3.1)	3 (8.3)	0.6163
Weight gain	4 (5.9)	0	4 (11.1)	0.1165
Syncope	4 (5.9)	2 (6.3)	2 (5.6)	1.0000

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AE Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)	Fisher's exact p-value
Urinary retention	4 (5.9)	2 (6.3)	2 (5.6)	1.0000
Esophageal pain	4 (5.9)	2 (6.3)	2 (5.6)	1.0000

GGT: Gamma-glutamyltransferase
Source: Table 14.3.1.2

The majority of AEs were of mild or moderate severity (324 and 275 events, respectively, out of 804 events in total). However, 165 events were reported with CTC grade 3, 26 events with CTC grade 4 and 5 events with CTC grade 5.

A total of 51 patients (75.0%) experienced a grade 3 AE, 15 patients (22.1%) experienced a grade 4 AE, and 4 patients (5.9%) experienced a grade 5 AE.

The most frequent grade 3-5 AEs were lung infection, leukopenia, anemia, esophagitis (11 patients each, 16.2%), and dysphagia (7 patients, 10.3%).

The only significant difference in severe AEs occurred for allergic reaction: 12.5% of patient in Arm A and 0 patients in Arm B experienced a severe allergic reaction (p = 0.0442). For all other severe AEs, the difference between the treatment groups was statistically not significant.

Table 15: Adverse events of grade 3-5 occurring in more than 1 patient (Safety Analysis Set)

AE Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)	Fisher's exact p-value
Lung infection	11 (16.2)	3 (9.4)	8 (22.2)	0.1962
White blood cell decreased	11 (16.2)	7 (21.9)	4 (11.1)	0.3255
Anemia	11 (16.2)	4 (12.5)	7 (19.4)	0.5213
Esophagitis	11 (16.2)	6 (18.8)	5 (13.9)	0.7441
Dysphagia	7 (10.3)	4 (12.5)	3 (8.3)	0.6986
Platelet count decreased	6 (8.8)	4 (12.5)	2 (5.6)	0.4095
Hypokalemia	5 (7.4)	3 (9.4)	2 (5.6)	0.6603
Neutrophil count decreased	5 (7.4)	2 (6.3)	3 (8.3)	1.0000
Allergic reaction	4 (5.9)	4 (12.5)	0	0.0442
Diarrhea	4 (5.9)	3 (9.4)	1 (2.8)	0.3357
Nausea	4 (5.9)	1 (3.1)	3 (8.3)	0.6163
Thromboembolic event	4 (5.9)	2 (6.3)	2 (5.6)	1.0000
Radiation dermatitis	3 (4.4)	3 (9.4)	0	0.0990
Dyspnea	3 (4.4)	2 (6.3)	1 (2.8)	0.5977
GGT increased	3 (4.4)	2 (6.3)	1 (2.8)	0.5977
Hypomagnesemia	3 (4.4)	3 (9.4)	0	0.0990
Acneiform rash	3 (4.4)	3 (9.4)	0	0.0990
Sepsis	3 (4.4)	1 (3.1)	2 (5.6)	1.0000
Dehydration	2 (2.9)	0	2 (5.6)	0.4943
Device-related infection	2 (2.9)	2 (6.3)	0	0.2177
Fatigue	2 (2.9)	0	2 (5.6)	0.4943
Gastric ulcer	2 (2.9)	1 (3.1)	1 (2.8)	NC
Hypertension	2 (2.9)	2 (6.3)	0	0.2177

AE Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)	Fisher's exact p-value
Infection	2 (2.9)	1 (3.1)	1 (2.8)	NC
Pleural effusion	2 (2.9)	1 (3.1)	1 (2.8)	NC
Syncope	2 (2.9)	1 (3.1)	1 (2.8)	NC
Vomiting	2 (2.9)	0	2 (5.6)	0.4943
Weight loss	2 (2.9)	1 (3.1)	1 (2.8)	NC

GGT: Gamma-glutamyltransferase; NC: not calculated
Source: Table 14.3.1.4

The most frequent AE, nausea, was of grade 1 or 2 in the majority of patients; only 4 patients (5.9%) experienced severe nausea. Also hypokalemia and fatigue mostly occurred in mild or moderate intensity. Of other very frequent AEs such as anemia, esophagitis or leukopenia, a higher percentage of patients experienced severe AEs: For anemia, 11 out of 26 patients had a severe event, for esophagitis, 11 out of 25 patients had a severe event, and for leukopenia, 11 out of 24 patients had a severe event.

Lung infection was experienced by 12 patients (17.6%); thereof, 11 patients had a severe event. Neutropenia occurred in 9 patients (13.2%), thereof, 5 patients had a severe event. Increased GGT was experienced by 6 patients (8.8%) and 3 patients had a severe event. 5 patients (7.4%) experienced a thromboembolic event, this was severe in 4 cases. 4 patients (5.9%) had an allergic reaction, this was severe in all 4 patients.

Table 16: Severe AEs (worst CTCAE grade 3-5) by overall frequency of occurrence of AEs (Safety Analysis Set)

AE Term	Total (N=68) n (%)	Grade 3-5 – total n (%)	Arm A (N=32) n (%)	Grade 3-5 – Arm A n (%)	Arm B (N=36) n (%)	Grade 3-5 – Arm B n (%)
Nausea	39 (57.4)	4 (5.9)	19 (59.4)	1 (3.1)	20 (55.6)	3 (8.3)
Hypokalemia	28 (41.2)	5 (7.4)	16 (50.0)	3 (9.4)	12 (33.3)	2 (5.6)
Fatigue	27 (39.7)	2 (2.9)	9 (28.1)	0	18 (50.0)	2 (5.6)
Anemia	26 (38.2)	11 (16.2)	13 (40.6)	4 (12.5)	13 (36.1)	7 (19.4)
Esophagitis	25 (36.8)	11 (16.2)	11 (34.4)	6 (18.8)	14 (38.9)	5 (13.9)
White blood cell decreased	24 (35.3)	11 (16.2)	16 (50.0)	7 (21.9)	8 (22.2)	4 (11.1)
Dysphagia	18 (26.5)	7 (10.3)	9 (28.1)	4 (12.5)	9 (25.0)	3 (8.3)
Platelet count decreased	18 (26.5)	6 (8.8)	11 (34.4)	4 (12.5)	7 (19.4)	2 (5.6)
Constipation	17 (25.0)	0	6 (18.8)	0	11 (30.6)	0
Hypomagnesemia	16 (23.5)	3 (4.4)	13 (40.6)	3 (9.4)	3 (8.3)	0
Vomiting	13 (19.1)	2 (2.9)	6 (18.8)	0	7 (19.4)	2 (5.6)
Lung infection	12 (17.6)	11 (16.2)	3 (9.4)	3 (9.4)	9 (25.0)	8 (22.8)
Diarrhea	12 (17.6)	4 (5.9)	7 (21.9)	3 (9.4)	5 (13.9)	1 (2.8)
Mucositis oral	12 (17.6)	0	8 (25.0)	0	4 (11.1)	0
Weight loss	12 (17.6)	2 (2.9)	9 (28.1)	1 (3.1)	3 (8.3)	0
Cough	12 (17.6)	0	5 (15.6)	0	7 (19.4)	0
Hypocalcemia	11 (16.2)	1 (1.5)	9 (28.1)	1 (3.1)	2 (5.6)	0
Acneiform rash	11 (16.2)	3 (4.4)	11 (34.4)	3 (9.4)	0	0
Radiation dermatitis	10 (14.7)	3 (4.4)	9 (28.1)	3 (9.4)	1 (2.8)	0

AE Term	Total (N=68) n (%)	Grade 3-5 – total n (%)	Arm A (N=32) n (%)	Grade 3-5 – Arm A n (%)	Arm B (N=36) n (%)	Grade 3-5 – Arm B n (%)
Edema	10 (14.7)	1 (1.5)	6 (18.8)	0	4 (11.1)	1 (2.8)
Neutrophil count decreased	9 (13.2)	5 (7.4)	5 (15.6)	2 (6.3)	4 (11.1)	3 (8.3)
Dizziness	8 (11.8)	1 (1.5)	5 (15.6)	1 (3.1)	3 (8.3)	0
Dyspnea	8 (11.8)	3 (4.4)	3 (9.4)	2 (6.3)	5 (13.9)	1 (2.8)
Rash maculopapular	8 (11.8)	0	7 (21.9)	0	1 (2.8)	0
Pain	7 (10.3)	0	5 (15.6)	0	2 (5.6)	0
Insomnia	7 (10.3)	0	2 (6.3)	0	5 (13.9)	0
Alopecia	7 (10.3)	0	4 (12.5)	0	3 (8.3)	0
Pleural effusion	6 (8.8)	2 (2.9)	1 (3.1)	1 (3.1)	5 (13.9)	1 (2.8)
GGT increased	6 (8.8)	3 (4.4)	3 (9.4)	2 (6.3)	3 (8.3)	1 (2.8)
Infection (without further specification)	5 (7.4)	2 (2.9)	3 (9.4)	1 (3.1)	2 (5.6)	1 (2.8)
Paresthesia	5 (7.4)	0	1 (3.1)	0	4 (11.1)	0
Thromboembolic event	5 (7.4)	4 (5.9)	2 (6.3)	2 (6.3)	3 (8.3)	2 (5.6)
Allergic reaction	4 (5.9)	4 (4.9)	4 (12.5)	4 (12.5)	0	0
Dehydration	4 (5.9)	2 (2.9)	2 (6.3)	0	2 (5.6)	2 (5.6)
Stoma site infection	4 (5.9)	1 (1.5)	3 (9.4)	0	1 (2.8)	1 (2.8)
Hyponatremia	4 (5.9)	0	1 (3.1)	0	3 (8.3)	0
Weight gain	4 (5.9)	0	0	0	4 (11.1)	0
Syncope	4 (5.9)	2 (2.9)	2 (6.3)	1 (3.1)	2 (5.6)	1 (2.8)
Urinary retention	4 (5.9)	0	2 (6.3)	0	2 (5.6)	0
Esophageal pain	4 (5.9)	1 (1.5)	2 (6.3)	0	2 (5.6)	1 (2.8)

GGT: Gamma-glutamyltransferase
Source: Tables 14.3.1.2 and 14.3.1.4

Relationship to cetuximab

69 AEs in 19 patients were considered possibly related, 16 AEs in 9 patients were considered probably related, and 37 AEs in 22 patients were considered certainly/definitively related to cetuximab.

For the following AEs, the AE was evaluated as at least possibly related to cetuximab in half or more than half of the patients from Arm A experiencing the AE: fatigue (6/9 patients), hypomagnesemia (8/13 patients), mucositis oral (4/8 patients), acneiform rash (8/11 patients), radiation dermatitis (5/9 patients), maculopapular rash (7/7 patients), allergic reaction (2/4 patients [for 2 patients, causality was not assigned]).

Table 17: AE with possible, probable or certain/definite relationship to cetuximab, as evaluated by the investigator (Safety Analysis Set)

AE Term	Total (N=68) n (%)	Related – total n (%)	Arm A (N=32) n (%)	Related – Arm A n (%)
Nausea	39 (57.4)	6 (8.8)	19 (59.4)	6 (18.8)
Hypokalemia	28 (41.2)	1 (1.5)	16 (50.0)	1 (3.1)
Fatigue	27 (39.7)	6 (8.9)	9 (28.1)	6 (18.8)

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AE Term	Total (N=68) n (%)	Related – total n (%)	Arm A (N=32) n (%)	Related – Arm A n (%)
Anemia	26 (28.2)	3 (4.4)	13 (40.6)	3 (9.4)
Esophagitis	25 (36.8)	4 (5.9)	11 (34.4)	4 (12.5)
White blood cell decreased	24 (35.3)	7 (10.3)	16 (50.0)	7 (21.9)
Dysphagia	18 (26.5)	1 (1.5)	9 (28.1)	1 (3.1)
Platelet count decreased	18 (26.5)	3 (4.4)	11 (34.4)	3 (9.4)
Hypomagnesemia	16 (23.5)	8 (11.8)	13 (40.6)	8 (25.0)
Vomiting	13 (19.1)	2 (2.9)	6 (18.8)	2 (6.3)
Lung infection	12 (17.6)	1 (1.5)	3 (9.4)	1 (3.1)
Diarrhea	12 (17.6)	3 (4.4)	7 (21.9)	3 (9.4)
Mucositis oral	12 (17.6)	4 (5.9)	8 (25.0)	4 (12.5)
Weight loss	12 (17.6)	1 (1.5)	9 (28.1)	1 (3.1)
Hypocalcemia	11 (16.2)	1 (1.5)	9 (28.1)	1 (3.1)
Acneiform rash	11 (16.2)	8 (11.8)	11 (34.4)	8 (25.0)
Radiation dermatitis	10 (14.7)	5 (7.4)	9 (28.1)	5 (15.6)
Dizziness	8 (11.8)	1 (1.5)	5 (15.6)	1 (3.1)
Dyspnea	8 (11.8)	1 (1.5)	3 (9.4)	1 (3.1)
Rash maculo-papular	8 (11.8)	7 (10.3)	7 (21.9)	7 (21.9)
Allergic reaction	4 (5.9)	2 (2.9)	4 (12.5)	2 (6.3)
Dehydration	4 (5.9)	1 (1.5)	2 (6.3)	1 (3.1)

Source: Table 14.3.1.5

AEs leading to discontinuation of cetuximab

Eight patients experienced at least one AE that led to discontinuation of cetuximab.

- Four patients experienced an allergic reaction (all grade 3) to the first dose of cetuximab; this AE was evaluated as possibly or definitively related to cetuximab in 2 patients, and the causal relationship was not evaluated in the other 2 patients. However, all 4 patients discontinued cetuximab due to an allergic reaction. For one of those patients, also diarrhea (grade 3) and dyspnea (grade 3) were recorded as AEs leading to discontinuation of cetuximab.

- One patient discontinued cetuximab due to leukopenia (grade 4), febrile neutropenia (grade 4), and lung infection (grade 3, all evaluated as possibly related to cetuximab and definitively related to CT).

- One patient discontinued cetuximab due to nephrotoxicity and an impaired tubular function (grade 3, evaluated as possibly related to cetuximab and definitively related to CT).

- One patient discontinued cetuximab due to pneumonitis (grade 3, evaluated as definitively related to cetuximab).

- One patient discontinued cetuximab due to thrombocytopenia (grade 2, evaluated as not likely related to cetuximab and RT and definitively related to CT).

AEs leading to discontinuation of radiotherapy (RT)

One patient in Arm B discontinued radiotherapy due to the AE lung infection (grade 3, evaluated as definitively related to CT).

AEs leading to discontinuation of chemotherapy (CT)

Thirteen patients discontinued chemotherapy due to AEs:
- Arm A:
  - One patient due to hypoalbuminemia (grade 3, evaluated as definitively related to CT)
  - One patient due to esophagitis (grade 3, evaluated as possibly related to cetuximab definitively related to CT and RT)
  - One patient due to leukopenia (grade 3, evaluated as definitively related to CT) and esophagitis (grade 3, evaluated as definitively related to CT and RT)
  - One patient due to leukopenia (grade 4), anemia (grade 4), febrile neutropenia (grade 4), and lung infection (grade 3, all events evaluated as possibly related to cetuximab and definitively related to CT)
  - One patient due to pneumonitis (grade 3, evaluated as definitively related to cetuximab)
  - One patient due to non-cardiac chest pain (grade 1), hypertension (grade 3), and atrioventricular block first degree (grade 1, all events evaluated as probably related to CT)
  - One patient due to nephrotoxicity and impaired tubular function (grade 3, evaluated as possibly related to cetuximab and definitively related to CT)
- Arm B:
  - One patient due to leukopenia (grade 3, evaluated as not related to CT and RT)
  - One patient due to renal failure, stoma site infection, abdominal infection, lung infection (all grade 3 and evaluated as definitively related to CT)
  - One patient due to palmar-plantar erythrodysesthesia syndrome (grade 3, evaluated as definitively related to CT)
  - One patient due to myocardial infarction (grade 4, evaluated as possible related to CT) and tachyarrhythmia (grade 2, evaluated as probably related to CT)
  - One patient due to nausea (grade 1, evaluated as possibly related to CT and probably related to RT), immune system disorders (grade 2, evaluated as possibly related to RT) and urinary tract infection (grade 2, evaluated as not likely related to CT and RT)
  - One patient due to dyspnea (grade 2, evaluated as probably related to RT), lung infection (grade 3), dehydration (grade 4), sepsis (grade 4), and acute kidney injury (grade 4, all evaluated as not related to CT and RT)

Further details on AEs leading to discontinuation of one of the components of study treatment are given in Tables 14.3.1.6 – 14.3.1.8.

Note: In Tables 14.3.1.6-14.3.1.8, further patients in Arm B are listed, in whom the treatment was discontinued according to the CRF data. However, those patients had their medication discontinued due to death and are not listed above.

One patient (010002) had a fatal lung infection that was evaluated as not likely related to chemotherapy and radiotherapy. For one patient (100004), the AE term was Death NOS, evaluated as not related to chemotherapy and radiotherapy.

One patient (010007) in Arm B died from tumour bleeding.

12.2.3 Analysis of adverse events

The majority of AEs were as expected owing to the known side effects of the treatment components administered and the severity of the underlying disease.

The most common AE was nausea (57.4% of patients), further common gastrointestinal AEs were esophagitis (36.8%), dysphagia (26.5%), constipation (25.0%), vomiting (19.1%), diarrhea (17.6%), and mucositis oral (17.6%). Gastrointestinal side effects are known for cetuximab (diarrhea, nausea and vomiting are common according to current SmPC), 5-FU (mucositis, esophagitis, diarrhea, nausea and vomiting in all grades are very common according to current SmPC), and cisplatin (anorexia, nausea, vomiting and diarrhea are very common according to current SmPC). In our study, most of the gastrointestinal AEs occurred at similar percentages in both treatment arms, only constipation was observed more frequently in Arm B (18.8% vs. 30.6%, p = 0.4006), whereas diarrhea and oral mucositis were observed more frequently in Arm A (21.9% vs. 13.9% and 25.0% vs. 11.1%, respectively, p = 0.5268 and p = 0.2031). However, the differences were not statistically significant and the number of patients was too small to make a general statement that the addition of cetuximab to standard therapy would place the patient at additional risk for gastrointestinal side effects.

Except for esophagitis and dysphagia, the majority of gastrointestinal AEs were of mild to moderate intensity. Esophagitis was severe in 11 out of 25 patients (severe in 6 patients [18.8%] in Arm A and 5 patients [13.9%] in Arm B, p = 0.7441), and dysphagia was severe in 7 out of 18 patients (severe in 4 [12.5%] and 3 [8.3%] patients, respectively, p = 0.6986). Those AEs, as well as mucositis are also associated with radiation therapy which might have synergistic effects.

According to the current SmPC of cetuximab, patients receiving cetuximab in combination with platinum-based chemotherapy have an increased risk for severe leuko- and/or neutropenia which may lead to subsequent infectious complications such as febrile neutropenia, lung infection or sepsis. For 5-FU very frequent immune suppression with an increased infection rate is reported in the current SmPC, also myelosuppression is described as very frequent and dose-depending

side effect. For cisplatin, frequent cases of infection and sepsis, as well as very frequent (25-30% of patients) dose-dependent, cumulative leukopenia, thrombocytopenia and anemia are known (see current SmPC).

This is consistent with our findings of haematological AEs as well as infection-related AEs: Anemia (38.2%), leukopenia (35.3%), thrombocytopenia (26.5%), and neutropenia (13.2%) were amongst the most frequent AEs in general and also amongst the most frequent severe AEs (11/26 severe anemia, 11/24 severe leukopenia, 6/18 severe thrombocytopenia, and 5/9 severe neutropenia). Regarding leukopenia and thrombocytopenia (any grade) more cases were observed in Arm A (50.0% vs. 22.2% and 34.4% vs. 19.4%, respectively, p = 0.0228 and p = 1816); anaemia was similar in both groups (40.6% vs. 36.1%, p = 0.8042).

Lung infection occurred in 17.6% of patients which might be explained with the immunosuppressive potential of chemotherapy. The majority of the lung infections were experienced by patients in Arm B (9 patients vs. 3 patients in Arm A), so there seemed to be no additional risk by the addition of cetuximab.

Further frequently observed AEs were hypokalemia (41.2%), hypomagnesemia (23.5%), and hypocalcemia (16.2%). Especially hypomagnesemia was observed mostly in Arm A, 13 of 16 patients experiencing this AE were treated with cetuximab. This is consistent with the fact the hypomagnesemia is a very common adverse reaction to cetuximab, as described in the current SmPC. Progressively decreasing serum magnesium levels occur frequently.

Particularly with the combination of cetuximab and platinum-based chemotherapy, the risk for severe hypocalcemia may be increased. This is consistent with the finding that hypocalcemia occurred in 9 patients in Arm A, but only in 2 patients in Arm B. The nephrotoxicity of cisplatin might also result in electrolyte disturbances. Hypokalemia might be developed as a consequence of diarrhea. It was observed in 16 patients in Arm A and 12 patients in Arm B.

Besides lung infection, other pulmonary/respiratory AEs such as cough (17.6% of patients) and dyspnea (11.8%) were observed. Both events might be symptoms of lung infections or other AEs. For some patients also a smoking history was recorded.

Four of 32 patients in Arm A experienced an allergic reaction at the first administration which is an expected adverse reaction to cetuximab. Infusion-related reactions are described as common side effects of cetuximab in the current SmPC of cetuximab. Some of those infusion-related reactions are anaphylactic reactions. Anaphylactic reactions usually occur with the first administration and can occur despite the use of premedication. All allergic reactions observed in our study were severe and therefore led to discontinuation of cetuximab according to the instructions in the protocol.

Skin reactions are very common under cetuximab treatment according to current SmPC. They may develop in more than 80% of patients and mainly present as acne-like rash. Consistent with

this, in our study, all 11 patients (11.2%) who experienced acneiform rash were in Arm A, so this AE is clearly associated with cetuximab. In 3 patients the acneiform rash was severe. Another skin disorder, maculopapular rash, occurred in 8 patients (11.8%), thereof, 7 patients were in Arm A. The occurrence of those skin reactions was significantly higher in the cetuximab arm.

Radiation dermatitis was more frequent in Arm A with 9 out of 10 patients experiencing this AE being treated in Arm A. Likely, cetuximab increases this side effect of radiotherapy. Radiation dermatitis was severe in 3 patients (all of them Arm A).

Fatigue occurred in 39.7% of patients and might be secondary to other AEs such as anemia, gastrointestinal events etc. Also the severity of the underlying disease might play a role. Fatigue was more frequent in Arm B (18 vs. 9 patients).

Weight loss was observed in 17.6% of patients. Weight loss might be secondary to nausea, vomiting, diarrhea, anorexia, or dysphagia and might also result from the underlying disease. However, weight loss was observed more often in Arm A (9 vs. 3 patients).

12.2.4 Listing of adverse events by patient

Listings of AEs by patient are presented in Appendix 16.2.3.1.

12.3 Deaths, other serious adverse events, and other significant adverse events

12.3.1 Listing of deaths, other serious adverse events and other significant adverse events

12.3.1.1 Deaths

A total of 33 patients (48.5%) died during the course of the study. Two patients (patient IDs: 100004 and 010007) died during the treatment phase (see narratives below). In Arm A, 13 patients (40.6%) died, and in Arm B 20 patients (55.6%) died. The difference was not statistically significant (p = 0.2188).

The majority of patients died from progressive disease: This was the reason for death in 6 patients (46.2% of Arm A deaths) in Arm A and in 11 patients (55.0% of Arm B deaths) in Arm B. The exploratory Chi-square test for the difference between the treatment groups had a p-value of 0.2618.

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Table 18: Reason for death (Safety Analyses Set)

Reason for death	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)	p-value (exploratory Chi square test)
Total deaths	33 (48.5)	13 (40.6)	20 (55.6)	0.2188
Death due to				
Progressive disease	17 (25.0)[1]	6 (18.8)[1]	11 (30.6)	0.2618
Sepsis	2 (2.9)	1 (3.1)	1 (2.8)	
Renal failure following surgery for gastric ulcer	1 (1.5)	1 (3.1)	0	
Pneumonia	1 (1.5)	0	1 (2.8)	
Death NOS	1 (1.5)	0	1 (2.8)	
Unknown	11 (16.2)	5 (15.6)	6 (16.7)	

Source: Table 14.2.2.10 and 14.3.1.10

[1] Thereof, in one patient the reason for death was given as progressive disease, renal failure, metabolic acidosis, ileus paralytic, infection unknown

12.3.1.2 Other serious adverse events

A total of 129 serious adverse events (SAEs) was reported. 45 patients in total (66.2%) experienced at least one SAE. The most frequently reported SAEs were lung infection (12 patients, 17.6%) and esophagitis (11 patients, 16.2%).

Table 19: Serious adverse events (Safety Analysis Set)

AE Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Lung infection	12 (17.6)	3 (9.4)	9 (25.0)
Esophagitis	11 (16.2)	6 (18.8)	5 (13.9)
White blood cell decreased	5 (7.4)	3 (9.4)	2 (5.6)
Thromboembolic event	4 (5.9)	2 (6.3)	2 (5.6)
Diarrhea	3 (4.4)	2 (6.3)	1 (2.8)
Nausea	3 (4.4)	1 (3.1)	2 (5.6)
Vomiting	3 (4.4)	0	3 (8.3)
Hypokalemia	3 (4.4)	1 (3.1)	2 (5.6)
Sepsis	3 (4.4)	1 (3.1)	2 (5.6)
Stoma site infection	3 (4.4)	2 (6.3)	1 (2.8)
Dysphagia	2 (2.9)	0	2 (5.6)
Dyspnea	2 (2.9)	1 (3.1)	1 (2.8)
Neutrophil count decreased	2 (2.9)	0	2 (5.6)
Anemia	2 (2.9)	1 (3.1)	1 (2.8)
GGT increased	2 (2.9)	1 (3.1)	1 (2.8)
Allergic reaction	2 (2.9)	2 (6.3)	0
Infection (without further specification)	2 (2.9)	1 (3.1)	1 (2.8)
Pancytopenia	1 (1.5)	1 (3.1)	0
Febrile neutropenia	1 (1.5)	1 (3.1)	0
Atrial fibrillation	1 (1.5)	1 (3.1)	0
Myocardial infarction	1 (1.5)	0	1 (2.8)
Ventricular tachycardia	1 (1.5)	1 (3.1)	0
Abdominal pain	1 (1.5)	0	1 (2.8)
Esophageal haemorrhage	1 (1.5)	0	1 (2.8)

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AE Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Gastric haemorrhage	1 (1.5)	0	1 (2.8)
Gastric ulcer	1 (1.5)	1 (3.1)	0
Gastrointestinal fistula	1 (1.5)	0	1 (2.8)
GI bleeding (haemorrhagic shock)	1 (1.5)	1 (3.1)	0
Peritonitis with sepsis	1 (1.5)	0	1 (2.8)
Hematemesis	1 (1.5)	1 (3.1)	0
Death NOS	1 (1.5)	0	1 (2.8)
Fatigue	1 (1.5)	0	1 (2.8)
Fever	1 (1.5)	0	1 (2.8)
Immune system disorders	1 (1.5)	0	1 (2.8)
Appendicitis	1 (1.5)	1 (3.1)	0
Device related infection	1 (1.5)	1 (3.1)	0
Abdominal infection	1 (1.5)	0	1 (2.8)
Enterocolitis infectious	1 (1.5)	1 (3.1)	0
Nail infection	1 (1.5)	1 (3.1)	0
Infection unclear origin	1 (1.5)	1 (3.1)	0
Skin infection	1 (1.5)	1 (3.1)	0
Upper respiratory infection	1 (1.5)	1 (3.1)	0
Wound infection	1 (1.5)	0	1 (2.8)
Radiation dermatitis	1 (1.5)	1 (3.1)	0
Anastomotic leak	1 (1.5)	0	1 (2.8)
Fistula	1 (1.5)	0	1 (2.8)
Morphine overdose	1 (1.5)	0	1 (2.8)
Tumour bleeding	1 (1.5)	0	1 (2.8)
PEG dislocation	1 (1.5)	0	1 (2.8)
Platelet count decreased	1 (1.5)	1 (3.1)	0
Alanine aminotransferase increased	1 (1.5)	0	1 (2.8)
Elevation of liver enzymes	1 (1.5)	0	1 (2.8)
Acidosis	1 (1.5)	1 (3.1)	0
Alkalosis	1 (1.5)	1 (3.1)	0
Dehydration	1 (1.5)	0	1 (2.8)
Exsiccosis	1 (1.5)	1 (3.1)	0
Hypoalbuminemia	1 (1.5)	1 (3.1)	0
Hypocalcemia	1 (1.5)	1 (3.1)	0
Hypomagnesemia	1 (1.5)	1 (3.1)	0
Cognitive disturbance	1 (1.5)	1 (3.1)	0
Seizure	1 (1.5)	1 (3.1)	0
Stroke	1 (1.5)	1 (3.1)	0
Vertigo	1 (1.5)	1 (3.1)	0
Acute renal failure	1 (1.5)	1 (3.1)	0
Renal failure	1 (1.5)	0	1 (2.8)
Renal incompetence	1 (1.5)	1 (3.1)	0
Nephrotoxicity, tubular function impaired	1 (1.5)	1 (3.1)	0
Acute reduction of GFR	1 (1.5)	0	1 (2.8)
Pulmonary fistula	1 (1.5)	0	1 (2.8)
Pneumonitis	1 (1.5)	1 (3.1)	0
Pleural effusion	1 (1.5)	0	1 (2.8)
Pneumothorax	1 (1.5)	1 (3.1)	0
Palmar-plantar erythrodysesthesia syndrome	1 (1.5)	0	1 (2.8)
Acneiform rash	1 (1.5)	1 (3.1)	0

AE Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Reduced overall health condition	1 (1.5)	1 (3.1)	0

GFR: glomerular filtration rate; GI: Gastrointestinal; NOS: no other specified; PEG: percutaneous endoscopic gastrostomy

12.3.1.3 Other significant adverse events

No other significant adverse events were reported by the investigators during the course of the study.

12.3.2 Narratives of deaths, other serious adverse events and certain other significant adverse events

Narratives of serious adverse reactions to cetuximab (not including death that were excluded from SAE reporting, e.g. death due to progressive disease):

Allergic reaction to cetuximab grade 3, patient 070003, Arm A:

A male patient born in 1939 developed chills, watery and red eyes, urticaria, symptomatic bronchospasm with retrosternal pain 10 minutes after the start of the first dose of cetuximab on Aug11, 2016. An allergic reaction grade 3 was diagnosed. The cetuximab infusion was stopped immediately and the patient was treated with prednisolone and antihistamines i.v. Also O_2 and Nitrospray were given. The symptoms resolved after treatment and the patient was discharged on Aug11, 2016. On Aug15, 2016 chemotherapy and radiotherapy started, all 4 chemotherapy cycles were administered. The last dose was administered on Nov27, 2016. The patient died on Jun27, 2017.

Skin infection grade 2-3 and pneumonitis, patient 010025, Arm A:
Patient 01-0025, a female patient born in 1956, suffered from skin infection Grade 2-3 and was hospitalized on Nov05, 2015. The last dose of cetuximab prior to the SAE was given on Oct30, 2015, cetuximab was started on Sep15, 2015. Due to the skin infection, cetuximab was permanently interrupted. The SAE was resolved on Nov24, 2015.
For the same patient, pneumonitis was reported as an SAE on Nov13, 2015. The pneumonitis was persisting until death of the patient on Dec18, 2015.

Leukopenia grade 4 and esophagitis grade 3, patient 010023, Arm A:
Patient 01-0023, a male patient born in 1937, was hospitalized on Aug21, 2015 due to leucopenia G4. The SAE was reported belatedly. The last doses of cetuximab and background chemotherapy

had been given on Aug13, 2015 and Aug08, 2015, respectively. The leucopenia improved on Aug23, 2015 to grade 3, on Aug24, 2015 to grade 2, and was resolved on Aug29, 2015.

For the same patient, esophagitis Grade 3 was reported as an important medical event. The esophagitis started on Sep11, 2015. The last administrations of cetuximab and chemotherapy prior to the SAE had been on Aug13, 2015 (day 15) and Aug08, 2015 (cycle 2), respectively. The esophagitis was still ongoing on the day of discharge of the hospital on Oct05, 2015.

Both SAE were considered related to cetuximab, 5-FU and cisplatin.

On Sep17, 2015 the patient had the end of treatment visit, reason for EOT was progression of disease. The patient died on Dec08, 2015 from progressive disease.

Reduced overall health condition grade 3, patient 100019, Arm B:

Patient 10-0019, a male patient born in 1968, was hospitalized on Nov14, 2015 due to a reduced overall health condition grade 3. The last doses of cetuximab and chemotherapy prior to the SAE had been given on Nov09, 2015 and Nov12, 2015, respectively. The SAE was resolved on Nov30, 2015.

The SAE were considered related to cetuximab, 5-FU and cisplatin.

Dermatitis/rash grade 3, patient 010028, Arm A:

Patient 01-0028, a female patient born in 1972, developed a grade 3 dermatitis/rash on Apr04, 2016. This event was judged as an important medical event and therefore reported as an SAE. The last administrations of cetuximab, chemotherapy, and radiotherapy prior to the SAE were on Mar29, 2016, Mar11, 2016, and Apr01, 2016, respectively. The skin reaction improved to grade 2 on Apr10, 2016 and then stepwise to grade 1.

The SAE was reported as related to cetuximab, background chemotherapy and radiotherapy.

Infection of unknown origin, patient 100015, Arm A:

Patient 10-0015, a male patient born in 1954, suffered of infection unknown origin which led to hospitalization from Apr03, 2015 to Apr16, 2015. The SAE was reported as related to Cetuximab, 5-FU and cisplatin.

Allergic reaction grade 3, patient 030006, Arm A:

On Dec09, 2013, a female patient born in 1936 experienced a grade 3 allergic reaction with dyspnea 15 minutes after the administration of the loading dose of cetuximab. The event was life-threatening. Background chemotherapy had not yet been administered according to protocol. The patient was treated with antihistaminics and prednisolone and the event was resolved. No

cetuximab was administered subsequently, also no chemotherapy and radiotherapy were started. The patient had the EOT visit on Dec16, 2013 and died on Jan02, 2014 due to sepsis.

Radiation dermatitis grade 3, patient 010012, Arm A:

The female patient born in 1937 has experienced dermatitis soon after the first administration of study therapy on Apr16, 2013 that remained stable due to specific skin care and antibiotics until the second cycle. On Jun04, 2013, the patient was hospitalized due to radiation dermatitis grade III, described as erythema grade II-III, pain of skin grade III, and paronychia grade II. The event was judged by the investigator to be related to cetuximab and background radiotherapy. Both therapies were temporarily interrupted. The last dose of cetuximab prior to the SAE was on May30, 2013, and the last radiotherapy was administered on Jun03, 2013. The patient was treated with antibiotics and analgesics, and the SAE was resolved on Jun20, 2013. Therapy with cetuximab was restarted on Jun19, 2013, radiotherapy was restarted on Jun17, 2013.

Nail infection grade 3, patient 010001, Arm A:

The female patient, born in 1940, experienced a nail infection (panaritium) grade 3 on Nov24, 2011 which led to hospitalisation. The SAE was resolved on Dec13, 2011. The event was considered related to cetuximab. Cetuximab was initially administered on Sep21, 2011, the last dose prior to the SAE was administered on Nov24, 2011 (250 mg/m²). On Dec02, 2011, cetuximab was temporarily interrupted and re-started on Dec14, 2011. Also chemotherapy was interrupted from Dec08, 2011 – Dec15, 2011. The nail infection was operated and treated with antibiotics.

No SUSAR occurred during the course of the clinical trial.

Narrative of death of patient 100004, Arm B:

The male patient, born in 1948, died on Apr28, 2013. The SAE event term was "Death NOS". The event was not considered related to study treatment, but had a cardiovascular reason, possibly a stroke. Pre-existing conditions were arterial hypertension, strong smoking history and obesity. Chemotherapy had been administered from Apr22 – Apr25, 2013, radiotherapy from Apr22 – Apr26, 2013. The patient died while sleeping without any additional cramps, symptoms or disease-related AEs.

Narrative of death of patient 010007, Arm B:

The female patient born in 1943 had a tumour bleeding on Sep18, 2012 which resulted in death. The event was considered related to the underlying disease. The last dose of 5-FU and cisplatin was administered on Aug22, 2012, start of treatment was Aug17, 2012. Radiotherapy had been

done from Aug01 – Sep09, 2012. Relevant medical history included esophagitis grade 3, dyspnea due to tumour progression and a tracheal compression due to tumour progression. A tracheal stent had been placed on Sep17, 2012. On the following day the tumour bleeding occurred during a routine control tracheoscopy.

<u>Narratives of non-serious infusion related reactions:</u>

Allergic reaction grade 3, patient 1400001, Arm A:

The female patient born in 1947 received the loading dose of cetuximab on Mar26, 2014. During or after the infusion the patient experienced an allergic reaction grade 3. Neither further cetuximab nor chemotherapy or radiotherapy were administered afterwards. The patient had the EOT visit on Mar31, 2018, follow-up assessments were done according to protocol.

Allergic reaction grade 3, patient 190001, Arm A:

The male patient born in 1953 received the first dose of cetuximab on Oct02, 2013. During or after the infusion the patient experienced an allergic reaction grade 3. The patient had the EOT visit on Oct08, 2013, no chemotherapy and radiotherapy were administered. Follow-up assessments were done according to protocol. The patient died on Apr06, 2017 due to progressive disease.

12.3.3 Analysis and discussion of deaths, other serious adverse events and other significant adverse events

The main reason for death was progressive disease; this was the reason for 17/33 deaths. Two patients died during the treatment phase; none of the deaths were associated with study treatment, but to the underlying disease and cardiovascular disorders. In total, more patients treated with standard therapy died compared to patients treated with cetuximab plus standard therapy (55.6% vs. 40.6%).

During the study, 65.6% of patients in Arm A and 66.7% of patients in Arm B experienced at least one SAE, so no increase of SAEs by the addition of cetuximab was recognizable, although some were clearly known as related to cetuximab. The most frequent SAE was lung infection which was reported in 12 patients. In all patients experiencing lung infection, the event was serious. The second most frequent SAE was esophagitis, which was serious in 11 out of 25 patients who experienced the event. The occurrence of lung infection is discussed in Section 12.2.3.

No new safety issues occurred when comparing deaths or occurrence of SAEs in the treatment arms.

12.4 Clinical laboratory evaluation

12.4.1 Listing of individual laboratory measurements by patient (16.2.4)

Please refer to section 16.2.4 of this CSR.

12.4.2 Evaluation of each laboratory parameter

Analysis of laboratory parameters was carried out on the safety analysis set (n=68).

Clinical chemistry

Clinical chemistry was measured at the beginning of each chemotherapy cycle. The following parameters were evaluated: Creatinine, bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, sodium, potassium, calcium, magnesium, and gamma-GT.

For evaluation of the laboratory values, it has to be considered that of the 68 patients who started study treatment 25 patients 22 patients achieved resectability after 4-4.5 weeks and did therefore not receive cycles 3 and 4, so had a shorter exposure to study medication. 27 patients were still on study in cycle 3.

Creatinine

The median creatinine value decreased from 0.79 mg/dl at screening to 0.69 mg/dl at cycle 3 day 1, but increased later on again to 0.78 mg/dl in cycle 4. In Arm A, the median creatinine value decreased from screening (0.77 mg/dl) to cycle 4 (0.63 mg/dl), whereas it remained constant in Arm B (screening: 0.81 mg/dl, cycle 4: 0.81 mg/dl).

More patients in Arm A had abnormal, but clinically not relevant values in cycles 3 and 4 compared to Arm B (Arm A: 31.3% in cycle 3 and 35.7% in cycle 4, Arm B: 16.7% in cycle 3 and 18.2% in cycle 4). However, the percentage of patients with abnormal, clinically not relevant creatinine values was 22.6% and 25.8% in Arm A and B, respectively, at EOT. One patient in each arm had an abnormal, clinically relevant creatinine value at EOT.

Bilirubin

The median bilirubin value dropped from 0.46 mg/dl at screening to 0.35 mg/dl at cycle 4. No major differences between Arm A and Arm B occurred. Abnormal values were rare and, when they occurred, were evaluated as clinically not relevant.

SGOT/AST

The median SGOT value decreased from screening (19 U/l) to cycle 4 (17 (U/l) with similar values in Arm A and Arm B. Six patients (8.8%) had abnormal, clinically not relevant, SGOT values at screening (thereof, 5 patients in Arm A and 1 patient in Arm B). Those numbers even decreased

during the course of the study. In cycle 4, all SGOT values were within normal ranges. No patient had abnormal, clinically relevant SGOT values.

SGPT/ALT

The median SGPT value decreased from screening (17.5 U/l) to cycle 4 (12 U/l), but was 18 U/l at EOT again. The dimensions were similar in both treatment arms. In Arm A, 5 patients (15.6%) had abnormal, clinically not relevant SGPT values at screening; this number varied in both directions during the course of the study. In Arm B, abnormal SGOT values only occurred at EOT (3 patients, 9.7%, all clinically not relevant). No patient had abnormal, clinically relevant SGOT values.

LDH

The median LDH value widely remained constant over time (screening: 186 U/l, cycle 4: 180 U/l, EOT: 197.5 U/l). In general, values were lower in Arm B, but patients in Arm A had a higher median screening value (Arm A: 191.5 U/l, Arm B: 180 U/l). The percentage of patients with abnormal LDH values was similar in both treatment arms. No patient had abnormal, clinically relevant LDH values.

Alkaline phosphatase (AP)

The median AP value remained constant during the course of the study (screening: 72.5 U/l, cycle 4: 77 U/l, EOT: 76 U/l). No major differences between the treatment arms occurred. Also the number of patients with abnormal AP values did not differ between the treatment arms and remained on baseline level. No patient had abnormal, clinically relevant AP values.

Sodium

No changes in the median sodium values occurred during the course of the study (screening: 139 mmol/l, cycle 4: 138 mmol/l). The percentage of abnormal, clinically not relevant sodium values increased from baseline to cycle 4 and EOT (Arm A: 9.7% of patients at screening, 21.4% at cycle 4, 25.8% at EOT; Arm B: 13.9% at screening, 27.3% at cycle 4, 24.2% at EOT). Abnormal, clinically relevant values occurred in one patient in Arm A at cycle 3 and in one patient in Arm B at cycle 2.

Potassium

The overall median potassium values remained constant over the course of the study (screening: 4.14 mmol/l, cycle 4: 4.11 mmol/l). However, in cycles 3 and 4, the median potassium value decreased to 3.76 mmol/l and 3.95 mmol/l in Arm A, whereas in Arm B, it increased to 4.38 mmol/l

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and 4.24 mmol/l, respectively. At EOT, the median potassium values were 3.96 mmol/l in Arm A and 4.07 mmol/l in Arm B.

There were several patients with abnormal, clinically relevant potassium values in Arm A: One patients (3.3%) at cycle 1, 3 patients (11.5%) at cycle 2, 2 patients (12.5%) at cycle 3, and 1 patient (3.2%) at EOT. In Arm B, 2 patients (6.1%) hat abnormal, clinically relevant potassium values at EOT.

Calcium

The decrease of the median calcium value over time was more obvious in Arm A with 2.38 mmol/l at screening and 2.23 mmol/l at cycle 4 than it was in Arm B with 2.39 mmol/l at screening and 2.32 mmol/l at cycle 4. In cycles 3 and 4, also more patients in Arm A had abnormal, clinically not relevant calcium values (25.0% and 35.7%, respectively) than in Arm B (8.3% and 0%, respectively). At cycle 1 day 1, one patient in Arm A (3.3%) and at EOT, 2 patients in Arm A (6.7%) had an abnormal, clinically relevant calcium value.

Magnesium

The decrease of the median magnesium value was more distinct in Arm A (screening: 0.82 mmol/l, cycle 4: 0.62 mmol/l) than in Arm B (screening: 0.84 mmol/l, cycle 4: 0.71 mmol/l). From cycle 2 onwards, considerably more patients in Arm A had abnormal magnesium values compared to Arm B. In cycle 1, 7.7% of patients in Arm A and 6.9% of patients in Arm B had abnormal magnesium values. In cycle 2, 54.2% and 12.5% of patients in Arm A and B had abnormal magnesium values; thereof, the abnormal value was clinically relevant in 1 patient of Arm A (7.7%). In cycle 3, the percentage of patients with abnormal magnesium values was 81.3% and 14.3% in Arm A and B whereas the abnormal values were clinically relevant in 2 patients in Arm A (15.4%). In cycle 4, 76.9% and 20.0% of patients in Arm A and B had abnormal magnesium values; thereof, the abnormal values were clinically relevant in 1 patient in Arm A (10.0%). At EOT, the percentage of patients with abnormal magnesium values was 66.6% and 26.1% in Arm A and B; the abnormal values were clinically relevant in 2 patients in Arm A (12.5%).

Gamma-GT

Gamma-GT values remained constant until cycle 2 and showed a strong increase from cycle 3 in both treatment arms. The median gamma-GT value was 34 U/l at screening (total patient population) and cycle 1, 35 U/l at cycle 2, 61.5 U/l at cycle 3, 61 U/l at cycle 4, and 56.5 U/l at EOT. Also the percentage of patients with abnormal gamma-GT values increased from 19.4% in Arm A and 11.1% in Arm B at screening to 60.0% and 44.4%, respectively, at cycle 3. At EOT, the percentages were 51.9% and 35.5%, respectively. Most of these abnormal values were not clinically relevant. Only one patient in Arm A had an abnormal, clinically relevant gamma-GT value during cycles 1 and 2.

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Haematology

Haematology was measured at screening, weekly during the treatment phase, and at EOT. The following parameters were evaluated: Haemoglobin, erythrocytes, platelets, leucocytes, and neutrophils.

Haemoglobin

The median haemoglobin value started to decrease from day 15 after start of treatment in both arms. At screening, the median haemoglobin value was 13.6 g/d, at cycle 1 day 15, the median value was 12.7 g/dl. Towards the end of cycle 2, the median haemoglobin value was 11.75 g/dl (cycle 2 day 15) and 10.9 g/dl (cycle 2 day 22). Towards the end of cycle 3, the median haemoglobin value dropped again to 10.3 g/dl (cycle 3 day 15) and 10.2 g/dl (cycle 3 day 22). Afterwards, the median haemoglobin value remained constant or even slightly increased. At EOT, the median haemoglobin value was 11.7 g/dl (12.0 g/dl in Arm A and 11.4 g/dl in Arm B).

At screening, 38.2% of patients had abnormal haemoglobin values (31.3% in Arm A and 44.4% in Arm B). This percentage increased after start of treatment to 47.6% at cycle 1 day 8 (clinically relevant in one patient in Arm B, 4.8%), 59.9% at cycle 1 day 15 (clinically relevant in 3 patients in Arm B, 15.8%), 65.4% at cycle 1 day 22 (clinically relevant in 1 patient in Arm A, 6.7%) etc. The highest percentage of patients with abnormal haemoglobin values occurred on day 15 of cycle 4, when 12 out of 13 patients (92.3%) had abnormal haemoglobin values (all clinically not relevant).

The increase of percentage of patients with abnormal haemoglobin values was fast in Arm B compared to Arm A. At cycle 2 day 1, 55.6% in Arm A and 80.0% in Arm B had abnormal haemoglobin values (clinically relevant in 1 patient in Arm A, 6.7%). The percentages equalised at cycle 3 (day 1: 87.6% in Arm A and 91.7% in Arm B) and roughly remained at this level.

Erythrocytes

Similar than the haemoglobin value, the erythrocytes value started to decrease from day 15 after start of treatment in both treatment arms. At screening, the median erythrocytes value was 4.42 /pl, at cycle 1 day 15, the median erythrocytes value was 4.08 /pl. At cycle 2 day 15, the median erythrocytes value was 3.76 /pl, at cycle 3 day 15, the median erythrocytes value was 3.3 /pl. The lowest median erythrocytes value was reached at cycle 4 day 1 with 3.2 /pl. At EOT, the median erythrocytes value was 3.63 /pl.

At screening, 18 patients (26.5%) had abnormal erythrocytes values (all clinically not relevant), thereof 7 patients (21.9%) in Arm A and 11 patients (30.6%) in Arm B. The number of patients with abnormal erythrocytes values increased at cycle 1 day 15 to 34 patients (57.6%, thereof clinically relevant in 3 patients [8.8%], all of them in Arm B), with a similar distribution in both treatment arms. At cycle 2 day 15, 34 patients (73.9%) had abnormal erythrocytes values (thereof clinically relevant in 1 patient, 2.9%), still with rising tendency. At cycle 3 day 8, 92.3% of patients

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had abnormal, but clinically not relevant erythrocytes values, and this level remained until cycle 4 day 22, where all 9 patients analysed had abnormal, clinically not relevant erythrocytes values. No major differences were observed between the treatment arms.

Platelets

The platelet value decreased over time in both treatment arms at approximately the same extent. The median baseline value was 274 /nl. At cycle 1 day 8, the median platelet value was 221 /nl, and at cycle 1 day 15, it was 141 /nl. Variation within each cycle were observed: at day 1 of a cycle the platelet value was tendentially high, on day 15 of a cycle it was at the lowest value within the cycle. At EOT, the median platelet value was 217 /nl.

At screening, 20.6% of patients had abnormal platelet values. This percentage increased on cycle 1 day 15 to 52.7% (thereof clinically relevant in 1 patient, 3.2%). A similar tendency as for the median values was observed with respect to the percentage of patients with abnormal platelet values. A tendency was recognisable that on days 15 and 22 of a cycle, the platelet values were higher than on the respective cycle starting days.

At day 15 of a cycle, 50% and more patients had abnormal platelet values, whereas at day 1 of a cycle, less patients had abnormal platelet values.

Abnormal, clinically relevant platelet values occurred at the following timepoints: cycle 1 day 15 in 1 patient in Arm B; at cycle 2 day 1 in 1 patient in Arm A; at cycle 2 day 8 in 2 patients in Arm A and 1 patient in Arm B; at cycle 2 day 15 in 2 patients in Arm A and 1 patient in Arm B; at cycle 2 day 22 in 2 patients in Arm A.

Leukocytes

The leukocyte values showed big variations over time, and also between the treatment arms. As a tendency, the values were higher at day 1 of a cycle and at the lowest point at day 15/22 of a cycle. In cycle 1, the largest drop was observed. At screening, the median leukocyte value was 7.67 /nl (7.58 /nl in Arm A and 8.26 /nl in Arm B). At cycle 1 day 15, the median leukocyte value was 5.1 /nl (5.61 /nl in Arm A and 4.81 /nl in Arm B). One week later, the median leukocyte value was 3.85 /nl (3.94 /nl in Arm A and 3.06 /nl in Arm B). However, at cycle 2 day 1, the median leukocyte value increased to 4.3 /nl (5.06 /nl in Arm A and 4.28 /nl in Arm B) and even to 5 /nl at cycle 2 day 8 (4.70 /nl in Arm A, 5.83 /nl in Arm B). From day 15 the median leukocyte value dropped again to 3.63 /nl on day 15 and to 2.93 /nl on day 22. At cycle 3 day 1, the leukocyte value had recovered to 5 /nl. A similar pattern was observed for the following cycles.

Correspondingly, the percentage of patients with abnormal leukocyte values sometimes was higher on days 15 and 22 of a cycle, but no general trend was obvious. Abnormal, clinically relevant leukocyte values occurred in Arm A at cycle 1 day 15 (2 patients), cycle 1 day 22 (1 patient), cycle 2 day 8 (1 patient), cycle 2 day 15 (1 patient), and cycle 3 day 22 (1 patient) and in Arm B at screening (1 patient), cycle 1 day 1 (1 patient), cycle 1 day 15 (2 patients), cycle 2 day

15 (2 patients), cycle 2 day 22 (1 patient), cycle 3 day 1 (1 patient), cycle 3 day 15 (1 patient), and EOT (1 patient).

Neutrophils

As the other haematological parameters, neutrophils started to drop on day 15 of cycle 1 (median screening value: 5.1 /nl, median value at cycle 1 day 22: 2.5 /nl). The values remained on this level until cycle 3. From cycle 3 onwards, the neutrophil values remained around median values of 3-4 /nl with lower values on days 22 of cycle 3 and 4 (median value at cycle 3 day 22: 2.4 /nl, at cycle 4 day 22: 2.3 /nl). At EOT, the median neutrophil value had increased to 3.73 /nl.

Differences between the treatment group occurred, but not with a systematic pattern. The median screening value in Arm A was lower than in Arm B (4.90 /nl vs. 5.77 /nl). So mostly, the median values in Arm B were higher, but lower for example at cycle 1 day 22 (2.08 /nl in Arm B vs. 2.675 /nl in Arm A) or cycle 4 day 15 (2.36 /nl vs. 4.2 /nl).

If the neutrophil values were abnormal, they were evaluated as clinically not relevant in most cases. Clinically relevant abnormal neutrophil values occurred in Arm A at cycle 1 day 15 (2 patients), cycle 1 day 22 (1 patient), cycle 2 day 22 (1 patient), and cycle 3 day 22 (1 patient), and in Arm B at screening (1 patient), cycle 1 day 1 (1 patient), cycle 1 day 15 (1 patient), cycle 2 day 15 (2 patients), cycle 2 day 22 (1 patient), cycle 3 day 1 (1 patient), cycle 3 day 15 (1 patient) and at EOT (1 patient).

12.5 Vital signs, physical findings and other observations related to safety

Vital signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate) were measured at screening, weekly during the treatment phase, and at EOT.

The median systolic blood pressure showed variations between 100 and 130 mmHg during the course of the study. Only on day 22 of cycle 4, the value was 140 mmHg; however, these are data of only 1 patient in Arm A. No major differenced were observed between the treatment groups. At EOT, the median systolic blood pressure was 120 mmHg in both arms (with screening values of 130 mmHg in Arm A and 120 mmHg in Arm B at screening).

The median diastolic blood pressure varied around 70 mmHg throughout the treatment phase, with a minimum median of 60 mmHg and a maximum median of 80 mmHg. At EOT, the median diastolic blood pressure was 80 mmHg in Arm A and 78 mmHg in Arm B (screening: 74 and 70 mmHg, respectively).

The heart rate increased in both treatment arms, whereas the increase was more evident in Arm B over time. At screening, the median heart rate was 76 beats/min in both arms. At the beginning of cycle 2, the median heart rate was 80 beats/min in Arm A and 82.5 beats/min in Arm B. At cycle 3 day 1, the median heart rate was 78 beats/min in Arm A and 84 beats/min in Arm B. At cycle 4

day 1, the median heart rate was 74 beats/min in Arm A and 80 beats/min in Arm B. At EOT, the heart rate was 80 beats/min in both treatment arms.

Physical examination/Body weight

In both arms, a weight loss of similar extent was observed. At screening, the median body weight was 73.5 kg in Arm A and 71.8 kg in Arm B. At the beginning of cycle 2, the median body weight was 68.7 kg in Arm A and 67.0 kg in Arm B. At cycle 3 day 1, the median body weight was 63.5 kg in Arm A and 69.0 kg in Arm B, and at cycle 4 day 1, the median body weight was 65.1 kg in Arm A and 67.0 kg in Arm B. The median body weight at EOT was 68.8 kg in Arm A and 67.0 kg in Arm B.

The median body height at screening was 170.5 cm in Arm A and 173.5 cm in Arm B. The median BSA at screening was 1.9 m² in Arm A and 1.8 m² in Arm B.

Descriptive statistics of body weight, body height and BSA are presented in Table 14.3.3.1.

Karnofsky Performance Status (KPS)

The KPS aggravated during the course of the study. At screening, 31 patients in Arm A (96.9%) and 34 patients in Arm B (94.4%) had a KPS of 100-80%. One (3.1%) and 2 (5.6%) patients, respectively, had a KPS of 70%.

During the course of the study, the KPS showed a trend towards lower values, but the majority of patients still had a KPS of 100-80%. At cycle 4, 4 patients out of 14 evaluated patients (28.6%) in Arm A and 3 out of 11 evaluated patients (27.3%) in Arm B had a KPS of 50-70%. At EOT 6 out of 30 evaluated patients in Arm A (20.0%) and 6 out of 31 evaluated patients (19.4%) had a KPS of 50-70% and 4 patients in Arm B (12.9%) had a KPS of 10-14%.

Quality of Life

QLQ-C30

The scores were scaled to 0-100. Higher scores represented a higher level of QoL, higher level of functioning or higher level of symptomatology/problems, depending on the item. The patients were asked to complete the questionnaires at screening, re-evaluation and EOT.

For global health status score, the median value decreased from 66.7 at screening to 50.0 at EOT in Arm A and stayed constant at 50.0 at screening and EOT in Arm B with even an improvement to a median of 62.5 at the time of re-evaluation.

The physical functioning score decreased in both arms (Arm A: 86.7 at screening to 60.0 at EOT, Arm B: 86.7 at screening to 73.3 at EOT).

A big decrease was observed for the median score for role functioning: In Arm A, the median score was 83.3 at screening and 33.3 at EOT. In Arm B, the median score was 66.7 at screening and 50 at EOT.

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For emotional functioning, we detected only a small decrease, no major differences between the treatment groups at screening and EOT (median score 66.7 at screening and 58.3 and 62.5 at EOT, respectively). Only at re-evaluation, the median score was 75.0 in Arm B and 66.7 in Arm A.

Cognitive functioning remained constant in Arm B (median score: 83.3 at screening and EOT), in Arm A, there was a drop from 100.0 to 83.3.

Also social functioning remained constant in Arm B (median score: 66.7 at screening and EOT), and Arm A there was a small decrease in median from 66.7 at screening to 58.3 at EOT.

For the item scales of fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties described in the following, higher scores on the scale from 0-100 mean a higher level of symptomatology/problems.

For fatigue, the median score increased from 33.3 at screening (both arms) to 55.6 in Arm A and 52.8 in Arm B at EOT, which is consistent with the high occurrence of the AE Fatigue as discussed above.

Nausea and vomiting worsened during the course of the study as well. Both events had a median score of 0 at screening, and a median of 16.7 at EOT, so there were no differences between the treatment groups. This is also consistent with our findings on the occurrence of the AEs nausea and vomiting.

The median score for pain remained constant in Arm A (33.3 at screening and EOT) and worsened in Arm B (16.7 at screening, 33.3 at EOT).

Dyspnea only worsened in Arm B where the median score increased from 0 at screening to 33.3 at EOT. In Arm A the median score was 0, although the maximum score was 100.0 at all timepoints.

For insomnia, an improvement was found in Arm A (median score 33.3 at screening and 0 at EOT), whereas the median score increased in Arm B from 0 at screening to 33.3 at EOT.

Appetite loss increased equally in both treatment groups. In Arm A the median score was 0 at screening and 33.3 at EOT, and in Arm B the median score was 33.3 at screening and 66.7 at EOT. However, anorexia was reported as AE in 4 patients only (4.4%).

Constipation remained constant with a median score of 0 at screening and EOT in Arm A, but an increase at the time of re-evaluation to 33.3. In Arm B, the median score aggravated from 0 at screening to 33.3 at re-evaluation and improved again at EOT to 16.7. Constipation was reported as AE in 17 of all 68 patients (25%), thereof 11 patients (64.7) were treated in Arm B.

Diarrhea remained constant at a median score of 0 at screening and EOT for both arms. Diarrhea was reported as AE in 12/68 patients.

Financial difficulties remained constant at a median score of 0 in Arm A and showed an increase in the median score from 0 at screening to 16.7 at EOT in Arm B.

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The scores were scaled to 0-100. Higher scores represented a higher level of QoL, higher level of functioning or higher level of symptomatology/problems, depending on the item. The patients were asked to complete the questionnaires at screening, re-evaluation and EOT.

The median score for eating started low in Arm A (33.3 at screening), increased to 50.0 at re-evaluation, and decreased again to 41.7 at EOT. In contrary, in Arm B, the median score decreased from 58.3 to 43.1 at both re-evaluation and EOT.

Problems with reflux also increased in Arm A from a median score of 16.7 at screening to 33.3 at EOT, whereas in Arm B, it remained constant at 16.7.

The median score for pain remained constant in Arm A (22.2 at screening, re-evaluation and EOT) and slightly improved in Arm B from 27.8 at screening to 33.3 at re-evaluation, but worsened again to 22.2 at EOT.

The median score for trouble swallowing saliva increase in Arm A from 0 at screening to 33.3 at re-evaluation and EOT. In Arm B, the median score was 0 at screening and EOT, but 33.3 at re-evaluation.

The function scale for dysphagia had a median score of 44.4 at screening and 38.9 at EOT in both groups. At re-evaluation after 4-4.5 weeks of treatment, the median score increased to 61.1 in Arm A and to 44.4 in Arm B.

The median score for choking when swallowing was 0 over the time in both arms.

At screening the median score for dry mouth was 0 in both arms. This worsened to a median score of 33.3 at re-evaluation and EOT in both arms. A similar behaviour was seen in the median score of trouble with taste and trouble with coughing.

12.6 Safety conclusions

Altogether, the addition of cetuximab to the chosen standard radiochemotherapy was feasible. The experienced adverse events were consistent with the known safety profiles of cetuximab, 5-FU, cisplatin and radiotherapy as well as with the severity of the underlying disease. No unexpected risks occurred. Patients with cetuximab had a higher risk for skin disorders such as acneiform rash and rash maculopapular rash, radiation dermatitis, leukopenia, hypomagnesemia, hypocalcemia, and allergic reaction (all grades). The risk for severe AEs was only higher with cetuximab in terms of allergic reactions. All allergic reactions could be well managed and resolved without sequelae. Skin reactions such as acneiform rash, maculopapular rash and radiation dermatitis as well as laboratory abnormalities such as hypomagnesemia, hypocalcemia and leucopenia were resolved at 6 weeks after EOT in most patients.

13 DISCUSSION AND OVERALL CONCLUSION

With this phase 2 study we aimed to investigate if the addition of the EGFR antibody cetuximab to standard radiochemotherapy with cisplatin and 5-FU is advantageous over standard radiochemotherapy alone. In our previous phase 1 study LEOPARD-1[36] we established the maximum tolerated dose of 5-FU in this combined regimen: 59.4 Gy of radiotherapy with concurrently 2 four week cycles of cisplatin (20 mg/m², d1-4) and 5-FU (1000 mg/m², d1-4), followed 5 weeks later by 2 four week cycles of cisplatin (20.mg/m², d1-4) and 5-FU (750 mg/m² d1-4). Cetuximab was administered according to label at a loading dose of 400 mg/m² followed by 250 mg/m² weekly for up to 14 weeks.

The primary endpoint of our present study (LEOPARD-2) was 2-year OS. In Arm A, the 2-year OS was 71% (95% CI: 55%; 87%) based on Kaplan-Meier estimation. Since the 2-sided 95% Kaplan-Meier-CI excluded the 40% rate of the null hypothesis, the null hypothesis could be rejected and the combination of cetuximab plus standard radiochemotherapy can be considered a promising treatment. In the control arm, the 2-year OS was with 53% also higher than the historical values assumed for the test of the primary endpoint (40%); however, the 95% CI in Arm B was 36-71% including the 40% threshold. For the primary endpoint, no formal comparison between the treatment arms but comparison to historical data was planned in the study.

The study also has shown an improved median overall survival with 49.1 months in the experimental arm vs. 24.1 months in the control arm (HR = 0.60 [95%CI: 0.30; 1.21] for the cetuximab combination); this did not show statistical significance (p = 0.1470). This suggests that the addition of cetuximab to standard radiochemotherapy with cisplatin and 5-FU may be a promising treatment.

With regards to the secondary endpoints PFS, LC and MFS, strong trends were observed for improvement in PFS (p = 0.0600) and MFS (p = 0.0568) with the addition of cetuximab. No significant impact or a strong trend was observed with respect to LC (p = 0.1505).

In a study by Ruhstaller et al.[37] from Switzerland – SAKK 75/80 – in patients with resectable esophageal cancer who received neoadjuvant chemotherapy, chemoradiation and surgery with or without cetuximab, cetuximab also improved loco-regional control and led to improvements in PFS and OS which were clinically relevant, but not statistically significant. In this randomised, open-label phase 3 study patients received docetaxel and cisplatin followed by radiochemotherapy and surgery, with or without neoadjuvant and adjuvant cetuximab. The median OS times were 5.1 years vs. 3.0 years for the cetuximab arm and the control arm, respectively (p = 0.055). The time to loco-regional failure was significantly longer with cetuximab (HR = 0.53; 95% CI: 0.31; 0.90, p = 0.017); the MFS was similar in both groups (HR = 1.01; 95% CI: 0.64; 1.59, p = 0.97).

In contrast to the findings of the Swiss trial, the addition of cetuximab to paclitaxel, cisplatin and radiotherapy in the phase 3 randomised RTOG 0436[38] trial in patients with esophageal cancer did not improve OS. The 2-year OS rate was 45% in the cetuximab arm and 44% in the control arm. 56% of patients in the experimental arm and 58% of patients in the control arm reached a CR (p

= 0.66). In our study 81.3% in the experimental arm and 41.7% of patients in the control arm achieved CR.

In the SCOPE-1 trial[39], a phase 2/3 randomised trial that had been stopped after phase 2, 258 patients received radiochemotherapy with cisplatin and capecitabine either with or without cetuximab. Patients in the cetuximab arm had shorter median OS with 22.1 vs. 24.5 months, and fewer patients had no treatment failure at 24 weeks in the cetuximab arm (66.4% vs. 76.9%). In 2017, the long-term results of the SCOPE-1 trial were published[40]. The median OS times were 34.5 months in the radiochemotherapy arm and 24.7 months in the radiochemotherapy + cetuximab arm (p=0.137). Median PFS times were 24.1 and 15.9 months, respectively (p=0.114).

Data on the addition of cetuximab to platinum-based chemotherapy are also available from clinical trials of patients with head and neck cancer. Cetuximab in combination with cisplatin or carboplatin and 5-FU has been demonstrated to be effective in first-line therapy of recurrent or metastatic squamous cell carcinoma of the head and neck.[41] It significantly prolonged the median OS from 7.4 months in the control group to 10.1 months in the chemotherapy plus cetuximab group (HR for death: 0.80, 95% CI: 0.64; 0.99, p = 0.04). The median PFS was prolonged from 3.3 to 5.6 months.

Contrary to those results, in the RTOG 0522[42] trial investigating the addition of cetuximab to radiotherapy and cisplatin in patients with stage III/IV head and neck cancer, no significant differences in OS, PFS or loco-regional failure were demonstrated. The 3-year OS rates were 75.8% in the experimental arm including cetuximab and 72.9% in the radiotherapy plus cisplatin arm. The 3-year PFS rates were 58.9% vs. 61.2%, respectively. The addition of cetuximab resulted in more frequent interruptions of radiotherapy (26.9% in the experimental arm vs. 15.1% in the control arm), and more grade 3/4 radiation mucositis (43.2% vs. 33.3%), rash, fatigue, anorexia, and hypokalemia and was, therefore, not recommended for routine use.

A European study[43] of combined cetuximab, cisplatin and hyperfractionated accelerated radiotherapy (HART) in 74 patients with locally advanced inoperable SCC of the head and neck in a single-arm phase 2 design on the other hand showed acceptable results of weekly cisplatin with HART and cetuximab in this patient population. 35% of the patients achieved CR, and the 2-year OS rate was 64%.

The most frequent AEs in our study were nausea (59.4% of patients in the cetuximab arm vs. 55.6% of patients in the control arm, p = 0.8091), hypokalemia (50.0% vs. 33.3%, p = 0.2186), fatigue (28.1% vs. 50.0, p = 0.0846), anemia (40.6% vs. 36.1%, p = 0.8042), esophagitis (34.4% vs. 38.9%, p = 0.8028), leukopenia (50.0% vs. 22.2%, p = 0.0228), dysphagia (28.1% vs. 25.0%, p = 0.7901), and thrombocytopenia (34.4% vs. 19.4%, p = 0.1816). The difference regarding leukopenia was significant (p = 0.0228). Altogether, the AE profile of the control group was comparable to the expected AE profile for this kind of radiochemotherapy. It was not affected by the addition of cetuximab except for leukopenia, hypomagnesemia, hypocalcemia, rash

(acneiform and maculopapular), radiation dermatitis and allergic reactions, for which a higher rate occurred in the cetuximab arm than in the control arm. Those are known side effects of the EGFR antibody, and the toxicity profile was consistent with the known safety profiles of the medications used.

The most common grade 3-5 AEs in the cetuximab and control arms were not significantly different: Lung infection (9.4% vs. 22.2%, p = 0.1962), leukopenia (21.9% vs. 11.1%, p = 0.3255), anemia (12.5% vs. 19.4%, p = 0.5213), esophagitis (18.8% vs. 13.9%, p = 0.7441), dysphagia (12.5% vs. 8.3%, p = 0.6986), and thrombopenia (12.5% vs. 5.6%, p = 0.4095). A significant difference between the treatment arms for severe AEs was found for allergic reactions which were experienced by 12.5% of patients in Arm A and no patients in Arm B (p = 0.0442). In addition, trends were found for increased radiation dermatitis (9.4% vs. 0%, p = 0.0990), acneiform rash (9.4% vs. 0%, p = 0.0990) and hypomagnesemia (9.4% vs. 0%, p = 0.0990) in the experimental arm. All of these AEs could be well managed.

Haematological adverse events were the most common grade 3/4 AEs in the study by Vermorken[41] (cisplatin/carboplatin and 5-FU plus/minus cetuximab): anemia (19% in the cetuximab group and 13% in the control group), neutropenia (23% and 22%) and thrombocytopenia (11% in both groups). Nine of 219 patients in the cetuximab group and 1 of 220 patients in the control group experienced sepsis (p = 0.02). 9% of patients receiving cetuximab had grade 3 skin reactions; in our study, we similarly detected a rate of grade 3/4 acneiform rash of 9.4%.

In the RTOG 0436 trial[38] where cetuximab was added to cisplatin, paclitaxel and radiotherapy, the most frequent grade 3-5 AEs were leukopenia (28.8% of patients in the cetuximab arm vs. 24.7% of patients in the control arm), neutropenia (19.6% vs. 14.5%), fatigue (14.4% vs. 10.2%), dehydration (22.9% vs. 14.5%), dysphagia (11.8% vs. 13.3%), esophagitis (12.4% vs. 12.0%), nausea (12.4% vs. 12.0%), and dermatologic/skin disorders (10.5% vs. 0.6%). This is widely consistent with our observations of grade 3-5 leukopenia, dysphagia, esophagitis, and skin reactions. We, however, had fewer patients experiencing grade 3-5 neutropenia (6.3% vs. 8.3%), fatigue (0% vs. 5.6%), and dehydration (0% vs. 5.6%).

The most common grade ≥ 3 toxicities in the study of Kuhnt et al.[43] were mucositis (58%), dysphagia (52%), dermatitis in the radiation field (53%), grade ≥ 3 skin reactions outside the irradiated field in 15% of patients, and grade ≥ 3 neutropenia in 10% of patients.

The combination of cetuximab with docetaxel, cisplatin and radiotherapy only showed minor differences compared to radiochemotherapy alone[37]. Cetuximab led to higher percentages of hypomagnesemia and allergic reactions, as observed in our study as well. In this study of Ruhstaller et al. the addition of cetuximab seemed to rather reduce adverse events typically caused by radiotherapy such as dysphagia and esophagitis in this combination; this was not observed in our study, where we had similar rates of esophagitis and dysphagia in both groups.

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When cetuximab was added to radiochemotherapy with cisplatin and capecitabine, a prodrug of 5-FU, (SCOPE1 trial[39]) patients in the cetuximab arm had more non-haematological grade 3/4 AEs than patients in the control arm (79% vs. 63%, p = 0.004). The most common grade 3/4 toxicities were leukopenia (11% in the cetuximab arm vs. 16% in the control arm), neutropenia (12% vs. 19%, respectively), and dysphagia (27% vs. 29%, respectively)[39].

Altogether, findings related to toxicity were widely consistent across multiple trials. An exception was the high occurrence of grade 3-5 lung infection in our study that was experienced by 8 patients (22.2%) in the control arm and 3 patients (9.4%) in the cetuximab arm (p = 0.1962). An explanation for this might be the immunosuppressive potential of cisplatin and especially 5-FU. Clearly, cetuximab seemed not to increase the potential for lung infection.

We analysed several factors such as age, baseline Karnofsky performance status, tumour location, tumour histology, histologic grade, T-stage, N-stage and haemoglobin (Hb) before radiotherapy for their prognostic value for OS. Only for pre-radiotherapy Hb, a trend was perceptible. In the subgroup of patients with Hb levels < 12 g/dl, the patients in Arm A had a significantly lower risk for death than the patients in Arm B with a HR of 0.15 (95% CI 0.03; 0.79). For the group of patients with other Hb values (12-14 g/dl, > 14 gdl), no clear statements could be made. It is known that anemia leads to tumour hypoxia which can impair the effect of radiochemotherapy[44]. A negative impact of lower Hb-levels on outcomes of radio(chemo)therapy in patients with esophageal cancer has already been described for Hb-levels measured prior to radio(chemo)therapy and during concurrent radiochemotherapy[45,46]. These findings support the choice of Hb value as prognostic factor for further investigation.

One limiting factor of our study surely was the small number of patients. It was, however, within 5 years not possible to include more patients; the main reason for non-inclusion was resectability of the cancer. Thus, for future prospective trials, this point should be taken into account for an appropriate choice of inclusion and exclusion criteria.

In summary, the addition of cetuximab to radiochemotherapy with cisplatin/5-FU in patients with esophageal cancer was feasible and not associated with a significant increase in most adverse events. This regimen showed promising outcomes that were favorable when compared to radiochemotherapy without cetuximab, although statistical significance was not reached. However, trends were observed for better PFS and MFS in the cetuximab group. Since the fact that the non-achievement of statistical significance was not achieved might be due to the relatively small number of patients and, as a consequence, the large difference in outcomes required to reach significance, an additional trial including a cohort of patients sufficiently large to demonstrate significant differences between radiochemotherapy plus cetuximab and radiochemotherapy alone is warranted.

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Moreover, the chemotherapy regimen including cisplatin and 5-FU used in this trial may be replaced as standard therapy by the CROSS scheme including carboplatin and paclitaxel[47], which led to very good long-term results in a randomised controlled trial with patients with resectable, locally advanced cancer of the esophagus and esophageal junction. Therefore, the combination of cetuximab with the CROSS regimen might be a further treatment option to be investigated in patients with locally advanced esophageal cancer.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic data

14.1   Demographic data

Table 14.1-1: Relevant screening assessments

	Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Karnofsky Performance Status	n (%) – total	68 (100.0)	32 (100.0)	36 (100.0)
	n (%) – 100%	19 (27.9)	9 (28.1)	10 (27.8)
	n (%) – 90%	32 (47.1)	17 (53.1)	15 (41.7)
	n (%) – 80%	14 (20.6)	5 (15.6)	9 (25.0)
	n (%) – 70%	3 (4.4)	1 (3.1)	2 (5.6)
FEV_1 (l)	n	68	32 (100.0)	36 (100.0)
	mean	2.61	2,63	2.60
	SD	0.73	0.69	0.77
	median	2.58	2.57	2.61
	min, max	1.14; 4.21	1.14; 4.21	1.19; 3.85
ECG	n	66	31	35
	normal – n(%)	51 (77.3)	26 (83.9)	25 (71.4)
	abnormal, CNR – n(%)	15 (22.7)	5 (16.1)	10 (28.6)
	abnormal, CR – n(%)	0	0	0
Systolic blood pressure (mmHg)	n	67	31	36
	mean	124.2	127.3	121.6
	SD	16.44	17.05	15.66
	median	120.0	130.0	120.0
	min, max	94, 180	100, 180	94, 150
Diastolic blood pressure (mmHg)	n	67	31	36
	mean	74.1	74.8	73.6
	SD	8.40	8.12	8.72
	median	71.0	74.0	70.0
	min, max	54, 90	60, 90	54, 90
Heart rate (beats/min)	n	67	31	36
	mean	76.9	77.3	76.3
	SD	10.34	10.63	10.21
	median	76.0	76.0	76.0
	min, max	55, 100	55, 100	59, 98
Body height (cm)	n	68	32	36
	mean	172.8	171.8	173.8
	SD	7.53	7.52	7.53
	median	172.5	170.5	173.5
	min, max	158, 192	159, 192	158, 189
Body weight (kg)	n	68	32	36
	mean	74.8	78.0	71.9
	SD	17.17	18.89	15.18
	median	72.0	73.5	71.8
	min, max	50, 133	52, 133	50, 121
Body surface area (m²)	n	68	32	36
	mean	1.9	1.9	1.8

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	Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	SD	0.23	0.25	0.21
	median	1.9	1.9	1.8
	min, max	1.5, 2.6	1.6, 2.6	1.5, 2.5
Creatinine clearance (ml/min)	n	67	31	36
	mean	104.94	109.48	101.02
	SD	44.58	54.12	34.69
	median	98	101.8	95.35
	min; max	54.9; 359.7	54.9; 359.7	56; 222.6
	normal – n(%)	53 (79.1)	25 (80.6)	28 (77.8)
	abnormal, CNR – n(%)	13 (19.4)	5 (16.1)	8 (22.2)
	abnormal, CR – n(%)	0	0	0
	Evaluation ND	1 (1.5)	1 (3.2)	0

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done, SD: Standard deviation

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Table 14.1-2: Relevant diseases other than esophageal cancer

Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Patients with any relevant diseases other than esophageal cancer	52 (76.5)	25 (78.1)	27 (75.0)
Hypertension	28 (41.2)	13 (40.6)	15 (41.7)
COPD	5 (7.4)	1 (3.1)	4 (11.1)
Diabetes mellitus	5 (7.4)	1 (3.1)	4 (11.1)
Dysphagia	5 (7.4)	4 (12.5)	1 (2.8)
Weight loss	5 (7.4)	3 (9.4)	2 (5.6)
Hypothyreosis	4 (5.9)	1 (3.1)	3 (8.3)
Depression	3 (4.4)	0	3 (8.3)
Glaucoma	3 (4.4)	2 (6.3)	1 (2.8)
Anemia	2 (2.9)	2 (6.3)	0
Arthrosis	2 (2.9)	0	2 (5.6)
Asthma bronchiale	2 (2.9)	1 (3.1)	1 (2.8)
Cholecystolithiasis	2 (2.9)	0	2 (5.6)
Embolism/Pulmonary embolism	2 (2.9)	1 (3.1)	1 (2.8)
Esophagitis	2 (2.9)	1 (3.1)	1 (2.8)
Gastritis	2 (2.9)	2 (6.3)	0
Hypersalivation	2 (2.9)	1 (3.1)	1 (2.8)
Liver cirrhosis	2 (2.9)	2 (6.3)	0
Refluxesophagitis	2 (2.9)	1 (3.1)	1 (2.8)
Sarcoidosis	2 (2.9)	1 (3.1)	1 (2.8)
Smoking history/Past nicotin abusus	2 (2.9)	1 (3.1)	1 (2.8)
Steatohepatitis	2 (2.9)	2 (6.3)	0
Tachycardia	2 (2.9)	2 (6.3)	0
Thrombosis	2 (2.9)	0	2 (5.6)
Alcohol abusus	1 (1.5)	1 (3.1)	0
Allergy	1 (1.5)	1 (3.1)	0
Allergy to Penicillin	1 (1.5)	1 (3.1)	0
Apoplexia	1 (1.5)	1 (3.1)	0
Appendectomy	1 (1.5)	0	1 (2.8)
Arterial sclerosis	1 (1.5)	1 (3.1)	0
Asthenia	1 (1.5)	1 (3.1)	0
Back pain	1 (1.5)	0	1
Cachexia	1 (1.5)	0	1 (2.8)
Carotis Stenosis	1 (1.5)	1 (3.1)	0
Cataract	1 (1.5)	1 (3.1)	0
Chronic pain syndrome	1 (1.5)	1 (3.1)	0
Chronic renal insufficiency	1 (1.5)	1 (3.1)	0
Depressed fracture-lumbar	1 (1.5)	1 (3.1)	0
Diabetic foot syndrome	1 (1.5)	1 (3.1)	0
Diabetic polyneuropathy	1 (1.5)	1 (3.1)	0
Diabetic retinopathy	1 (1.5)	1 (3.1)	0
Distal esophagus stenosis	1 (1.5)	0	1 (2.8)
Double ACVB surgery	1 (1.5)	1 (3.1)	0
Edema legs	1 (1.5)	1 (3.1)	0
Erysipelas	1 (1.5)	1 (3.1)	0
Esophageal candida infection	1 (1.5)	1 (3.1)	0
Fracture	1 (1.5)	1 (3.1)	0
Gamma-GT increased	1 (1.5)	1 (3.1)	0
GERD	1 (1.5)	0	1 (2.8)
Gout	1 (1.5)	1 (3.1)	0
Hemorrhoids	1 (1.5)	1 (3.1)	0
Hernia umbilicalis	1 (1.5)	0	1 (2.8)

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Term	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Hypercholesterinemia	1 (1.5)	1 (3.1)	0
Hyperthyroidism	1 (1.5)	1 (3.1)	0
Hyperurikemia	1 (1.5)	0	1 (2.8)
Hypomagnesemia	1 (1.5)	1 (3.1)	0
Hyponatremia	1 (1.5)	1 (3.1)	0
Hypothophy kidney left	1 (1.5)	1 (3.1)	0
Hysterectomy (Myoma)	1 (1.5)	1 (3.1)	0
IDDM at Diabetes mellitus Type 1	1 (1.5)	1 (3.1)	0
Infection/dislocation of jejunal stent	1 (1.5)	1 (3.1)	0
Knee TEP right	1 (1.5)	1 (3.1)	0
Lipomatosa clavicular 2 swell	1 (1.5)	1 (3.1)	0
Macular degeneration	1 (1.5)	1 (3.1)	0
Malignant Melanoma in 2000	1 (1.5)	1 (3.1)	0
Mediasclerosis	1 (1.5)	1 (3.1)	0
Myocardial infarction	1 (1.5)	1 (3.1)	0
Myocarditis	1 (1.5)	0	1 (2.8)
Nausea	1 (1.5)	1 (3.1)	0
Obesity	1 (1.5)	0	1 (2.8)
Occlusion of right A. carotis	1 (1.5)	1 (3.1)	0
Pace XX implantation (indication: AV block II)	1 (1.5)	1 (3.1)	0
Pain	1 (1.5)	1 (3.1)	0
Pancreatitis	1 (1.5)	1 (3.1)	0
pAVK of both thighs	1 (1.5)	1 (3.1)	0
Peripheral arterial disease	1 (1.5)	0	1 (2.8)
Polyneuropathy	1 (1.5)	0	1 (2.8)
Prostate carcinoma in 2007	1 (1.5)	0	1 (2.8)
Prostate hyperplasia	1 (1.5)	1 (3.1)	0
Recurrensparesis	1 (1.5)	1 (3.1)	0
Renal arterial stenosis	1 (1.5)	1 (3.1)	0
Spinal canal stenosis	1 (1.5)	1 (3.1)	0
Status after ACVB surgery	1 (1.5)	1 (3.1)	0
Status after ankle fracture	1 (1.5)	1 (3.1)	0
Status after joint splitting	1 (1.5)	1 (3.1)	0
Status after PCI venous bypass	1 (1.5)	1 (3.1)	0
Status after VW infarction	1 (1.5)	1 (3.1)	0
Status of gastric perforation with Bilroth II-surgery	1 (1.5)	0	1 (2.8)
Stent	1 (1.5)	1 (3.1)	0
Steroid dermatitis	1 (1.5)	1 (3.1)	0
Stomach ulcer	1 (1.5)	1 (3.1)	0
Tuberculosis	1 (1.5)	0	1 (2.8)
Ventricular arrhythmia	1 (1.5)	1 (3.1)	0
Vomiting	1 (1.5)	1 (3.1)	0

A: arteria; ACVB: aortocoronary venous bypass; AV: atrioventricular; COPD: chronic obstructive pulmonary disease; GERD: gastro-esophageal reflux disease; GT: glutamyl transferasis; PCI: percutaneous coronary intervention; TEP: total endoprothesis

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14.2 Efficacy data

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Leopard II study, Efficacy tables

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Table 14.2.1.1 Kaplan Meier and Cox proportional hazards results for overall survival (PP)

Evaluation	Cetuximab (N=32)	Control (N=36)	Total (N=68)
Number of events	13 (40.63 %)	20 (55.56 %)	33 (48.53 %)
Median* survival (months)	49.05 (24.43; -)	24.13 (12.30; 49.28)	38.37 (23.74; 52.21)
Log-rank test for difference between treatment groups (p-value)	0.1470		
1-year survival rate [95% CI]	0.74 [0.59 ; 0.90]	0.70 [0.54 ; 0.86]	
2-year survival rate [95% CI]	0.71 [0.55 ; 0.87]	0.53 [0.36 ; 0.71]	
Hazard ratio Cetuximab vs. Control [95% CI]**	0.60 [0.30 ; 1.21]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
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Table Generation: 25SEP2018 12:39:12 PM

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14.2 Efficacy data
Figure 14.2.1.1 Kaplan-Meier curves for Overall survival (PP)
Overall population

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14.2 Efficacy data
Figure 14.2.1.1 Kaplan-Meier curves for Overall survival (PP)
By treatment group

Table 14.2.1.2 Kaplan Meier and Cox proportional hazards results for progression-free survival (PP)

Evaluation	Cetuximab (N=32)	Control (N=36)	Total (N=68)
Number of events	12 (37.50 %)	22 (61.11 %)	34 (50.00 %)
Median* survival (months)	- (8.91; -)	17.59 (9.73; 31.60)	27.16 (11.08; 38.37)
Log-rank test for difference between treatment groups (p-value)	0.0600		
1-year survival rate [95% CI]	0.64 [0.47 ; 0.82]	0.58 [0.40 ; 0.75]	
2-year survival rate [95% CI]	0.56 [0.37 ; 0.75]	0.44 [0.26 ; 0.62]	
Hazard ratio Cetuximab vs. Control [95% CI]**	0.51 [0.25 ; 1.04]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
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14.2 Efficacy data
Figure 14.2.1.2 Kaplan-Meier curves for Progression-free survival (PP)
Overall population

14.2 Efficacy data

Figure 14.2.1.2 Kaplan-Meier curves for Progression-free survival (PP)

By treatment group
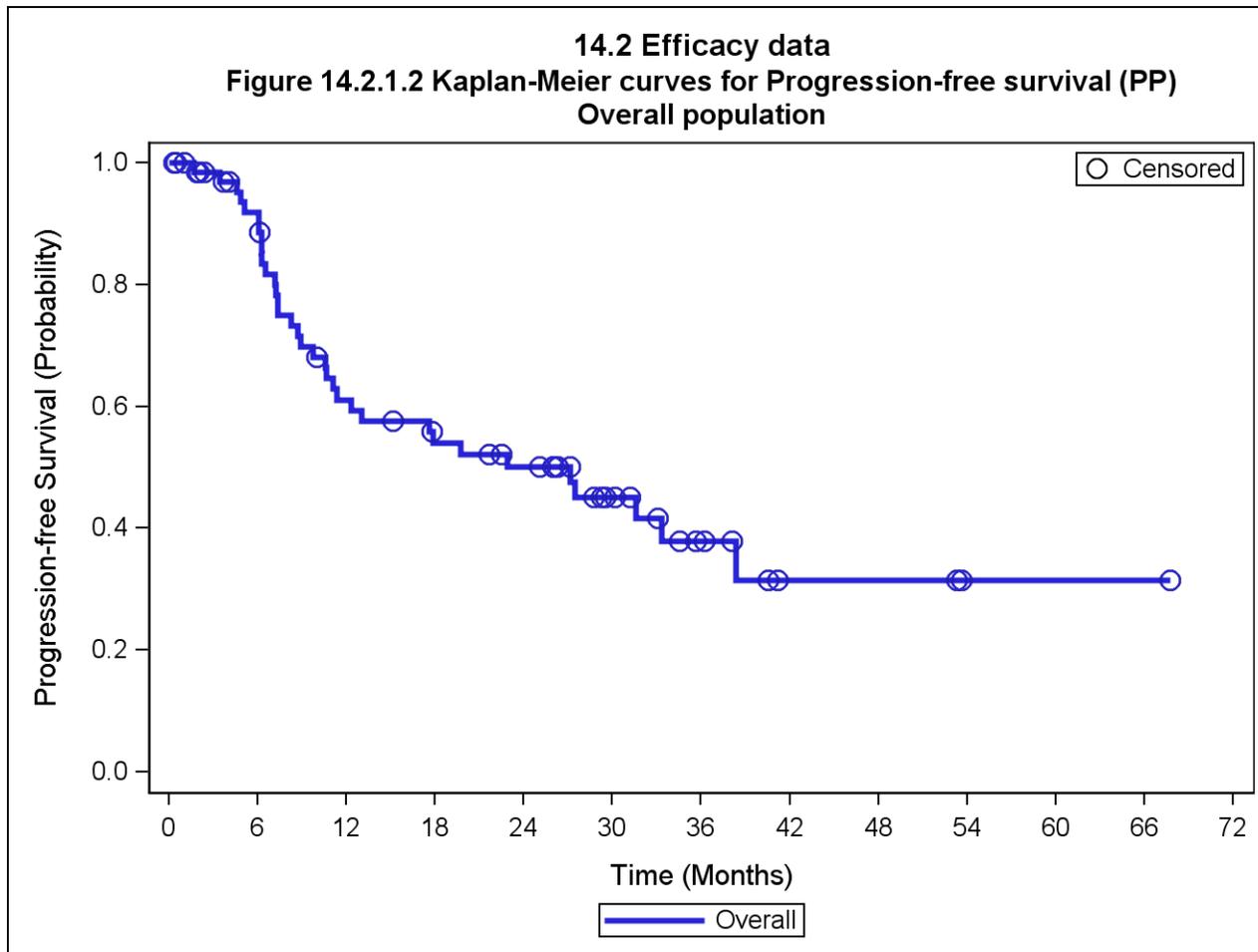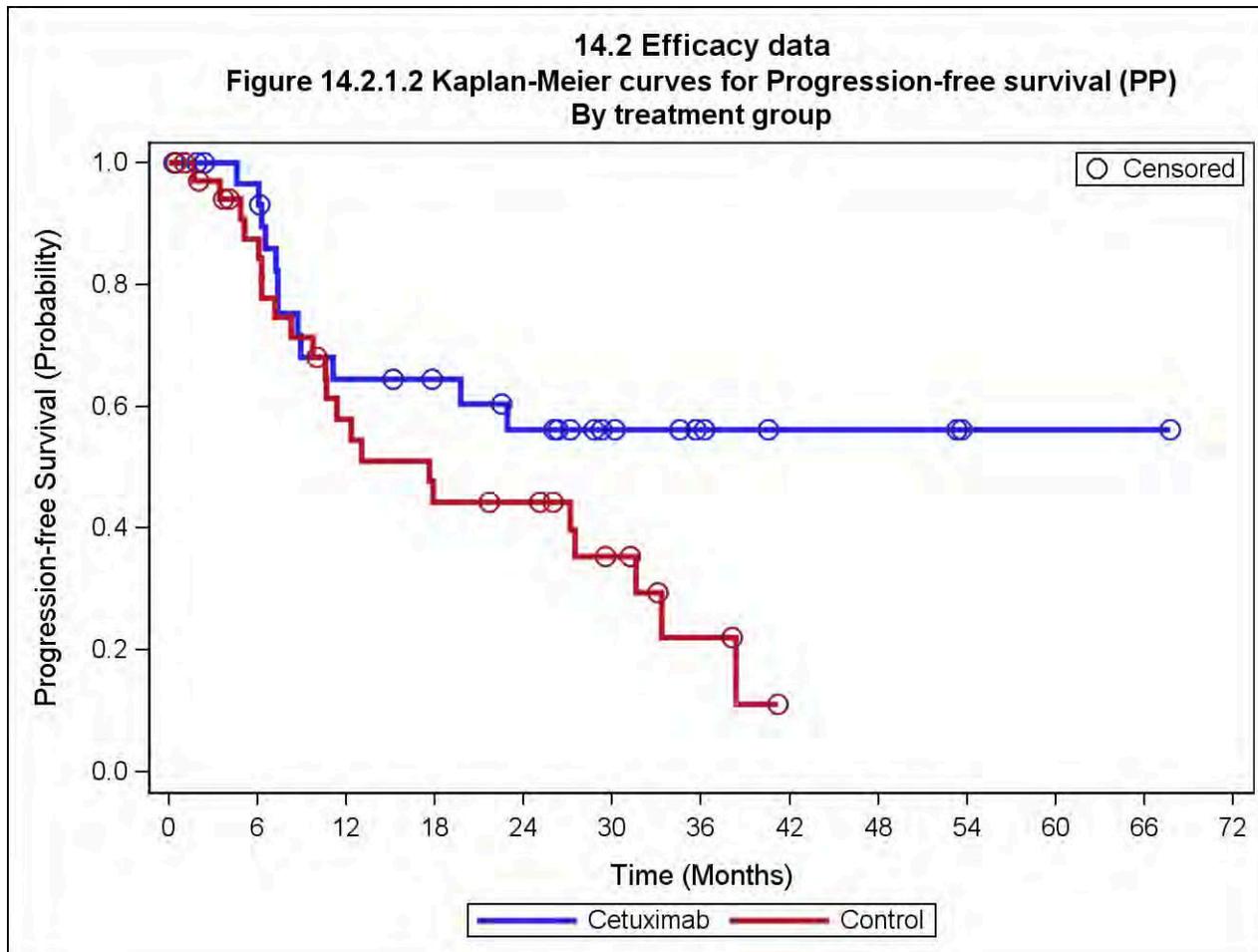
Table 14.2.1.3 Kaplan Meier and Cox proportional hazards results for loco-regional control (PP)

Evaluation	Cetuximab (N=32)	Control (N=36)	Total (N=68)
Number of events	4 (12.50 %)	9 (25.00 %)	13 (19.12 %)
Median* survival (months)	- (-; -)	- (27.16; -)	- (-; -)
Log-rank test for difference between treatment groups (p-value)	0.1505		
1-year survival rate [95% CI]	0.89 [0.77 ; 1.01]	0.81 [0.67 ; 0.95]	
2-year survival rate [95% CI]	0.84 [0.70 ; 0.99]	0.72 [0.55 ; 0.89]	
Hazard ratio Cetuximab vs. Control [95% CI]**	0.43 [0.13 ; 1.40]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
Program: T14-2-1-3lc.sas
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14.2 Efficacy data
Figure 14.2.1.3 Kaplan-Meier curves for Loco-regional control (PP)
Overall population

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14.2 Efficacy data
Figure 14.2.1.3 Kaplan-Meier curves for Loco-regional control (PP)
By treatment group
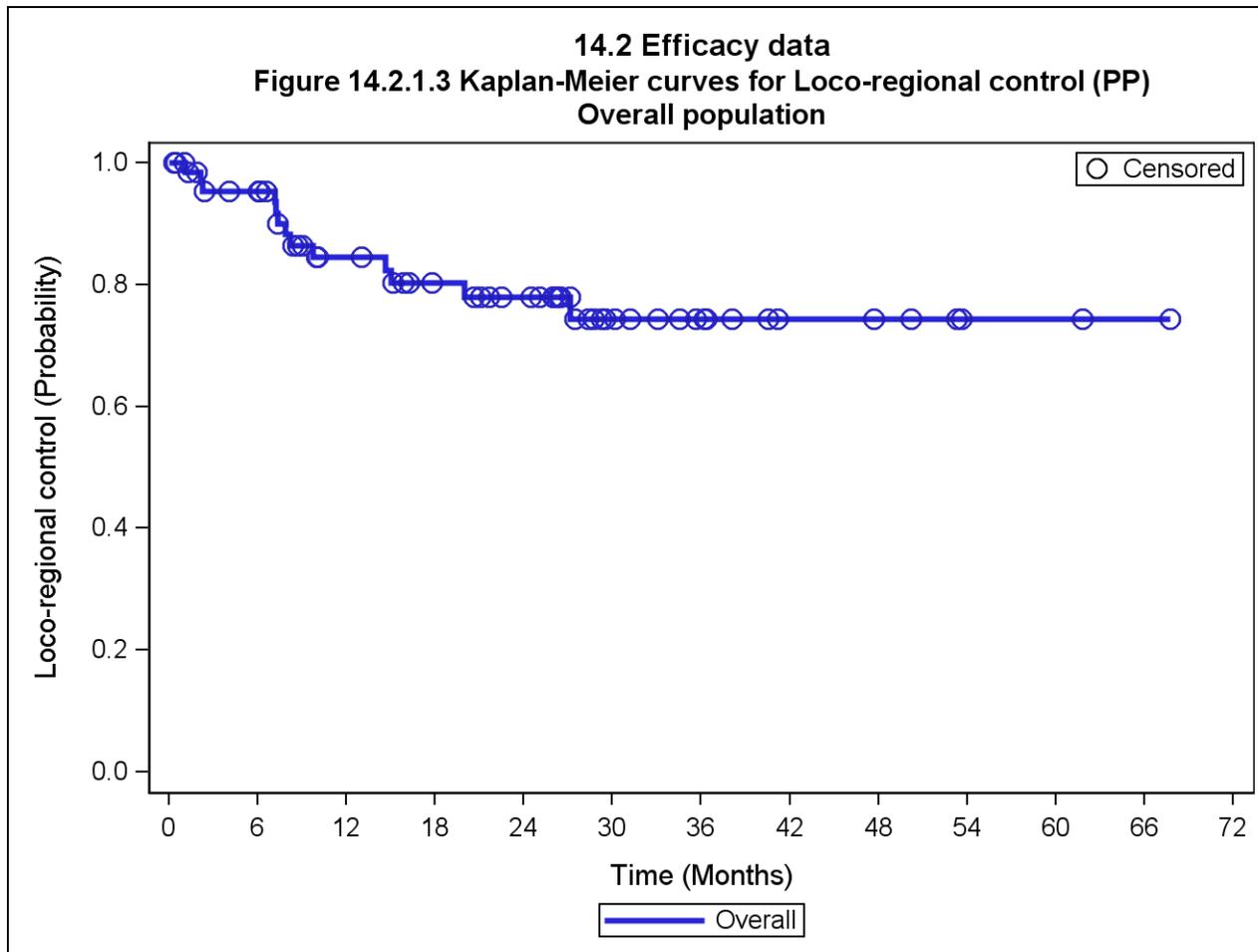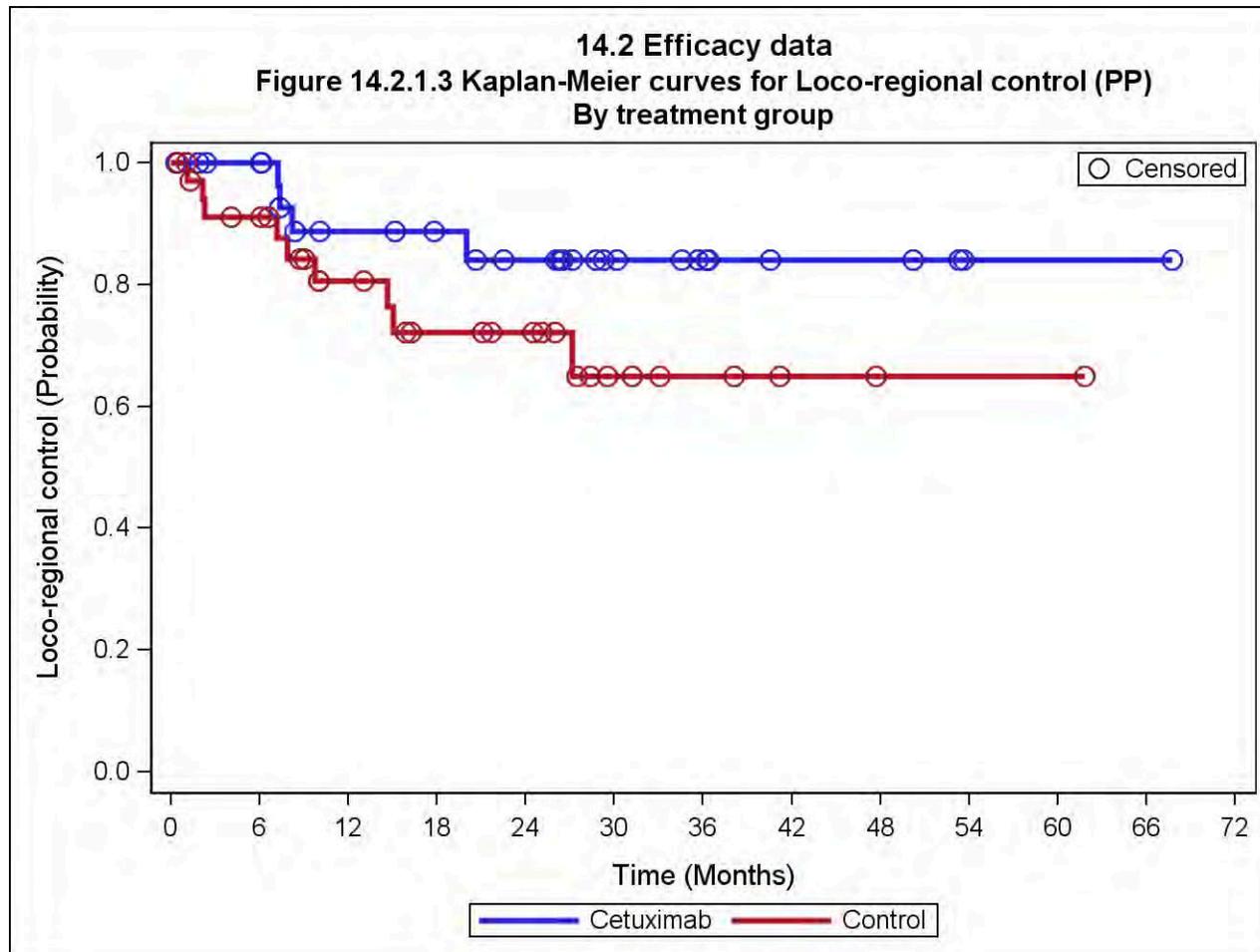
Table 14.2.1.4 Kaplan Meier and Cox proportional hazards results for metastases-free survival (PP)

Evaluation	Cetuximab (N=32)	Control (N=36)	Total (N=68)
Number of events	7 (21.88 %)	15 (41.67 %)	22 (32.35 %)
Median* survival (months)	- (.; -)	31.27 (8.25; -)	- (22.88; -)
Log-rank test for difference between treatment groups (p-value)	0.0568		
1-year survival rate [95% CI]	0.79 [0.64 ; 0.94]	0.70 [0.53 ; 0.86]	
2-year survival rate [95% CI]	0.74 [0.57 ; 0.91]	0.54 [0.36 ; 0.73]	
Hazard ratio Cetuximab vs. Control [95% CI]**	0.43 [0.17 ; 1.05]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
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14.2 Efficacy data
Figure 14.2.1.4 Kaplan-Meier curves for Metastases-free survival (PP)
Overall population

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14.2 Efficacy data

Figure 14.2.1.4 Kaplan-Meier curves for Metastases-free survival (PP)

By treatment group

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Table 14.2.1.5 The best overall response with chi-square test for treatment differences (PP)

Variable	Category	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)	Total (N= 68) N (%)	DF	Chi-square test Statistic	P-value
Best overall response	CR	26 (81.3)	15 (41.7)	41 (60.3)	1	10.25	0.0014
	PR		10 (27.8)	10 (14.7)			
	SD	4 (12.5)	4 (11.1)	8 (11.8)			
	PD	1 (3.1)	4 (11.1)	5 (7.4)			
	Missing	1 (3.1)	3 (8.3)	4 (5.9)			
Responder (best overall response CR or PR)	Yes	26 (81.3)	25 (69.4)	51 (75.0)	1	1.26	0.2618
	No	6 (18.8)	11 (30.6)	17 (25.0)			

Program: T14-2-1-5recist.sas
Table Generation: 02OCT2018 3:59:28 PM

Table 14.2.2.1 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by age (<= 60 years vs. > 60 years) (PP)

Evaluation	Age <= 60 years (N=22)	Age > 60 years (N=46)	Total (N=68)
Number of events	9 (40.91 %)	24 (52.17 %)	33 (48.53 %)
Median* survival (months)	42.35 (11.24; -)	38.37 (14.86; 52.21)	38.37 (23.74; 52.21)
Log-rank test for difference between age groups (p-value)	0.6830		
1-year survival rate [95% CI]	0.65 [0.45 ; 0.86]	0.75 [0.62 ; 0.88]	
2-year survival rate [95% CI]	0.65 [0.45 ; 0.86]	0.61 [0.46 ; 0.75]	
Hazard ratio Age <= 60 years vs. > 60 years [95% CI]**	0.85 [0.40 ; 1.84]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
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14.2 Efficacy data

Figure 14.2.2.1 Prognostic factors: Kaplan Meier curves for Overall survival by age (PP)
By age group

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Table 14.2.2.2 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by Karnofsky performance status (100%-80% vs. 70%) (PP)

Evaluation	Karnofsky performance status 100-80% (N=65)	Karnofsky performance status 70% (N=3)	Total (N=68)
Number of events	31 (47.69 %)	2 (66.67 %)	33 (48.53 %)
Median* survival (months)	42.35 (23.74; 52.21)	38.37 (3.85; 38.37)	38.37 (23.74; 52.21)
Log-rank test for difference between Karnofsky status groups (p-value)	0.6120		
1-year survival rate [95% CI]	0.72 [0.61 ; 0.84]	0.67 [0.13 ; 1.20]	
2-year survival rate [95% CI]	0.62 [0.49 ; 0.74]	0.67 [0.13 ; 1.20]	
Hazard ratio KPS 100-80% vs. 70% [95% CI]**	0.69 [0.16 ; 2.92]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
Program: T14-2-2-2os-karnofsky.sas
Table Generation: 25SEP2018 12:45:58 PM

14.2 Efficacy data

Figure 14.2.2.2 Prognostic factors: Kaplan Meier curves for Overall survival by Karnofsky performance status (PP)
By Karnofsky performance status group

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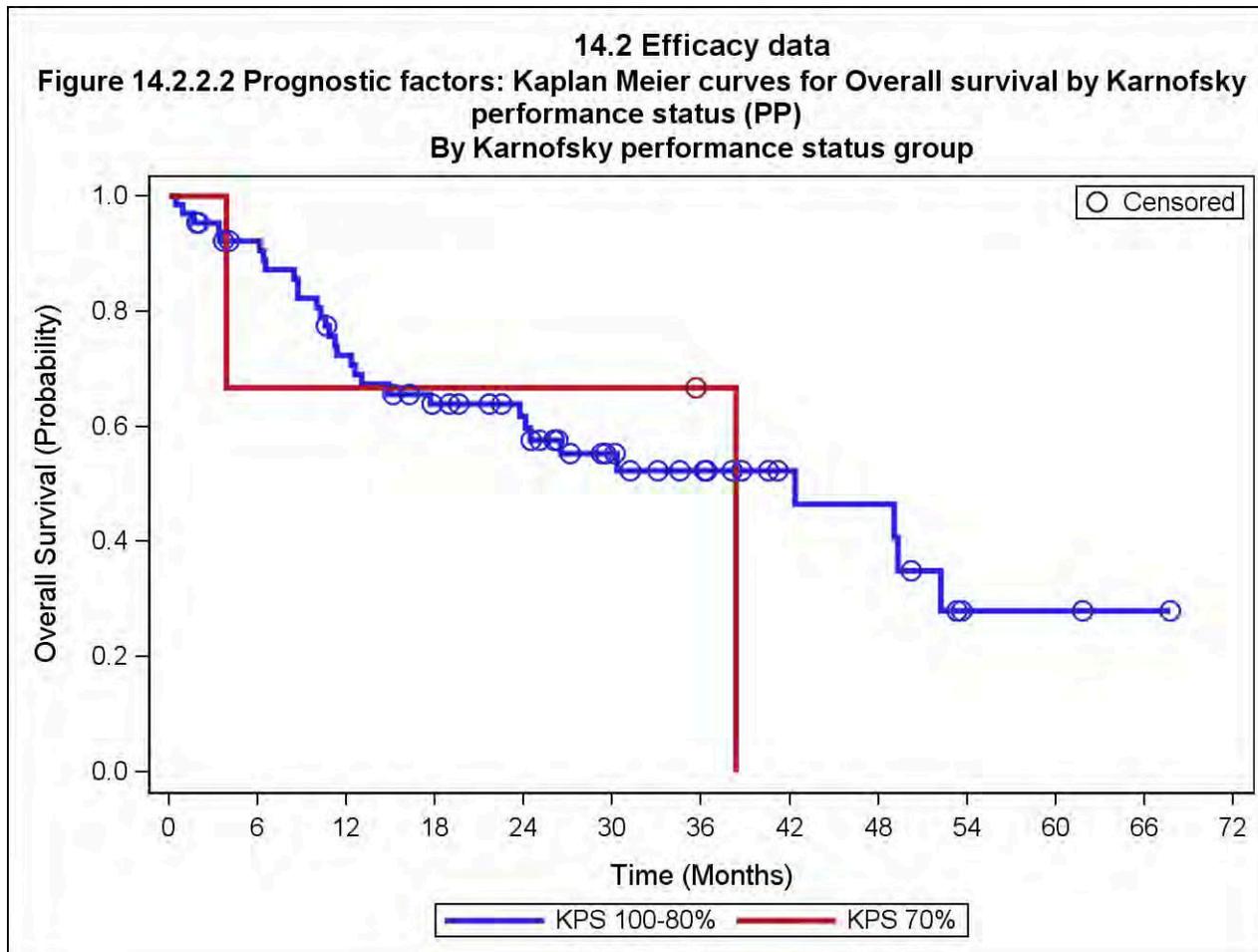
Table 14.2.2.3 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by tumor location (upper third vs. middle third vs. lower third) (PP)

Evaluation	Lower third (N=26)	Middle third (N=25)	Upper third (N=17)	Total (N=68)
Number of events	11 (42.31 %)	13 (52.00 %)	9 (52.94 %)	33 (48.53 %)
Median* survival (months)	30.31 (17.66; 52.21)	42.35 (10.85; -)	24.13 (10.22; -)	38.37 (23.74; 52.21)
Log-rank test for difference between tumor location groups (p-value)	0.9388			
1-year survival rate [95% CI]	0.79 [0.62 ; 0.95]	0.72 [0.54 ; 0.90]	0.63 [0.39 ; 0.87]	
2-year survival rate [95% CI]	0.65 [0.45 ; 0.84]	0.63 [0.44 ; 0.82]	0.57 [0.32 ; 0.81]	
Hazard ratio Lower third vs. Middle third [95% CI]**	0.99 [0.44 ; 2.24]			
Hazard ratio Lower third vs. Upper third [95% CI]**	0.87 [0.36 ; 2.11]			
Hazard ratio Middle third vs. Upper third [95% CI]**		0.87 [0.37 ; 2.05]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
NOTE: Patients with missing tumor location were categorized to lower third group, patients with both lower and middle to middle third group, and patients with both middle and upper to upper third group.
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Table Generation: 25SEP2018 12:47:17 PM

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14.2 Efficacy data

Figure 14.2.2.3 Prognostic factors: Kaplan Meier curves for Overall survival by tumor location (PP)

By tumor location group

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Table 14.2.2.4 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by histology (adenocarcinoma vs. squamous cell carcinoma) (PP)

Evaluation	Adenocarcinoma (N=13)	Squamous cell carcinoma (N=55)	Total (N=68)
Number of events	8 (61.54 %)	25 (45.45 %)	33 (48.53 %)
Median* survival (months)	30.31 (13.05; 52.21)	49.05 (14.86; -)	38.37 (23.74; 52.21)
Log-rank test for difference between histology groups (p-value)	0.7791		
1-year survival rate [95% CI]	0.85 [0.65 ; 1.04]	0.69 [0.56 ; 0.82]	
2-year survival rate [95% CI]	0.68 [0.43 ; 0.94]	0.61 [0.47 ; 0.74]	
Hazard ratio Adenocarcinoma vs. Squamous cell carcinoma [95% CI]**	1.12 [0.50 ; 2.49]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
Program: T14-2-2-4os-histology.sas
Table Generation: 25SEP2018 12:48:27 PM

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14.2 Efficacy data

Figure 14.2.2.4 Prognostic factors: Kaplan Meier curves for Overall survival by histology (PP)

By histology group

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Table 14.2.2.5 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by histologic grade (G1-2 vs. G3) (PP)

Evaluation	Grade 1-2 (N=47)	Grade 3 (N=21)	Total (N=68)
Number of events	20 (42.55 %)	13 (61.90 %)	33 (48.53 %)
Median* survival (months)	42.35 (17.66; -)	24.43 (11.34; 49.28)	38.37 (23.74; 52.21)
Log-rank test for difference between histologic grade groups (p-value)	0.2060		
1-year survival rate [95% CI]	0.73 [0.60 ; 0.86]	0.70 [0.50 ; 0.90]	
2-year survival rate [95% CI]	0.66 [0.52 ; 0.80]	0.53 [0.31 ; 0.76]	
Hazard ratio Grade 1-2 vs. Grade 3 [95% CI]**	0.64 [0.31 ; 1.29]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
NOTE: Patients with missing histologic grading information were categorized to Grade 1-2 group.
Program: T14-2-2-5os-histologic-grade.sas
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14.2 Efficacy data

Figure 14.2.2.5 Prognostic factors: Kaplan Meier curves for Overall survival by histologic grade (PP)

By histologic grade group
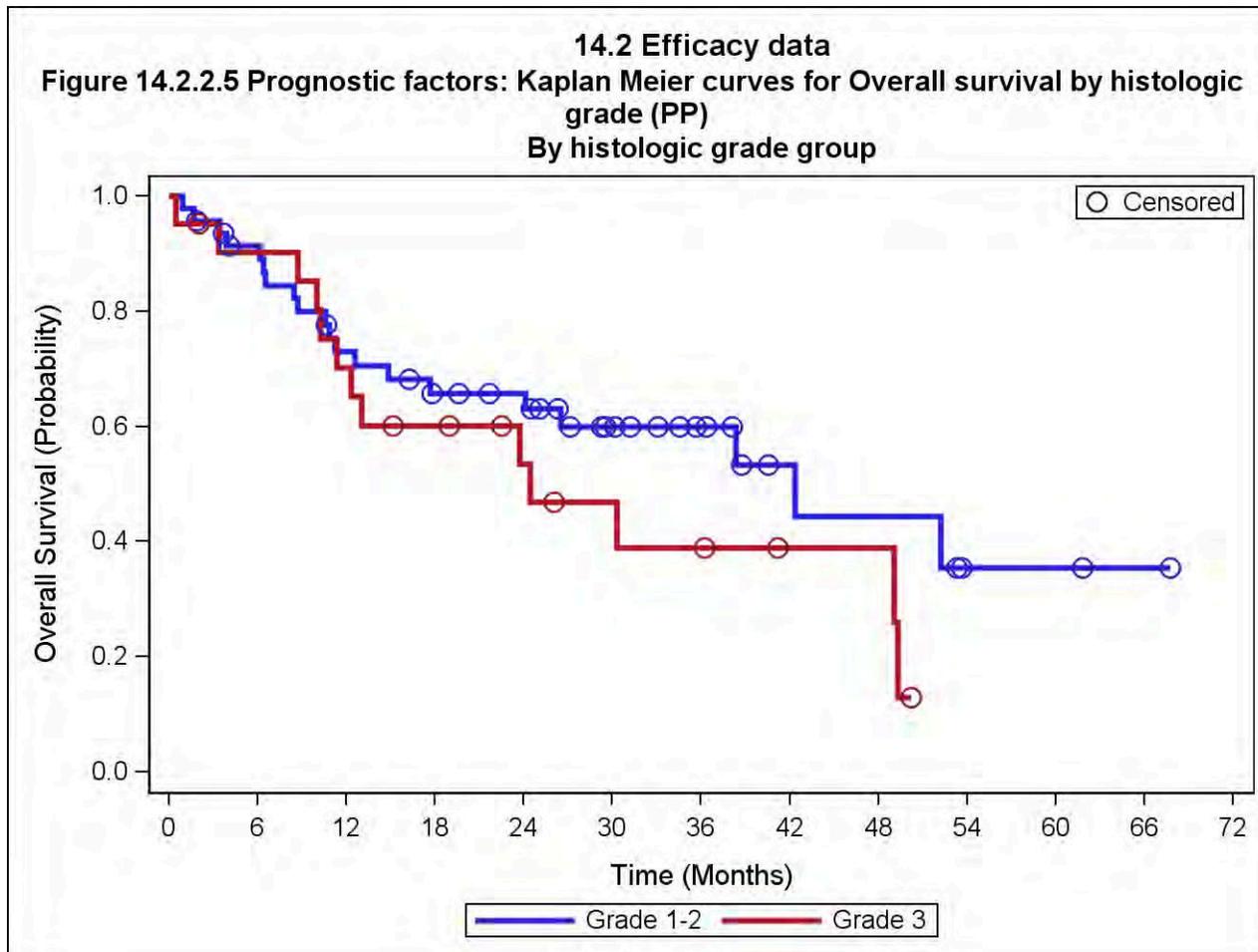
Table 14.2.2.6 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by T stage (T2-3 vs. T4) (PP)

Evaluation	T-stage 2-3 (N=47)	T-stage 4 (N=21)	Total (N=68)
Number of events	22 (46.81 %)	11 (52.38 %)	33 (48.53 %)
Median* survival (months)	42.35 (24.13; 52.21)	24.43 (9.99; -)	38.37 (23.74; 52.21)
Log-rank test for difference between T-stage groups (p-value)	0.7914		
1-year survival rate [95% CI]	0.76 [0.63 ; 0.88]	0.63 [0.42 ; 0.85]	
2-year survival rate [95% CI]	0.66 [0.53 ; 0.80]	0.52 [0.30 ; 0.75]	
Hazard ratio T-stage 2-3 vs. T-stage 4 [95% CI]**	1.10 [0.53 ; 2.31]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
NOTE: Patients with missing T-stage or T-stage of 1 were categorized to T-stage 2-3 group.
Program: T14-2-2-6os-T-stage.sas
Table Generation: 25SEP2018 1:05:33 PM

14.2 Efficacy data

Figure 14.2.2.6 Prognostic factors: Kaplan Meier curves for Overall survival by T-stage (PP)

By T-stage group

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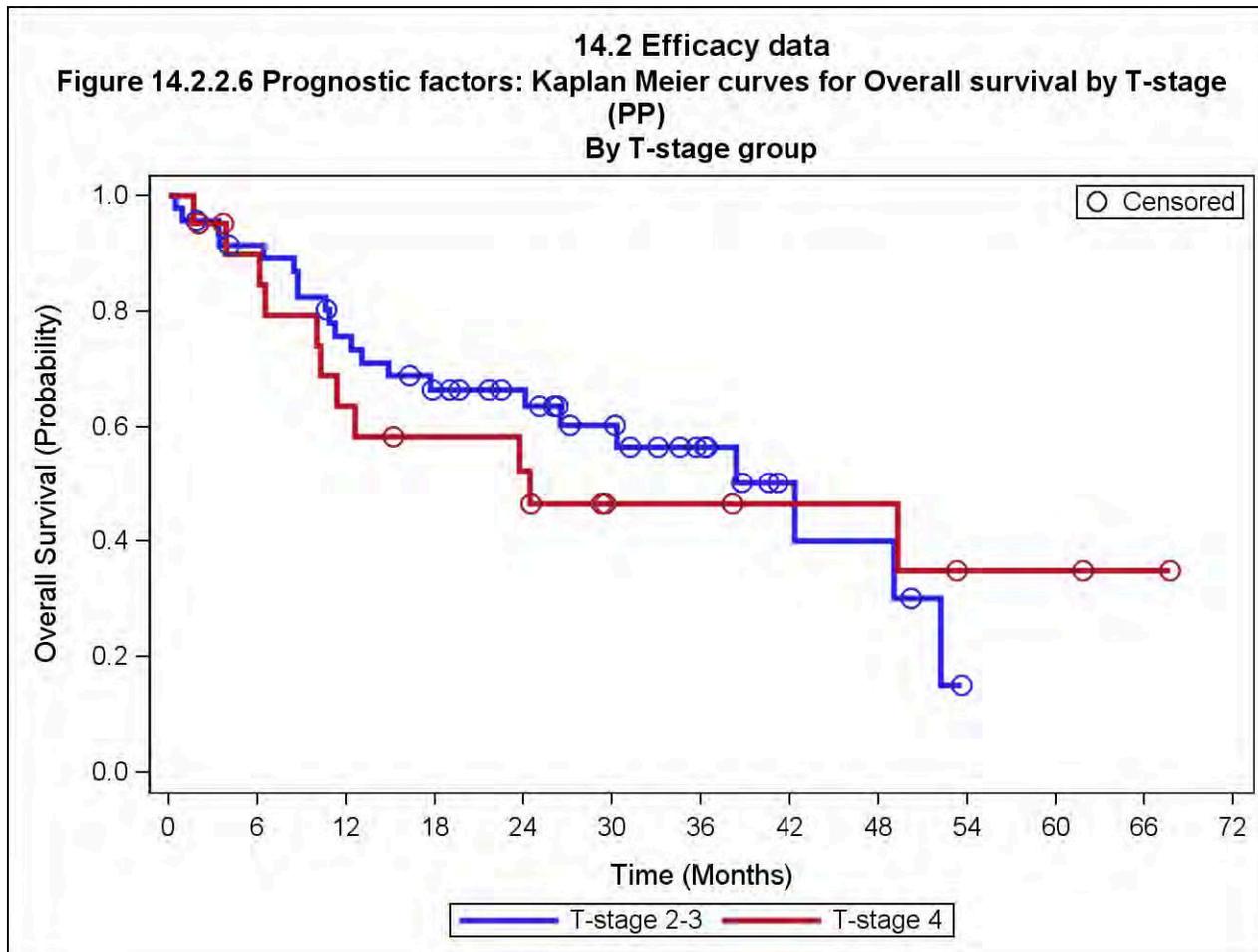
Table 14.2.2.7 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by N stage (N0 vs. N+) (PP)

Evaluation	N-stage 0 (N=16)	N-stage + (N=52)	Total (N=68)
Number of events	8 (50.00 %)	25 (48.08 %)	33 (48.53 %)
Median* survival (months)	38.37 (14.86; -)	42.35 (12.59; 52.21)	38.37 (23.74; 52.21)
Log-rank test for difference between N-stage groups (p-value)	0.7736		
1-year survival rate [95% CI]	0.81 [0.62 ; 1.00]	0.69 [0.56 ; 0.82]	
2-year survival rate [95% CI]	0.67 [0.42 ; 0.91]	0.60 [0.46 ; 0.74]	
Hazard ratio N-stage 0 vs. N-stage + [95% CI]**	1.12 [0.51 ; 2.50]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
NOTE: Patients with missing N-stage were categorized to N0 group, and patients with N-stage x to N+ group.
Program: T14-2-2-7os-N-stage.sas
Table Generation: 25SEP2018 1:06:43 PM

14.2 Efficacy data

Figure 14.2.2.7 Prognostic factors: Kaplan Meier curves for Overall survival by N-stage (PP)

By N-stage group

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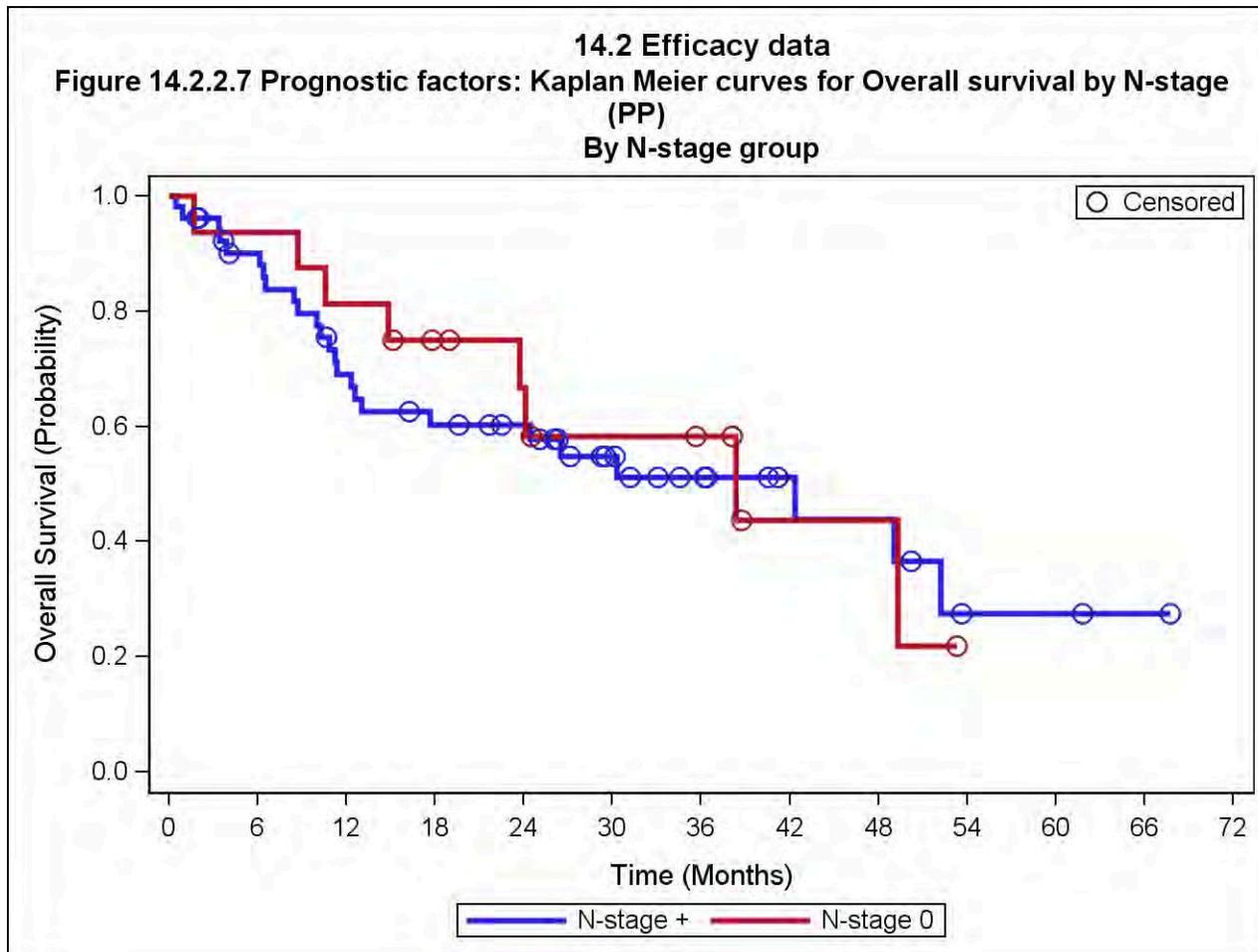
Table 14.2.2.8 Prognostic factors: Kaplan Meier and Cox proportional hazards results for overall survival by hemoglobin before radiotherapy (<12 vs. 12-14 vs. > 14 g/dl) (PP)

Evaluation	< 12 g/dl (N=10)	12-14 g/dl (N=32)	> 14 g/dl (N=26)	Total (N=68)
Number of events	8 (80.00 %)	16 (50.00 %)	9 (34.62 %)	33 (48.53 %)
Median* survival (months)	11.34 (1.68; 42.35)	49.05 (10.85; 49.28)	52.21 (23.74; -)	38.37 (23.74; 52.21)
Log-rank test for difference between hemoglobin groups (p-value)	0.0449			
1-year survival rate [95% CI]	0.46 [0.13 ; 0.78]	0.69 [0.53 ; 0.85]	0.87 [0.74 ; 1.01]	
2-year survival rate [95% CI]	0.46 [0.13 ; 0.78]	0.59 [0.42 ; 0.76]	0.73 [0.54 ; 0.91]	
Hazard ratio hemoglobin < 12 vs. 12-14 g/dl [95% CI]**	1.68 [0.70 ; 4.01]			
Hazard ratio hemoglobin < 12 vs. > 14 g/dl [95% CI]**	3.20 [1.23 ; 8.33]			
Hazard ratio hemoglobin 12-14 vs. > 14 g/dl [95% CI]**		1.91 [0.82 ; 4.42]		

*From product-limit (Kaplan-Meier) method
**Estimated with univariate Cox proportional hazards model
NOTE: Hemoglobin groups were defined based on screening values.
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14.2 Efficacy data

Figure 14.2.2.8 Prognostic factors: Kaplan Meier curves for Overall survival by hemoglobin before radiotherapy (PP)

By hemoglobin group

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Table 14.2.2.9 Multivariate Cox proportional hazards model for significant prognostic factors with treatment (PP)
Tests of fixed effects and hazard ratios with 95 % confidence intervals for treatment comparison within hemoglobin groups

Effect	DF	Chi-square value	p-value
Hemoglobin group	2	9.387	0.0092
Treatment	1	1.953	0.1622
Hemoglobin group*Treatment	2	4.409	0.1103

Comparison	Hazard ratio (95% CI)
Hemoglobin < 12 g/dl: Cetuximab vs. Control	0.15 (0.03; 0.79)
Hemoglobin 12-14 g/dl: Cetuximab vs. Control	1.07 (0.40; 2.88)
Hemoglobin > 14 g/dl: Cetuximab vs. Control	0.32 (0.07; 1.57)

Program: T14-2-2-9os-multivariate.sas
Table Generation: 25SEP2018 1:15:45 PM

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Table 14.2.2.10 Number of deaths overall and deaths due to progressive disease with chi-square test (PP)

| | | Cetuximab (N= 32) N (%) | Control (N= 36) N (%) | Total (N= 68) N (%) | Chi-square test | | |
| | | | | | DF | Statistic | P-value |
Variable	Category						
Death/ Alive	Death	13 (40.6)	20 (55.6)	33 (48.5)	1	1.51	0.2188
	Alive	19 (59.4)	16 (44.4)	35 (51.5)			
Death due to progressive disease/ Alive or death due to other reason	Death due to progressive disease	6 (18.8)	11 (30.6)	17 (25.0)	1	1.26	0.2618
	Alive or death due to other reason	26 (81.3)	25 (69.4)	51 (75.0)			

Program: T14-2-2-10deaths.sas
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14.3 Safety data

Leopard II study, Safety tables

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Table 14.3.1.1 Summary of all adverse events (Safety Population)

	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Any AEs	417 32 (100.0)	387 36 (100.0)	804 68 (100.0)
Serious AEs	60 21 (65.6)	69 24 (66.7)	129 45 (66.2)
Severe AEs [1]	105 26 (81.3)	91 27 (75.0)	196 53 (77.9)
Cetuximab-related AEs [2]	122 27 (84.4)	0 0 (0.0)	122 27 (39.7)
Chemotherapy-related AEs [2]	223 26 (81.3)	162 32 (88.9)	385 58 (85.3)
Radiotherapy-related AEs [2]	104 23 (71.9)	90 27 (75.0)	194 50 (73.5)
AEs Leading to Discontinuation (Cetuximab)	12 8 (25.0)	0 0 (0.0)	12 8 (11.8)
AEs Leading to Discontinuation (Chemotherapy)	13 7 (21.9)	21 9 (25.0)	34 16 (23.5)
AEs Leading to Discontinuation (Radiotherapy)	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
AEs Leading to Death	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
[1] Severity is defined as CTC Grade (3-5)
[2] Events are Cetuximab, Chemotherapy, or Radiotherapy related if the AE is classified as Possible, Probable, or Certain/Definite related to their respective treatments.
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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Any AEs	417 32 (100.0)	387 36 (100.0)	804 68 (100.0)	
Blood and lymphatic system disorder	19 15 (46.9)	16 13 (36.1)	35 28 (41.2)	0.4610
Anemia	15 13 (40.6)	16 13 (36.1)	31 26 (38.2)	0.8042
Blood and lymphatic systemdisorders - Other, specify: Pancytopenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Blood and lymphatic system disorders. Other - Low red blood cell count	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Febrile neutropenia	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Cardiac disorder	5 4 (12.5)	5 4 (11.1)	10 8 (11.8)	1.0000
Atrial fibrillation	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Atrioventricular block first degree	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Cardiac disorder - other: Arrhythmia	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Cardiac disorder - other: Tachyarrhytmia	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Cardiac disorder - other: paroxysmal atrial fibrillation	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Myocardial infarction	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Sinus tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Ventricular fibrillation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Ventricular tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Ear and labyrinth disorder	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)	0.6163
External ear inflammation	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	

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CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p- value
Vertigo	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)	1.0000
Eye disorder	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)	0.5977
Conjuctivitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Dry eye	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Eye disorder - other: Hordeolum	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Gastrointestinal disorder	93 29 (90.6)	127 29 (80.6)	220 58 (85.3)	0.3144
Abdominal pain	0 0 (0.0)	6 3 (8.3)	6 3 (4.4)	0.2414
Bloating	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Constipation	7 6 (18.8)	23 11 (30.6)	30 17 (25.0)	0.4006
Diarrhea	7 7 (21.9)	7 5 (13.9)	14 12 (17.6)	0.5268
Dry mouth	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Dyspepsia	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Dysphagia	11 9 (28.1)	12 9 (25.0)	23 18 (26.5)	0.7901
Enterocolitis infectious	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Esophageal hemorrhage	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Esophageal pain	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)	1.0000
Esophagitis	12 11 (34.4)	14 14 (38.9)	26 25 (36.8)	0.8028
Gastric hemorrhage	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Gastric ulcer	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)	0.5977
Gastroesophageal reflux disease	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)	0.2414
Gastrointestinal Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Gastrointestinal disorder - other: Heartburn	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Gastrointestinal disorders - Other, odynophagia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Gastrointestinal disorders - other: GI-bleeding (haemorrhagic shock)	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Gastrointestinal disorders - other: Peritonitis with sepsis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Gastrointestinal disorders - other: Slow gastrointestinal passage	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Gastrointestinal disorders - other: aperistalsis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Gastrointestinal disorders - other: hematemesis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Gastrointestinal disorders - other: hypersalivation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Gastrointestinal pain	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)	1.0000
Hemorrhoids	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Mucositis oral	9 8 (25.0)	4 4 (11.1)	13 12 (17.6)	0.2031
Nausea	24 19 (59.4)	34 20 (55.6)	58 39 (57.4)	0.8091
Oral pain	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Rectal hemorrhage	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Vomiting	6 6 (18.8)	11 7 (19.4)	17 13 (19.1)	1.0000

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category 　AE term	Cetuximab (N=32) f　n　(%)	Control (N=36) f　n　(%)	Overall (N=68) f　n　(%)	Fisher's exact test p-value
Gastrointestinal disorders	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Gastrointestinal disorders - other, Fur on tongue	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
General disorders and administration site conditions	33 19 (59.4)	39 23 (63.9)	72 42 (61.8)	0.8042
Death NOS	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Edema limbs	4 2 (6.3)	1 1 (2.8)	5 3 (4.4)	0.5977
Fatigue	10 9 (28.1)	21 18 (50.0)	31 27 (39.7)	0.0846
Fever	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)	1.0000
General disorders and administration site conditions - other: Asthenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
General disorders and administration site conditions - other: Edema	9 6 (18.8)	6 4 (11.1)	15 10 (14.7)	0.4980
General disorders and administration site conditions - other: Mucous congestions	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
General disorders and administration site conditions - other: Pain Post system	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
General disorders and administration site conditions - other: Pain retrosternal	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
General disorders and administration site conditions - other: Pain surgical wound	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
General disorders and administration site conditions - other: Reduced overall health condition	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Localized edema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Non-cardiac chest pain	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Pain	5 5 (15.6)	2 2 (5.6)	7 7 (10.3)	0.2409
Immunesystem disorder	4 4 (12.5)	1 1 (2.8)	5 5 (7.4)	0.1797

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Allergic reaction	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)	0.0442
Immune System Disorders- Other: Immune System Disorders	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Infections and infestations	24 17 (53.1)	27 16 (44.4)	51 33 (48.5)	0.6273
Abdominal infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Appendicitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Breast infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Bronchial infection	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)	
Device related infection	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Infections and infestations - other: Herpes labialis	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Infections and infestations - other: Infection, CRP elevated	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Infections and infestations - other: Infection, nos CRP high	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Infections and infestations - other: Infection, oral cavity, CRP high	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Infections and infestations - other: Influenza	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Infections and infestations - other: MRSA infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Infections and infestations - other: Unclear infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Infections and infestations - other: infection	3 3 (9.4)	2 2 (5.6)	5 5 (7.4)	0.6603
Infections and infestations - other: infection unclear origin	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Lung infection	3 3 (9.4)	11 9 (25.0)	14 12 (17.6)	0.1180

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Nail infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Paronychia	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Sepsis	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)	1.0000
Skin infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Stoma site infection	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)	0.3357
Upper respiratory infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Urinary tract Infection	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)	0.4943
Wound infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning and procedural complications	22 13 (40.6)	6 5 (13.9)	28 18 (26.5)	0.0153
Dermatitis radiation	9 9 (28.1)	1 1 (2.8)	10 10 (14.7)	0.0046
Fall	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, ACI stenosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Anastomotic leak	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Incisional hernia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Morphine overdose	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Port dermatitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, head wound	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Injury, poisoning andprocedural complications -Other, port closure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, port dislocation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, sunburn	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning and procedural complications - Other, Tumor bleeding	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning and procedural complications - Other, dislocation of jejunum tube	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning and procedural complications - other: PEG dislocation	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Wound complication	3 2 (6.3)	0 0 (0.0)	3 2 (2.9)	0.2177
Investigations	61 25 (78.1)	44 19 (52.8)	105 44 (64.7)	0.0420
Activated partial thromboplastin time prolonged	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)	
Alanine aminotransferase increased	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Creatinine increased	2 2 (6.3)	2 1 (2.8)	4 3 (4.4)	0.5977
GGT increased	3 3 (9.4)	3 3 (8.3)	6 6 (8.8)	1.0000
INR increased	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Investigations - Other, Increased CRP	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Investigations - Other, elevation of liver enzymes	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Investigations - Other: Neutrophil count increased	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Investigations - Other: Red blood count decreased	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)	
Neutrophil count decreased	5 5 (15.6)	6 4 (11.1)	11 9 (13.2)	0.7249

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Platelet count decreased	14 11 (34.4)	10 7 (19.4)	24 18 (26.5)	0.1816
Weight gain	0 0 (0.0)	4 4 (11.1)	4 4 (5.9)	0.1165
Weight loss	9 9 (28.1)	4 3 (8.3)	13 12 (17.6)	0.0539
White blood cell decreased	23 16 (50.0)	9 8 (22.2)	32 24 (35.3)	0.0228
Metabolism and nutrition disorders	57 22 (68.8)	29 15 (41.7)	86 37 (54.4)	0.0306
Acidosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Alkalosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Anorexia	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)	0.5977
Dehydration	2 2 (6.3)	3 2 (5.6)	5 4 (5.9)	1.0000
Hyperkalemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Hyperuricemia	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)	0.4943
Hypoalbuminemia	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)	0.5977
Hypocalcemia	9 9 (28.1)	2 2 (5.6)	11 11 (16.2)	0.0188
Hypoglycemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Hypokalemia	21 16 (50.0)	14 12 (33.3)	35 28 (41.2)	0.2186
Hypomagnesemia	15 13 (40.6)	3 3 (8.3)	18 16 (23.5)	0.0033
Hyponatremia	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)	0.6163
Metabolism and nutrition disorders - other: Exsiccose	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Musculoskeletal and connective tissue disorders	1 1 (3.1)	7 4 (11.1)	8 5 (7.4)	0.3605
Chest wall pain	1 1 (3.1)	3 2 (5.6)	4 3 (4.4)	1.0000
Pain in extremity	0 0 (0.0)	4 3 (8.3)	4 3 (4.4)	0.2414
Nervous systems disorders	16 10 (31.3)	12 10 (27.8)	28 20 (29.4)	0.7948
Akathisia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Amnesia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Aphonia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Cognitive Disturbance	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Dizziness	5 5 (15.6)	3 3 (8.3)	8 8 (11.8)	0.4605
Headache	1 1 (3.1)	3 1 (2.8)	4 2 (2.9)	
Paresthesia	1 1 (3.1)	4 4 (11.1)	5 5 (7.4)	0.3605
Peripheral motor neuropathy	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Seizure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Stroke	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Syncope	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)	1.0000
Psychiatric disorders	4 4 (12.5)	18 6 (16.7)	22 10 (14.7)	0.7389
Insomnia	2 2 (6.3)	17 5 (13.9)	19 7 (10.3)	0.4338
Psychiatric disorders - other, sleeping disorders	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Restlessness	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Renal and urinary disorders	10 7 (21.9)	8 7 (19.4)	18 14 (20.6)	1.0000
Acute kidney injury	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Cystitis nininfective	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Renal and urinary disorders - other, acute renal failure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Renal and urinary disorders - other, decreased creatinine clearance	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Renal and urinary disorders - other, renal failure	2 2 (6.3)	2 1 (2.8)	4 3 (4.4)	0.5977
Renal and urinary disorders, Other - nephrotoxicitiy, tubular function impaired	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Renal and urinary disorders, Other, micturition pain	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Renal and urinary disorders, Other: renal incompetence	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Renal and urinary disorders-other:acute reduction of GFR	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Urinary retention	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)	1.0000
Respiratory, thoracic and mediastinal disorders	13 9 (28.1)	28 19 (52.8)	41 28 (41.2)	0.0503
Cough	5 5 (15.6)	7 7 (19.4)	12 12 (17.6)	0.7576
Dyspnea	3 3 (9.4)	5 5 (13.9)	8 8 (11.8)	0.7134
Epistaxis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Hiccups	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)	0.4943
Hoarseness	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)	0.2414

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
Program: T14-3-1-2ae-ctc1-term.sas
Table Generation: 02OCT2018 2:50:19 PM

Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Pleural effusion	1 1 (3.1)	5 5 (13.9)	6 6 (8.8)	0.2025
Pleuritic pain	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Pneumonitis	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)	0.5977
Pneumothorax	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Productive cough	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Pulmonary edema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Pulmonary fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Skin and subcutaneous tissue disorders	43 24 (75.0)	10 9 (25.0)	53 33 (48.5)	<.0001
Alopecia	5 4 (12.5)	3 3 (8.3)	8 7 (10.3)	0.6986
Dry skin	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Erythroderma	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Nail ridging	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Palmar-plantar erythrodysesthesia syndrome	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)	0.4943
Pruritus	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Rash acneiform	12 11 (34.4)	0 0 (0.0)	12 11 (16.2)	<.0001
Rash maculo-papular	10 7 (21.9)	1 1 (2.8)	11 8 (11.8)	0.0219
Skin and subcutaneous tissuedisorders - Other, Exanthema	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Skin and subcutaneous tissuedisorders - Other, dry exanthema crook of the arm left side	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group

NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.

Program: T14-3-1-2ae-ctc1-term.sas

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Table 14.3.1.2 Adverse events by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p- value
Skin and subcutaneous tissuedisorders - Other, dry exanthema on arms, legs and trunk	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Skin and subcutaneous tissuedisorders - Other, tickel on the throat	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Skin and subcutaneous tissue disorders - Other, Rhagade fingers both hands	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Skin and subcutaneous tissue disorders - Other, Rhagade thumb, right hand	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Skin and subcutaneous tissue disorders - other, Acne	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)	0.0990
Skin and subcutaneous tissue disorders - other, Erythema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Skin and subcutaneous tissue disorders - other, Rhagads	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Skin and subcutaneous tissue disorders - other, Skin rash	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Skin hyperpegmentation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Surgical and medical procedures	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Surgical and medical procedures - other, PTCA and stent	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Vascular disorders	8 7 (21.9)	5 4 (11.1)	13 11 (16.2)	0.3255
Hematoma	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Hypertension	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)	0.0990
Hypotension	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Phlebitis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Thromboembolic event	2 2 (6.3)	3 3 (8.3)	5 5 (7.4)	1.0000

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
Program: T14-3-1-2ae-ctc1-term.sas
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Any AEs	417 32 (100.0)	387 36 (100.0)	804 68 (100.0)
CTC Grade 1	151 27 (84.4)	173 30 (83.3)	324 57 (83.8)
CTC Grade 2	158 28 (87.5)	117 30 (83.3)	275 58 (85.3)
CTC Grade 3	89 25 (78.1)	76 26 (72.2)	165 51 (75.0)
CTC Grade 4	14 7 (21.9)	12 8 (22.2)	26 15 (22.1)
CTC Grade 5	2 1 (3.1)	3 3 (8.3)	5 4 (5.9)
Missing	3 3 (9.4)	6 2 (5.6)	9 5 (7.4)
Blood and lymphatic system disorder	19 15 (46.9)	16 13 (36.1)	35 28 (41.2)
Anemia	15 13 (40.6)	16 13 (36.1)	31 26 (38.2)
CTC Grade 1	5 5 (15.6)	1 1 (2.8)	6 6 (8.8)
CTC Grade 2	6 5 (15.6)	6 5 (13.9)	12 10 (14.7)
CTC Grade 3	4 4 (12.5)	9 7 (19.4)	13 11 (16.2)
Blood and lymphatic systemdisorders - Other, specify: Pancytopenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Blood and lymphatic system disorders. Other - Low red blood cell count	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Febrile neutropenia	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Cardiac disorder	5 4 (12.5)	5 4 (11.1)	10 8 (11.8)
Atrial fibrillation	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Atrioventricular block first degree	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Cardiac disorder - other: Arrhythmia	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Cardiac disorder - other: Tachyarrhytmia	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Cardiac disorder - other: paroxysmal atrial fibrillation	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Myocardial infarction	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Sinus tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Ventricular fibrillation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Ventricular tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Ear and labyrinth disorder	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)
External ear inflammation	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category
  AE Term
    Severity
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

Vertigo	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
CTC Grade 1	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Eye disorder	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
Conjuctivitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Dry eye	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Eye disorder - other: Hordeolum	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorder	93 29 (90.6)	127 29 (80.6)	220 58 (85.3)
Abdominal pain	0 0 (0.0)	6 3 (8.3)	6 3 (4.4)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	5 2 (5.6)	5 2 (2.9)
Bloating	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Constipation	7 6 (18.8)	23 11 (30.6)	30 17 (25.0)
CTC Grade 1	5 4 (12.5)	17 9 (25.0)	22 13 (19.1)
CTC Grade 2	2 2 (6.3)	6 3 (8.3)	8 5 (7.4)
Diarrhea	7 7 (21.9)	7 5 (13.9)	14 12 (17.6)
CTC Grade 1	2 2 (6.3)	3 2 (5.6)	5 4 (5.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
Program: T14-3-1-3ae-severity.sas
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	2 2 (6.3)	3 3 (8.3)	5 5 (7.4)
CTC Grade 3	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)
Dry mouth	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Dyspepsia	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Dysphagia	11 9 (28.1)	12 9 (25.0)	23 18 (26.5)
CTC Grade 1	2 2 (6.3)	3 3 (8.3)	5 5 (7.4)
CTC Grade 2	5 4 (12.5)	4 4 (11.1)	9 8 (11.8)
CTC Grade 3	3 3 (9.4)	5 3 (8.3)	8 6 (8.8)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Enterocolitis infectious	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Esophageal hemorrhage	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Esophageal pain	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)
CTC Grade 1	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Esophagitis	12 11 (34.4)	14 14 (38.9)	26 25 (36.8)
CTC Grade 1	1 1 (3.1)	5 5 (13.9)	6 6 (8.8)
CTC Grade 2	4 4 (12.5)	4 4 (11.1)	8 8 (11.8)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 3	7 6 (18.8)	5 5 (13.9)	12 11 (16.2)
Gastric hemorrhage	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastric ulcer	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Gastroesophageal reflux disease	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
CTC Grade 1	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Missing	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorder - other: Heartburn	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - Other, odynophagia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: GI-bleeding (haemorrhagic shock)	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: Peritonitis with sepsis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorders - other: Slow gastrointestinal passage	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
Program: T14-3-1-3ae-severity.sas
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: aperistalsis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: hematemesis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: hypersalivation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal pain	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
CTC Grade 1	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hemorrhoids	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Mucositis oral	9 8 (25.0)	4 4 (11.1)	13 12 (17.6)
CTC Grade 1	6 5 (15.6)	3 3 (8.3)	9 8 (11.8)
CTC Grade 2	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)
Nausea	24 19 (59.4)	34 20 (55.6)	58 39 (57.4)
CTC Grade 1	11 10 (31.3)	16 13 (36.1)	27 23 (33.8)
CTC Grade 2	12 12 (37.5)	15 11 (30.6)	27 23 (33.8)
CTC Grade 3	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)
Oral pain	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Rectal hemorrhage	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Vomiting	6 6 (18.8)	11 7 (19.4)	17 13 (19.1)
CTC Grade 1	2 2 (6.3)	3 3 (8.3)	5 5 (7.4)
CTC Grade 2	4 4 (12.5)	2 2 (5.6)	6 6 (8.8)
CTC Grade 3	0 0 (0.0)	6 2 (5.6)	6 2 (2.9)
Gastrointestinal disorders	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorders - other, Fur on tongue	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions	33 19 (59.4)	39 23 (63.9)	72 42 (61.8)
Death NOS	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 5	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Edema limbs	4 2 (6.3)	1 1 (2.8)	5 3 (4.4)
CTC Grade 1	4 2 (6.3)	1 1 (2.8)	5 3 (4.4)
Fatigue	10 9 (28.1)	21 18 (50.0)	31 27 (39.7)
CTC Grade 1	6 6 (18.8)	15 13 (36.1)	21 19 (27.9)
CTC Grade 2	4 4 (12.5)	4 4 (11.1)	8 8 (11.8)
CTC Grade 3	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Fever	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
CTC Grade 1	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
General disorders and administration site conditions - other: Asthenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
General disorders and administration site conditions - other: Edema	9 6 (18.8)	6 4 (11.1)	15 10 (14.7)
CTC Grade 1	5 4 (12.5)	2 1 (2.8)	7 5 (7.4)
CTC Grade 2	4 2 (6.3)	3 2 (5.6)	7 4 (5.9)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Mucous congestions	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Pain Post system	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Pain retrosternal	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 1	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
General disorders and administration site conditions - other: Pain surgical wound	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Reduced overall health condition	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Localized edema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Non-cardiac chest pain	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 1	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Pain	5 5 (15.6)	2 2 (5.6)	7 7 (10.3)
CTC Grade 1	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)
Immunesystem disorder	4 4 (12.5)	1 1 (2.8)	5 5 (7.4)
Allergic reaction	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
CTC Grade 3	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
Immune System Disorders- Other: Immune System Disorders	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations	24 17 (53.1)	27 16 (44.4)	51 33 (48.5)
Abdominal infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Appendicitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Breast infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Bronchial infection	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
CTC Grade 2	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
Device related infection	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 3	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Infections and infestations - other: Herpes labialis	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 1	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Infections and infestations - other: Infection, CRP elevated	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Infections and infestations - other: Infection, nos CRP high	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: Infection, oral cavity, CRP high	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: Influenza	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: MRSA infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: Unclear infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: infection	3 3 (9.4)	2 2 (5.6)	5 5 (7.4)
CTC Grade 2	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
CTC Grade 3	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Infections and infestations - other: infection unclear origin	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Lung infection	3 3 (9.4)	11 9 (25.0)	14 12 (17.6)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	3 3 (9.4)	8 7 (19.4)	11 10 (14.7)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 5	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Nail infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Paronychia	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Sepsis	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
CTC Grade 3	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Stoma site infection	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)
CTC Grade 2	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Upper respiratory infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Urinary tract Infection	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 2	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Wound infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning and procedural complications	22 13 (40.6)	6 5 (13.9)	28 18 (26.5)
Dermatitis radiation	9 9 (28.1)	1 1 (2.8)	10 10 (14.7)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	5 5 (15.6)	1 1 (2.8)	6 6 (8.8)
CTC Grade 3	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Fall	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, ACI stenosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Missing	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Anastomotic leak	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Incisional hernia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Morphine overdose	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Port dermatitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, head wound	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, port closure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, port dislocation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category
  AE Term
    Severity
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, sunburn	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning and procedural complications - Other, Tumor bleeding	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 5	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning and procedural complications - Other, dislocation of jejunum tube	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Missing	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning and procedural complications - other: PEG dislocation	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Wound complication	3 2 (6.3)	0 0 (0.0)	3 2 (2.9)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
Investigations	61 25 (78.1)	44 19 (52.8)	105 44 (64.7)
Activated partial thromboplastin time prolonged	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
CTC Grade 1	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
Alanine aminotransferase increased	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Creatinine increased	2 2 (6.3)	2 1 (2.8)	4 3 (4.4)
CTC Grade 1	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
GGT increased	3 3 (9.4)	3 3 (8.3)	6 6 (8.8)
CTC Grade 1	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
INR increased	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Investigations - Other, Increased CRP	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Investigations - Other, elevation of liver enzymes	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Investigations - Other: Neutrophil count increased	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Investigations - Other: Red blood count decreased	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
Missing	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
Neutrophil count decreased	5 5 (15.6)	6 4 (11.1)	11 9 (13.2)
CTC Grade 2	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 3	2 2 (6.3)	4 2 (5.6)	6 4 (5.9)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Missing	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Platelet count decreased	14 11 (34.4)	10 7 (19.4)	24 18 (26.5)
CTC Grade 1	6 6 (18.8)	1 1 (2.8)	7 7 (10.3)
CTC Grade 2	4 4 (12.5)	5 4 (11.1)	9 8 (11.8)
CTC Grade 3	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)
CTC Grade 4	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Missing	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
Weight gain	0 0 (0.0)	4 4 (11.1)	4 4 (5.9)
CTC Grade 1	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Weight loss	9 9 (28.1)	4 3 (8.3)	13 12 (17.6)
CTC Grade 1	4 4 (12.5)	3 2 (5.6)	7 6 (8.8)
CTC Grade 2	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
CTC Grade 3	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
White blood cell decreased	23 16 (50.0)	9 8 (22.2)	32 24 (35.3)
CTC Grade 1	2 2 (6.3)	3 2 (5.6)	5 4 (5.9)
CTC Grade 2	10 9 (28.1)	2 2 (5.6)	12 11 (16.2)
CTC Grade 3	8 5 (15.6)	2 2 (5.6)	10 7 (10.3)
CTC Grade 4	3 3 (9.4)	2 2 (5.6)	5 5 (7.4)
Metabolism and nutrition disorders	57 22 (68.8)	29 15 (41.7)	86 37 (54.4)
Acidosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 5	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
Program: T14-3-1-3ae-severity.sas
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Alkalosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Anorexia	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
CTC Grade 1	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Dehydration	2 2 (6.3)	3 2 (5.6)	5 4 (5.9)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Hyperkalemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hyperuricemia	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Hypoalbuminemia	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
CTC Grade 2	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hypocalcemia	9 9 (28.1)	2 2 (5.6)	11 11 (16.2)
CTC Grade 1	4 4 (12.5)	2 2 (5.6)	6 6 (8.8)
CTC Grade 2	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hypoglycemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hypokalemia	21 16 (50.0)	14 12 (33.3)	35 28 (41.2)
CTC Grade 1	14 11 (34.4)	5 4 (11.1)	19 15 (22.1)
CTC Grade 2	4 4 (12.5)	7 6 (16.7)	11 10 (14.7)
CTC Grade 3	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hypomagnesemia	15 13 (40.6)	3 3 (8.3)	18 16 (23.5)
CTC Grade 1	6 6 (18.8)	2 2 (5.6)	8 8 (11.8)
CTC Grade 2	6 6 (18.8)	1 1 (2.8)	7 7 (10.3)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 4	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Hyponatremia	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)
CTC Grade 1	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Metabolism and nutrition disorders - other: Exsiccose	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Musculoskeletal and connective tissue disorders	1 1 (3.1)	7 4 (11.1)	8 5 (7.4)
Chest wall pain	1 1 (3.1)	3 2 (5.6)	4 3 (4.4)
CTC Grade 1	0 0 (0.0)	3 2 (5.6)	3 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Pain in extremity	0 0 (0.0)	4 3 (8.3)	4 3 (4.4)
CTC Grade 1	0 0 (0.0)	3 2 (5.6)	3 2 (2.9)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Nervous systems disorders	16 10 (31.3)	12 10 (27.8)	28 20 (29.4)
Akathisia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Amnesia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Aphonia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Cognitive Disturbance	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Dizziness	5 5 (15.6)	3 3 (8.3)	8 8 (11.8)
CTC Grade 1	4 4 (12.5)	3 3 (8.3)	7 7 (10.3)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Headache	1 1 (3.1)	3 1 (2.8)	4 2 (2.9)
CTC Grade 1	1 1 (3.1)	2 1 (2.8)	3 2 (2.9)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Paresthesia	1 1 (3.1)	4 4 (11.1)	5 5 (7.4)
CTC Grade 1	1 1 (3.1)	4 4 (11.1)	5 5 (7.4)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Peripheral motor neuropathy	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Seizure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Stroke	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Syncope	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)
CTC Grade 2	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 3	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Psychiatric disorders	4 4 (12.5)	18 6 (16.7)	22 10 (14.7)
Insomnia	2 2 (6.3)	17 5 (13.9)	19 7 (10.3)
CTC Grade 1	1 1 (3.1)	15 5 (13.9)	16 6 (8.8)
CTC Grade 2	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
Psychiatric disorders - other, sleeping disorders	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 1	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Restlessness	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Renal and urinary disorders	10 7 (21.9)	8 7 (19.4)	18 14 (20.6)
Acute kidney injury	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Cystitis nininfective	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders - other, acute renal failure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 5	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders - other, decreased creatinine clearance	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders - other, renal failure	2 2 (6.3)	2 1 (2.8)	4 3 (4.4)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
Renal and urinary disorders, Other - nephrotoxicitiy, tubular function impaired	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders, Other, micturition pain	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders, Other: renal incompetence	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders-other:acute reduction of GFR	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Urinary retention	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)
CTC Grade 2	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Respiratory, thoracic and mediastinal disorders	13 9 (28.1)	28 19 (52.8)	41 28 (41.2)
Cough	5 5 (15.6)	7 7 (19.4)	12 12 (17.6)
CTC Grade 1	3 3 (9.4)	4 4 (11.1)	7 7 (10.3)
CTC Grade 2	2 2 (6.3)	3 3 (8.3)	5 5 (7.4)
Dyspnea	3 3 (9.4)	5 5 (13.9)	8 8 (11.8)
CTC Grade 1	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
CTC Grade 2	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 3	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 4	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Epistaxis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Hiccups	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 1	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Hoarseness	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Pleural effusion	1 1 (3.1)	5 5 (13.9)	6 6 (8.8)
CTC Grade 1	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 2	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 3	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Pleuritic pain	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pneumonitis	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
CTC Grade 2	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Pneumothorax	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Productive cough	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pulmonary edema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pulmonary fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissue disorders	43 24 (75.0)	10 9 (25.0)	53 33 (48.5)
Alopecia	5 4 (12.5)	3 3 (8.3)	8 7 (10.3)
CTC Grade 1	4 4 (12.5)	3 3 (8.3)	7 7 (10.3)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Dry skin	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Erythroderma	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Nail ridging	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Palmar-plantar erythrodysesthesia syndrome	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pruritus	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Rash acneiform	12 11 (34.4)	0 0 (0.0)	12 11 (16.2)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	8 7 (21.9)	0 0 (0.0)	8 7 (10.3)
CTC Grade 3	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Rash maculo-papular	10 7 (21.9)	1 1 (2.8)	11 8 (11.8)
CTC Grade 1	5 4 (12.5)	1 1 (2.8)	6 5 (7.4)
CTC Grade 2	5 5 (15.6)	0 0 (0.0)	5 5 (7.4)
Skin and subcutaneous tissuedisorders - Other, Exanthema	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissuedisorders - Other, dry exanthema crook of the arm left side	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category
  AE Term
    Severity
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

Skin and subcutaneous tissuedisorders - Other, dry exanthema on arms, legs and trunk	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissuedisorders - Other, tickel on the throat	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissue disorders - Other, Rhagade fingers both hands	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissue disorders - Other, Rhagade thumb, right hand	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissue disorders - other, Acne	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Skin and subcutaneous tissue disorders - other, Erythema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissue disorders - other, Rhagads	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissue disorders - other, Skin rash	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin hyperpegmentation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 1	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Surgical and medical procedures	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Surgical and medical procedures - other, PTCA and stent	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.3 Adverse events by NCI CTC Category, AE term and severity (worst CTC grade) (Safety Population)

CTC Category AE Term Severity	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
CTC Grade 3	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Vascular disorders	8 7 (21.9)	5 4 (11.1)	13 11 (16.2)
Hematoma	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
CTC Grade 1	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Hypertension	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
CTC Grade 2	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
CTC Grade 3	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Hypotension	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
CTC Grade 2	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Phlebitis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 1	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Thromboembolic event	2 2 (6.3)	3 3 (8.3)	5 5 (7.4)
CTC Grade 2	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
CTC Grade 3	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
CTC Grade 4	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
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Table 14.3.1.4 Severe adverse events (worst CTC grade 3-5) by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p- value
Any AEs	105 26 (81.3)	91 27 (75.0)	196 53 (77.9)	0.5725
Blood and lymphatic system disorder	6 5 (15.6)	9 7 (19.4)	15 12 (17.6)	0.7576
Anemia	4 4 (12.5)	9 7 (19.4)	13 11 (16.2)	0.5213
Blood and lymphatic systemdisorders - Other, specify: Pancytopenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Febrile neutropenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Cardiac disorder	4 3 (9.4)	1 1 (2.8)	5 4 (5.9)	0.3357
Atrial fibrillation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Myocardial infarction	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Sinus tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Ventricular fibrillation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Ventricular tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
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Table 14.3.1.4 Severe adverse events (worst CTC grade 3-5) by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Gastrointestinal disorder	17 14 (43.8)	25 13 (36.1)	42 27 (39.7)	0.6217
Diarrhea	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)	0.3357
Dysphagia	4 4 (12.5)	5 3 (8.3)	9 7 (10.3)	0.6986
Esophageal pain	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Esophagitis	7 6 (18.8)	5 5 (13.9)	12 11 (16.2)	0.7441
Gastric hemorrhage	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Gastric ulcer	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Gastrointestinal Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Gastrointestinal disorders - other: GI-bleeding (haemorrhagic shock)	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Gastrointestinal disorders - other: Peritonitis with sepsis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Nausea	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)	0.6163
Vomiting	0 0 (0.0)	6 2 (5.6)	6 2 (2.9)	0.4943
General disorders and administration site conditions	1 1 (3.1)	4 4 (11.1)	5 5 (7.4)	0.3605
Death NOS	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Fatigue	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)	0.4943
General disorders and administration site conditions - other: Edema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
General disorders and administration site conditions - other: Reduced overall health condition	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Immunesystem disorder	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)	0.0442
Allergic reaction	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)	0.0442

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
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Table 14.3.1.4 Severe adverse events (worst CTC grade 3-5) by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Infections and infestations	11 10 (31.3)	16 10 (27.8)	27 20 (29.4)	0.7948
Abdominal infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Appendicitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Device related infection	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Infections and infestations - other: infection	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Lung infection	3 3 (9.4)	10 8 (22.2)	13 11 (16.2)	0.1962
Nail infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Sepsis	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)	1.0000
Skin infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Stoma site infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Upper respiratory infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Wound infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
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Table 14.3.1.4 Severe adverse events (worst CTC grade 3-5) by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p- value
Injury, poisoning and procedural complications	8 5 (15.6)	5 4 (11.1)	13 9 (13.2)	0.7249
Dermatitis radiation	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)	0.0990
Fall	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Anastomotic leak	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Incisional hernia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, Morphine overdose	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning andprocedural complications -Other, head wound	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Injury, poisoning and procedural complications - Other, Tumor bleeding	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Injury, poisoning and procedural complications - other: PEG dislocation	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Wound complication	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)	
Investigations	21 11 (34.4)	15 10 (27.8)	36 21 (30.9)	0.6064
Alanine aminotransferase increased	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
GGT increased	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)	0.5977
INR increased	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Investigations - Other, elevation of liver enzymes	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Neutrophil count decreased	2 2 (6.3)	5 3 (8.3)	7 5 (7.4)	1.0000
Platelet count decreased	4 4 (12.5)	2 2 (5.6)	6 6 (8.8)	0.4095
Weight loss	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
White blood cell decreased	11 7 (21.9)	4 4 (11.1)	15 11 (16.2)	0.3255

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
Program: T14-3-1-4ae-severe.sas
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Table 14.3.1.4 Severe adverse events (worst CTC grade 3-5) by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Metabolism and nutrition disorders	10 7 (21.9)	5 4 (11.1)	15 11 (16.2)	0.3255
Acidosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Alkalosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Dehydration	0 0 (0.0)	3 2 (5.6)	3 2 (2.9)	0.4943
Hypoalbuminemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Hypocalcemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Hypokalemia	3 3 (9.4)	2 2 (5.6)	5 5 (7.4)	0.6603
Hypomagnesemia	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)	0.0990
Nervous systems disorders	6 5 (15.6)	1 1 (2.8)	7 6 (8.8)	0.0923
Aphonia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Cognitive Disturbance	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Dizziness	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Seizure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Stroke	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Syncope	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Renal and urinary disorders	3 3 (9.4)	3 2 (5.6)	6 5 (7.4)	0.6603
Acute kidney injury	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Renal and urinary disorders - other, acute renal failure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Renal and urinary disorders - other, decreased creatinine clearance	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Renal and urinary disorders - other, renal failure	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)	
Renal and urinary disorders, Other - nephrotoxicitiy, tubular function impaired	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
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Table 14.3.1.4 Severe adverse events (worst CTC grade 3-5) by NCI CTC Category and AE term (Safety Population)

CTC Category AE term	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)	Fisher's exact test p-value
Respiratory, thoracic and mediastinal disorders	5 4 (12.5)	3 3 (8.3)	8 7 (10.3)	0.6986
Dyspnea	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)	0.5977
Pleural effusion	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)	
Pneumonitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Pneumothorax	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Pulmonary fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Skin and subcutaneous tissue disorders	4 4 (12.5)	2 2 (5.6)	6 6 (8.8)	0.4095
Palmar-plantar erythrodysesthesia syndrome	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Rash acneiform	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)	0.0990
Skin and subcutaneous tissuedisorders - Other, Exanthema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)	
Skin and subcutaneous tissue disorders - Other, Rhagade fingers both hands	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Surgical and medical procedures	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Surgical and medical procedures - other, PTCA and stent	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)	
Vascular disorders	4 4 (12.5)	2 2 (5.6)	6 6 (8.8)	0.4095
Hypertension	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)	0.2177
Thromboembolic event	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)	1.0000

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NOTE: Fisher's exact test comparing the incidence of an AE between treatment groups was computed for CTC category or AE Term with incidence of more than 5 % in either treatment group.
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category
  AE Term
    Causality
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

Any AEs	417 32 (100.0)	387 36 (100.0)	804 68 (100.0)
Not related	236 26 (81.3)	14 5 (13.9)	250 31 (45.6)
Not likely	42 12 (37.5)	0 0 (0.0)	42 12 (17.6)
Possible	69 19 (59.4)	0 0 (0.0)	69 19 (27.9)
Probable	16 9 (28.1)	0 0 (0.0)	16 9 (13.2)
Certain/Definite	37 22 (68.8)	0 0 (0.0)	37 22 (32.4)
NK	9 3 (9.4)	0 0 (0.0)	9 3 (4.4)
NA	8 3 (9.4)	373 35 (97.2)	381 38 (55.9)
Blood and lymphatic system disorder	19 15 (46.9)	16 13 (36.1)	35 28 (41.2)
Anemia	15 13 (40.6)	16 13 (36.1)	31 26 (38.2)
Not related	12 10 (31.3)	1 1 (2.8)	13 11 (16.2)
Possible	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
NA	0 0 (0.0)	15 12 (33.3)	15 12 (17.6)
Blood and lymphatic systemdisorders - Other, specify: Pancytopenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Blood and lymphatic system disorders. Other - Low red blood cell count	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Febrile neutropenia	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
Program: T14-3-1-5ae-causality.sas
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Cardiac disorder	5 4 (12.5)	5 4 (11.1)	10 8 (11.8)
Atrial fibrillation	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Atrioventricular block first degree	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Cardiac disorder - other: Arrhythmia	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Cardiac disorder - other: Tachyarrhytmia	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Cardiac disorder - other: paroxysmal atrial fibrillation	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Myocardial infarction	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Sinus tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Ventricular fibrillation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Ventricular tachycardia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
Program: T14-3-1-5ae-causality.sas
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Ear and labyrinth disorder	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)
External ear inflammation	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Vertigo	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
NK	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Eye disorder	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
Conjuctivitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Dry eye	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Eye disorder - other: Hordeolum	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorder	93 29 (90.6)	127 29 (80.6)	220 58 (85.3)
Abdominal pain	0 0 (0.0)	6 3 (8.3)	6 3 (4.4)
NA	0 0 (0.0)	6 3 (8.3)	6 3 (4.4)
Bloating	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Constipation	7 6 (18.8)	23 11 (30.6)	30 17 (25.0)
Not related	5 4 (12.5)	0 0 (0.0)	5 4 (5.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
Program: T14-3-1-5ae-causality.sas
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NK	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	23 11 (30.6)	23 11 (16.2)
Diarrhea	7 7 (21.9)	7 5 (13.9)	14 12 (17.6)
Not related	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
Possible	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	7 5 (13.9)	7 5 (7.4)
Dry mouth	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Dyspepsia	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Dysphagia	11 9 (28.1)	12 9 (25.0)	23 18 (26.5)
Not related	5 4 (12.5)	0 0 (0.0)	5 4 (5.9)
Not likely	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NK	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
NA	1 1 (3.1)	12 9 (25.0)	13 10 (14.7)
Enterocolitis infectious	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
Program: T14-3-1-5ae-causality.sas
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Esophageal hemorrhage	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Esophageal pain	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Esophagitis	12 11 (34.4)	14 14 (38.9)	26 25 (36.8)
Not related	7 6 (18.8)	0 0 (0.0)	7 6 (8.8)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
NA	0 0 (0.0)	14 14 (38.9)	14 14 (20.6)
Gastric hemorrhage	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastric ulcer	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastroesophageal reflux disease	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
NA	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
Gastrointestinal Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group

NA= Not applicable;   NK= Not known

Program: T14-3-1-5ae-causality.sas

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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category
  AE Term
    Causality
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorder - other: Heartburn	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorders - Other, odynophagia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: GI-bleeding (haemorrhagic shock)	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: Peritonitis with sepsis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorders - other: Slow gastrointestinal passage	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: aperistalsis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: hematemesis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal disorders - other: hypersalivation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Gastrointestinal pain	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
Not related	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Hemorrhoids	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Mucositis oral	9 8 (25.0)	4 4 (11.1)	13 12 (17.6)
Not related	5 5 (15.6)	0 0 (0.0)	5 5 (7.4)
Possible	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	4 4 (11.1)	4 4 (5.9)
Nausea	24 19 (59.4)	34 20 (55.6)	58 39 (57.4)
Not related	13 10 (31.3)	0 0 (0.0)	13 10 (14.7)
Not likely	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Possible	8 6 (18.8)	0 0 (0.0)	8 6 (8.8)
NA	0 0 (0.0)	34 20 (55.6)	34 20 (29.4)
Oral pain	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Rectal hemorrhage	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Vomiting	6 6 (18.8)	11 7 (19.4)	17 13 (19.1)
Not related	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
Possible	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
Program: T14-3-1-5ae-causality.sas
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
NA	0 0 (0.0)	11 7 (19.4)	11 7 (10.3)
Gastrointestinal disorders	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Gastrointestinal disorders - other, Fur on tongue	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions	33 19 (59.4)	39 23 (63.9)	72 42 (61.8)
Death NOS	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Edema limbs	4 2 (6.3)	1 1 (2.8)	5 3 (4.4)
Not related	3 1 (3.1)	0 0 (0.0)	3 1 (1.5)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Fatigue	10 9 (28.1)	21 18 (50.0)	31 27 (39.7)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
Probable	3 2 (6.3)	0 0 (0.0)	3 2 (2.9)
NA	2 2 (6.3)	21 18 (50.0)	23 20 (29.4)
Fever	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
General disorders and administration site conditions - other: Asthenia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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CTC Category
  AE Term
    Causality
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
General disorders and administration site conditions - other: Edema	9 6 (18.8)	6 4 (11.1)	15 10 (14.7)
Not related	9 6 (18.8)	0 0 (0.0)	9 6 (8.8)
NA	0 0 (0.0)	6 4 (11.1)	6 4 (5.9)
General disorders and administration site conditions - other: Mucous congestions	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Pain Post system	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Pain retrosternal	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Pain surgical wound	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
General disorders and administration site conditions - other: Reduced overall health condition	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Localized edema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Non-cardiac chest pain	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Pain	5 5 (15.6)	2 2 (5.6)	7 7 (10.3)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not likely	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Immunesystem disorder	4 4 (12.5)	1 1 (2.8)	5 5 (7.4)
Allergic reaction	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NK	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Immune System Disorders- Other: Immune System Disorders	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations	24 17 (53.1)	27 16 (44.4)	51 33 (48.5)
Abdominal infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Appendicitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Breast infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Bronchial infection	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
Not likely	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Device related infection	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Infections and infestations - other: Herpes labialis	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Infections and infestations - other: Infection, CRP elevated	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: Infection, nos CRP high	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: Infection, oral cavity, CRP high	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: Influenza	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: MRSA infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: Unclear infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Infections and infestations - other: infection	3 3 (9.4)	2 2 (5.6)	5 5 (7.4)
Not related	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group

NA= Not applicable; NK= Not known

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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Infections and infestations - other: infection unclear origin	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Lung infection	3 3 (9.4)	11 9 (25.0)	14 12 (17.6)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	11 9 (25.0)	11 9 (13.2)
Nail infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Paronychia	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Sepsis	1 1 (3.1)	2 2 (5.6)	3 3 (4.4)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Skin infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Stoma site infection	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)
Not related	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Upper respiratory infection	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category
  AE Term
    Causality
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Urinary tract Infection	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Wound infection	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning and procedural complications	22 13 (40.6)	6 5 (13.9)	28 18 (26.5)
Dermatitis radiation	9 9 (28.1)	1 1 (2.8)	10 10 (14.7)
Not related	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
Possible	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Fall	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, ACI stenosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NK	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Anastomotic leak	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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CTC Category
  AE Term
    Causality
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

Injury, poisoning andprocedural complications -Other, Incisional hernia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Morphine overdose	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, Port dermatitis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, head wound	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, port closure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, port dislocation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning andprocedural complications -Other, sunburn	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning and procedural complications - Other, Tumor bleeding	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Injury, poisoning and procedural complications - Other, dislocation of jejunum tube	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Injury, poisoning and procedural complications - other: PEG dislocation	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group

NA= Not applicable;   NK= Not known

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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Wound complication	3 2 (6.3)	0 0 (0.0)	3 2 (2.9)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Investigations	61 25 (78.1)	44 19 (52.8)	105 44 (64.7)
Activated partial thromboplastin time prolonged	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
Not related	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
Alanine aminotransferase increased	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Creatinine increased	2 2 (6.3)	2 1 (2.8)	4 3 (4.4)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
GGT increased	3 3 (9.4)	3 3 (8.3)	6 6 (8.8)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
INR increased	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Investigations - Other, Increased CRP	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Investigations - Other, elevation of liver enzymes	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Investigations - Other: Neutrophil count increased	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Investigations - Other: Red blood count decreased	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
Not related	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
Neutrophil count decreased	5 5 (15.6)	6 4 (11.1)	11 9 (13.2)
Not related	3 3 (9.4)	1 1 (2.8)	4 4 (5.9)
Not likely	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	5 3 (8.3)	5 3 (4.4)
Platelet count decreased	14 11 (34.4)	10 7 (19.4)	24 18 (26.5)
Not related	7 6 (18.8)	4 2 (5.6)	11 8 (11.8)
Not likely	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Possible	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
NK	2 1 (3.1)	0 0 (0.0)	2 1 (1.5)
NA	0 0 (0.0)	6 5 (13.9)	6 5 (7.4)
Weight gain	0 0 (0.0)	4 4 (11.1)	4 4 (5.9)
NA	0 0 (0.0)	4 4 (11.1)	4 4 (5.9)
Weight loss	9 9 (28.1)	4 3 (8.3)	13 12 (17.6)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group

NA= Not applicable;   NK= Not known

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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Not related	7 7 (21.9)	0 0 (0.0)	7 7 (10.3)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	4 3 (8.3)	4 3 (4.4)
White blood cell decreased	23 16 (50.0)	9 8 (22.2)	32 24 (35.3)
Not related	10 7 (21.9)	0 0 (0.0)	10 7 (10.3)
Not likely	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Possible	11 7 (21.9)	0 0 (0.0)	11 7 (10.3)
NA	0 0 (0.0)	9 8 (22.2)	9 8 (11.8)
Metabolism and nutrition disorders	57 22 (68.8)	29 15 (41.7)	86 37 (54.4)
Acidosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Alkalosis	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Anorexia	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Dehydration	2 2 (6.3)	3 2 (5.6)	5 4 (5.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 2 (5.6)	3 2 (2.9)
Hyperkalemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hyperuricemia	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Hypoalbuminemia	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Hypocalcemia	9 9 (28.1)	2 2 (5.6)	11 11 (16.2)
Not related	8 8 (25.0)	0 0 (0.0)	8 8 (11.8)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Hypoglycemia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hypokalemia	21 16 (50.0)	14 12 (33.3)	35 28 (41.2)
Not related	17 13 (40.6)	1 1 (2.8)	18 14 (20.6)
Not likely	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	13 11 (30.6)	13 11 (16.2)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Hypomagnesemia	15 13 (40.6)	3 3 (8.3)	18 16 (23.5)
Not related	5 4 (12.5)	1 1 (2.8)	6 5 (7.4)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	4 4 (12.5)	0 0 (0.0)	4 4 (5.9)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	4 3 (9.4)	0 0 (0.0)	4 3 (4.4)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Hyponatremia	1 1 (3.1)	3 3 (8.3)	4 4 (5.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
Metabolism and nutrition disorders - other: Exsiccose	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Musculoskeletal and connective tissue disorders	1 1 (3.1)	7 4 (11.1)	8 5 (7.4)
Chest wall pain	1 1 (3.1)	3 2 (5.6)	4 3 (4.4)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 2 (5.6)	3 2 (2.9)
Pain in extremity	0 0 (0.0)	4 3 (8.3)	4 3 (4.4)
NA	0 0 (0.0)	4 3 (8.3)	4 3 (4.4)
Nervous systems disorders	16 10 (31.3)	12 10 (27.8)	28 20 (29.4)
Akathisia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category 　AE Term 　　Causality	Cetuximab (N=32) f　n　(%)	Control (N=36) f　n　(%)	Overall (N=68) f　n　(%)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Amnesia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Aphonia	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Cognitive Disturbance	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Dizziness	5 5 (15.6)	3 3 (8.3)	8 8 (11.8)
Not related	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
Headache	1 1 (3.1)	3 1 (2.8)	4 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 1 (2.8)	3 1 (1.5)
Paresthesia	1 1 (3.1)	4 4 (11.1)	5 5 (7.4)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	4 4 (11.1)	4 4 (5.9)
Peripheral motor neuropathy	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;　 NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Seizure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Stroke	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Syncope	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Psychiatric disorders	4 4 (12.5)	18 6 (16.7)	22 10 (14.7)
Insomnia	2 2 (6.3)	17 5 (13.9)	19 7 (10.3)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	17 5 (13.9)	17 5 (7.4)
Psychiatric disorders - other, sleeping disorders	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Restlessness	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Renal and urinary disorders	10 7 (21.9)	8 7 (19.4)	18 14 (20.6)
Acute kidney injury	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Cystitis nininfective	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category
  AE Term
    Causality
	Cetuximab
	(N=32)
	f n (%)
		Control
		(N=36)
		f n (%)
			Overall
			(N=68)
			f n (%)

Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Renal and urinary disorders - other, acute renal failure	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders - other, decreased creatinine clearance	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Renal and urinary disorders - other, renal failure	2 2 (6.3)	2 1 (2.8)	4 3 (4.4)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	2 1 (2.8)	2 1 (1.5)
Renal and urinary disorders, Other - nephrotoxicitiy, tubular function impaired	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders, Other, micturition pain	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders, Other: renal incompetence	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Renal and urinary disorders-other:acute reduction of GFR	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Urinary retention	2 2 (6.3)	2 2 (5.6)	4 4 (5.9)
Not related	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Respiratory, thoracic and mediastinal disorders	13 9 (28.1)	28 19 (52.8)	41 28 (41.2)
Cough	5 5 (15.6)	7 7 (19.4)	12 12 (17.6)
Not related	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Not likely	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
NA	0 0 (0.0)	7 7 (19.4)	7 7 (10.3)
Dyspnea	3 3 (9.4)	5 5 (13.9)	8 8 (11.8)
Not related	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	4 4 (11.1)	4 4 (5.9)
Epistaxis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Hiccups	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Hoarseness	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
NA	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)
Pleural effusion	1 1 (3.1)	5 5 (13.9)	6 6 (8.8)
NA	1 1 (3.1)	5 5 (13.9)	6 6 (8.8)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
Program: T14-3-1-5ae-causality.sas
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Pleuritic pain	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pneumonitis	2 2 (6.3)	1 1 (2.8)	3 3 (4.4)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pneumothorax	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Productive cough	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pulmonary edema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Pulmonary fistula	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissue disorders	43 24 (75.0)	10 9 (25.0)	53 33 (48.5)
Alopecia	5 4 (12.5)	3 3 (8.3)	8 7 (10.3)
Not related	4 3 (9.4)	0 0 (0.0)	4 3 (4.4)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Dry skin	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Erythroderma	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Nail ridging	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Probable	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Palmar-plantar erythrodysesthesia syndrome	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
NA	0 0 (0.0)	2 2 (5.6)	2 2 (2.9)
Pruritus	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Rash acneiform	12 11 (34.4)	0 0 (0.0)	12 11 (16.2)
Not related	4 3 (9.4)	0 0 (0.0)	4 3 (4.4)
Certain/Definite	8 8 (25.0)	0 0 (0.0)	8 8 (11.8)
Rash maculo-papular	10 7 (21.9)	1 1 (2.8)	11 8 (11.8)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	9 6 (18.8)	0 0 (0.0)	9 6 (8.8)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissuedisorders - Other, Exanthema	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissuedisorders - Other, dry exanthema crook of the arm left side	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissuedisorders - Other, dry exanthema on arms, legs and trunk	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissuedisorders - Other, tickel on the throat	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissue disorders - Other, Rhagade fingers both hands	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissue disorders - Other, Rhagade thumb, right hand	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissue disorders - other, Acne	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Probable	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Skin and subcutaneous tissue disorders - other, Erythema	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Not related	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Skin and subcutaneous tissue disorders - other, Rhagads	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Certain/Definite	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Skin and subcutaneous tissue disorders - other, Skin rash	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Table 14.3.1.5 Adverse events by NCI CTC Category, AE term and relationship to cetuximab (Safety Population)

CTC Category AE Term Causality	Cetuximab (N=32) f n (%)	Control (N=36) f n (%)	Overall (N=68) f n (%)
Skin hyperpegmentation	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Surgical and medical procedures	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Surgical and medical procedures - other, PTCA and stent	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Vascular disorders	8 7 (21.9)	5 4 (11.1)	13 11 (16.2)
Hematoma	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Hypertension	3 3 (9.4)	0 0 (0.0)	3 3 (4.4)
Not related	2 2 (6.3)	0 0 (0.0)	2 2 (2.9)
Possible	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Hypotension	1 1 (3.1)	1 1 (2.8)	2 2 (2.9)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Phlebitis	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
NA	0 0 (0.0)	1 1 (2.8)	1 1 (1.5)
Thromboembolic event	2 2 (6.3)	3 3 (8.3)	5 5 (7.4)
Not related	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
Not likely	1 1 (3.1)	0 0 (0.0)	1 1 (1.5)
NA	0 0 (0.0)	3 3 (8.3)	3 3 (4.4)

NOTE: f = number of events, n = number of subjects, % = percentage of subjects within the group
NA= Not applicable;   NK= Not known
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Listing 14.3.1.6 Adverse events leading to discontinuation of cetuximab (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Action taken Cetuximab
010023	1937/male	yes	Blood and lymphatic system disorder	Febrile neutropenia	21/08/2015	24/08/2015	Cetuximab	Medication discontinued
010023	1937/male	yes	Infections and infestations	Lung infection	24/08/2015	30/09/2015	Cetuximab	Medication discontinued
010023	1937/male	yes	Investigations	White blood cell decreased	19/08/2015	10/09/2015	Cetuximab	Medication discontinued
010025	1956/female	yes	Respiratory, thoracic and mediastinal disorders	Pneumonitis	13/11/2015	NK	Cetuximab	Medication discontinued
030005	1942/male	yes	Renal and urinary disorders	Renal and urinary disorders, Other - nephrotoxicitiy, tubular function impaired	30/12/2013	13/02/2014	Cetuximab	Medication discontinued
030006	1936/female	yes	Immunesystem disorder	Allergic reaction	09/12/2013	09/12/2013	Cetuximab	Medication discontinued
030006	1936/female	yes	Gastrointestinal disorder	Diarrhea	09/12/2013	09/12/2013	Cetuximab	Medication discontinued
030006	1936/female	yes	Respiratory, thoracic and mediastinal disorders	Dyspnea	09/12/2013	09/12/2013	Cetuximab	Medication discontinued
070003	1939/male	yes	Immunesystem disorder	Allergic reaction	11/08/2016	11/08/2016	Cetuximab	Medication discontinued
100010	1934/male	yes	Investigations	Platelet count decreased	19/05/2014	07/08/2014	Cetuximab	Medication discontinued

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Listing 14.3.1.6 Adverse events leading to discontinuation of cetuximab (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Action taken Cetuximab
140001	1947/female	yes	Immunesystem disorder	Allergic reaction	26/03/2014	26/03/2014	Cetuximab	Medication discontinued
190001	1953/male	yes	Immunesystem disorder	Allergic reaction	02/10/2013	08/10/2013	Cetuximab	Medication discontinued

Program: L14-3-1-6ae-cetux-disc.sas
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Listing 14.3.1.7 Adverse events leading to discontinuation of radiotherapy (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Action taken Radiotherapy
010019	1959/female	yes	Infections and infestations	Lung infection	31/10/2014	06/11/2014	Control	Radiotherapy discontinued
100004	1948/male	yes	General disorders and administration site conditions	Death NOS	28/04/2013	28/04/2013	Control	Radiotherapy discontinued

Program: L14-3-1-7ae-radio-disc.sas
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Listing 14.3.1.8 Adverse events leading to discontinuation of chemotherapy (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Action taken Chemotherapy
010002	1962/male	yes	Infections and infestations	Lung infection	24/12/2011	04/01/2012	Control	Medication discontinued
010003	1945/male	yes	Metabolism and nutrition disorders	Hypoalbuminemia	17/02/2012	02/05/2012	Cetuximab	Medication discontinued
010007	1943/female	yes	Respiratory, thoracic and mediastinal disorders	Dyspnea	05/09/2012	NK	Control	Medication discontinued
010007	1943/female	yes	Injury, poisoning and procedural complications	Injury, poisoning and procedural complications - Other, Tumor bleeding	18/09/2012	18/09/2012	Control	Medication discontinued
010012	1937/female	yes	Gastrointestinal disorder	Esophagitis	01/05/2013	NK	Cetuximab	Medication discontinued
010017	1954/male	yes	Investigations	White blood cell decreased	26/03/2014	14/05/2014	Control	Medication discontinued
010018	1948/female	yes	Gastrointestinal disorder	Esophagitis	11/07/2014	NK	Cetuximab	Medication discontinued
010018	1948/female	yes	Investigations	White blood cell decreased	27/06/2014	09/10/2014	Cetuximab	Medication discontinued
010019	1959/female	yes	Infections and infestations	Abdominal infection	17/10/2014	27/10/2014	Control	Medication discontinued
010019	1959/female	yes	Infections and infestations	Lung infection	31/10/2014	06/11/2014	Control	Medication discontinued

Program: L14-3-1-8ae-chemo-disc.sas
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Listing 14.3.1.8 Adverse events leading to discontinuation of chemotherapy (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Action taken Chemotherapy
010019	1959/female	yes	Renal and urinary disorders	Renal and urinary disorders - other, renal failure	08/10/2014	NK	Control	Medication discontinued
010019	1959/female	yes	Renal and urinary disorders	Renal and urinary disorders - other, renal failure	05/11/2014	19/11/2014	Control	Medication discontinued
010019	1959/female	yes	Infections and infestations	Stoma site infection	09/10/2014	15/10/2014	Control	Medication discontinued
010020	1955/female	yes	Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome	13/05/2015	08/06/2015	Control	Medication discontinued
010023	1937/male	yes	Blood and lymphatic system disorder	Anemia	21/08/2015	02/10/2015	Cetuximab	Medication discontinued
010023	1937/male	yes	Blood and lymphatic system disorder	Febrile neutropenia	21/08/2015	24/08/2015	Cetuximab	Medication discontinued
010023	1937/male	yes	Infections and infestations	Lung infection	24/08/2015	30/09/2015	Cetuximab	Medication discontinued
010023	1937/male	yes	Investigations	White blood cell decreased	19/08/2015	10/09/2015	Cetuximab	Medication discontinued
010025	1956/female	yes	Respiratory, thoracic and mediastinal disorders	Pneumonitis	13/11/2015	NK	Cetuximab	Medication discontinued
020001	1941/male	yes	Cardiac disorder	Cardiac disorder - other: Tachyarrhytmia	24/01/2012	30/01/2012	Control	Medication discontinued

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Listing 14.3.1.8 Adverse events leading to discontinuation of chemotherapy (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Action taken Chemotherapy
020001	1941/male	yes	Cardiac disorder	Myocardial infarction	22/01/2012	28/01/2012	Control	Medication discontinued
030003	1948/male	yes	Cardiac disorder	Atrioventricular block first degree	14/06/2013	06/12/2013	Cetuximab	Medication discontinued
030003	1948/male	yes	Vascular disorders	Hypertension	12/06/2013	06/12/2013	Cetuximab	Medication discontinued
030003	1948/male	yes	General disorders and administration site conditions	Non-cardiac chest pain	12/06/2013	13/06/2013	Cetuximab	Medication discontinued
030005	1942/male	yes	Renal and urinary disorders	Renal and urinary disorders, Other - nephrotoxicitiy, tubular function impaired	30/12/2013	13/02/2014	Cetuximab	Medication discontinued
100004	1948/male	yes	General disorders and administration site conditions	Death NOS	28/04/2013	28/04/2013	Control	Medication discontinued
100008	1959/male	yes	Immunesystem disorder	Immune System Disorders- Other: Immune System Disorders	23/09/2013	27/09/2013	Control	Medication discontinued
100008	1959/male	yes	Gastrointestinal disorder	Nausea	23/09/2013	07/10/2013	Control	Medication discontinued
100008	1959/male	yes	Infections and infestations	Urinary tract Infection	23/09/2013	27/09/2013	Control	Medication discontinued
100014	1952/male	yes	Renal and urinary disorders	Acute kidney injury	10/02/2015	27/02/2015	Control	Medication discontinued

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Listing 14.3.1.8 Adverse events leading to discontinuation of chemotherapy (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Action taken Chemotherapy
100014	1952/male	yes	Metabolism and nutrition disorders	Dehydration	09/02/2015	10/02/2015	Control	Medication discontinued
100014	1952/male	yes	Respiratory, thoracic and mediastinal disorders	Dyspnea	09/02/2015	NK	Control	Medication discontinued
100014	1952/male	yes	Infections and infestations	Lung infection	09/02/2015	27/02/2015	Control	Medication discontinued
100014	1952/male	yes	Infections and infestations	Sepsis	10/02/2015	27/02/2015	Control	Medication discontinued

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010001	1940/female	yes	Gastrointestinal disorder	Diarrhea	11/11/2011	16/11/2011	Cetuximab	Yes
010001	1940/female	yes	Gastrointestinal disorder	Enterocolitis infectious	12/12/2011	28/12/2011	Cetuximab	Yes
010001	1940/female	yes	Infections and infestations	Nail infection	24/11/2011	13/12/2011	Cetuximab	Yes
010002	1962/male	yes	Gastrointestinal disorder	Dysphagia	20/11/2011	NK	Control	Yes
010002	1962/male	yes	Injury, poisoning and procedural complications	Injury, poisoning andprocedural complications - Other, Morphine overdose	20/11/2011	21/11/2011	Control	Yes
010002	1962/male	yes	Infections and infestations	Lung infection	20/11/2011	30/11/2011	Control	Yes
010002	1962/male	yes	Infections and infestations	Lung infection	24/12/2011	04/01/2012	Control	Yes
010003	1945/male	yes	Gastrointestinal disorder	Esophagitis	22/11/2011	NK	Cetuximab	Yes
010003	1945/male	yes	Gastrointestinal disorder	Esophagitis	03/02/2012	07/02/2012	Cetuximab	Yes
010003	1945/male	yes	Metabolism and nutrition disorders	Hypoalbuminemia	17/02/2012	02/05/2012	Cetuximab	Yes

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010003	1945/male	yes	Metabolism and nutrition disorders	Hypokalemia	09/01/2012	18/01/2012	Cetuximab	Yes
010003	1945/male	yes	Infections and infestations	Lung infection	19/12/2011	16/01/2012	Cetuximab	Yes
010003	1945/male	yes	Gastrointestinal disorder	Nausea	15/12/2011	01/03/2012	Cetuximab	Yes
010005	1948/male	yes	Metabolism and nutrition disorders	Dehydration	28/08/2012	04/09/2012	Control	Yes
010005	1948/male	yes	Gastrointestinal disorder	Esophagitis	22/05/2012	31/07/2012	Control	Yes
010005	1948/male	yes	Gastrointestinal disorder	Gastrointestinal Fistula	22/05/2012	15/06/2012	Control	Yes
010007	1943/female	yes	Respiratory, thoracic and mediastinal disorders	Dyspnea	05/09/2012	NK	Control	Yes
010007	1943/female	yes	Gastrointestinal disorder	Esophagitis	15/08/2012	NK	Control	Yes
010007	1943/female	yes	Injury, poisoning and procedural complications	Injury, poisoning and procedural complications - Other, Tumor bleeding	18/09/2012	18/09/2012	Control	Yes
010010	1961/male	yes	Vascular disorders	Thromboembolic event	27/05/2013	27/08/2013	Cetuximab	Yes

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Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010011	1945/male	yes	Investigations	Alanine aminotransferase increased	02/04/2013	15/04/2013	Control	Yes
010011	1945/male	yes	Gastrointestinal disorder	Diarrhea	23/04/2013	27/04/2013	Control	Yes
010011	1945/male	yes	Gastrointestinal disorder	Esophagitis	15/04/2013	NK	Control	Yes
010011	1945/male	yes	Infections and infestations	Infections and infestations - other: infection	02/05/2013	07/05/2013	Control	Yes
010011	1945/male	yes	Investigations	Neutrophil count decreased	10/04/2013	15/04/2013	Control	Yes
010011	1945/male	yes	Vascular disorders	Thromboembolic event	16/05/2013	NK	Control	Yes
010011	1945/male	yes	Investigations	White blood cell decreased	10/04/2013	08/05/2013	Control	Yes
010012	1937/female	yes	Blood and lymphatic system disorder	Blood and lymphatic systemdisorders - Other, specify: Pancytopenia	05/06/2013	11/06/2013	Cetuximab	Yes
010012	1937/female	yes	Injury, poisoning and procedural complications	Dermatitis radiation	03/05/2013	20/06/2013	Cetuximab	Yes
010012	1937/female	yes	Gastrointestinal disorder	Esophagitis	01/05/2013	NK	Cetuximab	Yes

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010012	1937/female	yes	Infections and infestations	Sepsis	05/06/2013	23/06/2013	Cetuximab	Yes
010012	1937/female	yes	Vascular disorders	Thromboembolic event	23/05/2013	12/08/2013	Cetuximab	Yes
010015	1954/female	yes	Renal and urinary disorders	Renal and urinary disorders, Other: renal incompetence	27/11/2013	11/12/2013	Cetuximab	Yes
010016	1946/male	yes	Blood and lymphatic system disorder	Anemia	24/01/2014	NK	Control	Yes
010016	1946/male	yes	Gastrointestinal disorder	Esophagitis	28/02/2014	NK	Control	Yes
010016	1946/male	yes	Metabolism and nutrition disorders	Hypokalemia	28/02/2014	28/03/2014	Control	Yes
010016	1946/male	yes	Investigations	Neutrophil count decreased	06/02/2014	14/02/2014	Control	Yes
010016	1946/male	yes	Investigations	Neutrophil count decreased	07/03/2014	14/03/2014	Control	Yes
010016	1946/male	yes	Infections and infestations	Sepsis	01/03/2014	01/04/2014	Control	Yes
010017	1954/male	yes	Investigations	White blood cell decreased	26/03/2014	14/05/2014	Control	Yes

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010018	1948/female	yes	Infections and infestations	Device related infection	30/07/2014	16/08/2014	Cetuximab	Yes
010018	1948/female	yes	Gastrointestinal disorder	Esophagitis	11/07/2014	NK	Cetuximab	Yes
010018	1948/female	yes	Investigations	White blood cell decreased	27/06/2014	09/10/2014	Cetuximab	Yes
010019	1959/female	yes	Infections and infestations	Abdominal infection	17/10/2014	27/10/2014	Control	Yes
010019	1959/female	yes	Infections and infestations	Lung infection	31/10/2014	06/11/2014	Control	Yes
010019	1959/female	yes	Renal and urinary disorders	Renal and urinary disorders - other, renal failure	08/10/2014	NK	Control	Yes
010019	1959/female	yes	Renal and urinary disorders	Renal and urinary disorders - other, renal failure	05/11/2014	19/11/2014	Control	Yes
010019	1959/female	yes	Infections and infestations	Stoma site infection	09/10/2014	15/10/2014	Control	Yes
010020	1955/female	yes	General disorders and administration site conditions	Fatigue	11/05/2015	22/05/2015	Control	Yes
010020	1955/female	yes	Gastrointestinal disorder	Gastrointestinal disorders - other: Peritonitis with sepsis	28/07/2015	16/08/2015	Control	Yes

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010020	1955/female	yes	Injury, poisoning and procedural complications	Injury, poisoning and procedural complications - other: PEG dislocation	29/07/2015	30/07/2015	Control	Yes
010020	1955/female	yes	Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome	13/05/2015	08/06/2015	Control	Yes
010021	1962/male	yes	Infections and infestations	Lung infection	21/07/2015	01/08/2015	Control	Yes
010021	1962/male	yes	Infections and infestations	Lung infection	21/07/2015	01/08/2015	Control	Yes
010021	1962/male	yes	Respiratory, thoracic and mediastinal disorders	Pulmonary fistula	20/07/2015	29/07/2015	Control	Yes
010022	1951/male	yes	Infections and infestations	Lung infection	30/08/2015	20/09/2015	Control	Yes
010022	1951/male	yes	Respiratory, thoracic and mediastinal disorders	Pleural effusion	02/09/2015	NK	Control	Yes
010023	1937/male	yes	Blood and lymphatic system disorder	Anemia	21/08/2015	02/10/2015	Cetuximab	Yes
010023	1937/male	yes	Cardiac disorder	Atrial fibrillation	20/08/2015	NK	Cetuximab	Yes
010023	1937/male	yes	Gastrointestinal disorder	Esophagitis	11/09/2015	NK	Cetuximab	Yes

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010023	1937/male	yes	Blood and lymphatic system disorder	Febrile neutropenia	21/08/2015	24/08/2015	Cetuximab	Yes
010023	1937/male	yes	Infections and infestations	Lung infection	24/08/2015	30/09/2015	Cetuximab	Yes
010023	1937/male	yes	Investigations	White blood cell decreased	19/08/2015	10/09/2015	Cetuximab	Yes
010024	1962/male	yes	Metabolism and nutrition disorders	Alkalosis	14/09/2015	15/09/2015	Cetuximab	Yes
010024	1962/male	yes	Gastrointestinal disorder	Esophagitis	11/09/2015	NK	Cetuximab	Yes
010024	1962/male	yes	Gastrointestinal disorder	Gastrointestinal disorders - other: hematemesis	01/12/2015	01/12/2015	Cetuximab	Yes
010025	1956/female	yes	Metabolism and nutrition disorders	Acidosis	18/12/2015	18/12/2015	Cetuximab	Yes
010025	1956/female	yes	Investigations	GGT increased	21/09/2015	NK	Cetuximab	Yes
010025	1956/female	yes	Gastrointestinal disorder	Gastric ulcer	09/12/2015	09/12/2015	Cetuximab	Yes
010025	1956/female	yes	Gastrointestinal disorder	Gastrointestinal disorders - other: GI-bleeding (haemorrhagic shock)	28/09/2015	01/10/2015	Cetuximab	Yes

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010025	1956/female	yes	Infections and infestations	Infections and infestations - other: infection	08/12/2015	18/12/2015	Cetuximab	Yes
010025	1956/female	yes	Investigations	Platelet count decreased	29/09/2015	18/12/2015	Cetuximab	Yes
010025	1956/female	yes	Respiratory, thoracic and mediastinal disorders	Pneumonitis	13/11/2015	NK	Cetuximab	Yes
010025	1956/female	yes	Renal and urinary disorders	Renal and urinary disorders - other, acute renal failure	16/12/2015	18/12/2015	Cetuximab	Yes
010025	1956/female	yes	Infections and infestations	Skin infection	05/11/2015	24/11/2015	Cetuximab	Yes
010026	1938/male	yes	Metabolism and nutrition disorders	Hypokalemia	27/02/2016	09/03/2016	Control	Yes
010026	1938/male	yes	Injury, poisoning and procedural complications	Injury, poisoning andprocedural complications - Other, Anastomotic leak	19/02/2016	17/03/2016	Control	Yes
010026	1938/male	yes	Injury, poisoning and procedural complications	Injury, poisoning andprocedural complications - Other, Fistula	17/03/2016	31/03/2016	Control	Yes
010026	1938/male	yes	Investigations	Investigations - Other, elevation of liver enzymes	17/02/2016	25/02/2016	Control	Yes
010026	1938/male	yes	Infections and infestations	Lung infection	15/03/2016	30/03/2016	Control	Yes

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Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
010027	1952/male	yes	Gastrointestinal disorder	Esophagitis	21/01/2016	21/01/2016	Control	Yes
010027	1952/male	yes	Investigations	GGT increased	06/02/2016	10/04/2016	Control	Yes
010027	1952/male	yes	Infections and infestations	Lung infection	25/02/2016	14/04/2016	Control	Yes
010027	1952/male	yes	Gastrointestinal disorder	Nausea	27/01/2016	03/02/2016	Control	Yes
010028	1972/female	yes	Gastrointestinal disorder	Esophagitis	07/03/2016	12/05/2016	Cetuximab	Yes
010028	1972/female	yes	Skin and subcutaneous tissue disorders	Rash acneiform	29/02/2016	NK	Cetuximab	Yes
010029	1951/female	yes	Infections and infestations	Lung infection	16/06/2016	30/06/2016	Control	Yes
010029	1951/female	yes	Renal and urinary disorders	Renal and urinary disorders-other:acute reduction of GFR	02/05/2016	NK	Control	Yes
010029	1951/female	yes	Infections and infestations	Wound infection	16/06/2016	05/07/2016	Control	Yes
010030	1963/male	yes	Infections and infestations	Lung infection	20/10/2016	28/10/2016	Cetuximab	Yes

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Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
020001	1941/male	yes	Cardiac disorder	Myocardial infarction	22/01/2012	28/01/2012	Control	Yes
020002	1943/female	yes	Gastrointestinal disorder	Abdominal pain	24/04/2013	27/04/2013	Control	Yes
020002	1943/female	yes	Gastrointestinal disorder	Gastric hemorrhage	10/04/2013	11/04/2013	Control	Yes
020003	1938/male	yes	General disorders and administration site conditions	Fever	12/04/2013	22/04/2013	Control	Yes
030001	1941/male	yes	Infections and infestations	Appendicitis	27/03/2013	30/03/2013	Cetuximab	Yes
030001	1941/male	yes	Nervous systems disorders	Stroke	12/04/2013	12/04/2013	Cetuximab	Yes
030002	1951/female	yes	Respiratory, thoracic and mediastinal disorders	Dyspnea	11/03/2013	09/08/2013	Cetuximab	Yes
030002	1951/female	yes	Respiratory, thoracic and mediastinal disorders	Pneumothorax	11/03/2013	15/03/2013	Cetuximab	Yes
030002	1951/female	yes	Infections and infestations	Upper respiratory infection	11/03/2013	04/04/2013	Cetuximab	Yes
030002	1951/female	yes	Investigations	White blood cell decreased	17/02/2013	11/03/2013	Cetuximab	Yes

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Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
030005	1942/male	yes	Metabolism and nutrition disorders	Hypocalcemia	02/12/2013	23/01/2014	Cetuximab	Yes
030005	1942/male	yes	Metabolism and nutrition disorders	Hypomagnesemia	26/12/2013	23/01/2014	Cetuximab	Yes
030005	1942/male	yes	Renal and urinary disorders	Renal and urinary disorders, Other - nephrotoxicitiy, tubular function impaired	30/12/2013	13/02/2014	Cetuximab	Yes
030005	1942/male	yes	Nervous systems disorders	Seizure	27/12/2013	02/01/2014	Cetuximab	Yes
030005	1942/male	yes	Cardiac disorder	Ventricular tachycardia	09/12/2013	11/12/2014	Cetuximab	Yes
030006	1936/female	yes	Immunesystem disorder	Allergic reaction	09/12/2013	09/12/2013	Cetuximab	Yes
070002	1949/male	yes	Gastrointestinal disorder	Esophageal hemorrhage	31/01/2013	06/02/2013	Control	Yes
070002	1949/male	yes	Gastrointestinal disorder	Nausea	01/02/2013	08/02/2013	Control	Yes
070003	1939/male	yes	Immunesystem disorder	Allergic reaction	11/08/2016	11/08/2016	Cetuximab	Yes
070003	1939/male	yes	Ear and labyrinth disorder	Vertigo	07/09/2016	12/09/2016	Cetuximab	Yes

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Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
090001	1951/male	yes	Infections and infestations	Lung infection	07/08/2015	18/08/2015	Control	Yes
100001	1952/male	yes	Infections and infestations	Stoma site infection	02/06/2012	11/06/2012	Cetuximab	Yes
100003	1949/male	yes	Gastrointestinal disorder	Vomiting	22/01/2013	30/01/2013	Control	Yes
100003	1949/male	yes	Gastrointestinal disorder	Vomiting	06/02/2013	09/02/2013	Control	Yes
100004	1948/male	yes	General disorders and administration site conditions	Death NOS	28/04/2013	28/04/2013	Control	Yes
100005	1946/male	yes	Vascular disorders	Thromboembolic event	21/08/2013	30/08/2013	Control	Yes
100008	1959/male	yes	Immunesystem disorder	Immune System Disorders- Other: Immune System Disorders	23/09/2013	27/09/2013	Control	Yes
100008	1959/male	yes	Gastrointestinal disorder	Vomiting	01/09/2013	04/09/2013	Control	Yes
100008	1959/male	yes	Gastrointestinal disorder	Vomiting	10/09/2013	12/09/2013	Control	Yes
100012	1952/male	yes	Gastrointestinal disorder	Dysphagia	12/08/2014	13/08/2014	Control	Yes

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Table Generation: 26SEP2018 4:00:40 PM

Listing 14.3.1.9 Serious adverse events (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	CTC Category	AE Term (CTC)	AE Start Date	AE End Date	Treatment	Serious AE
100012	1952/male	yes	Gastrointestinal disorder	Dysphagia	27/09/2014	30/09/2014	Control	Yes
100013	1956/male	yes	Gastrointestinal disorder	Diarrhea	07/10/2014	13/10/2014	Cetuximab	Yes
100014	1952/male	yes	Infections and infestations	Lung infection	09/02/2015	27/02/2015	Control	Yes
100014	1952/male	yes	Infections and infestations	Sepsis	10/02/2015	27/02/2015	Control	Yes
100014	1952/male	yes	Gastrointestinal disorder	Vomiting	19/01/2015	03/02/2015	Control	Yes
100015	1954/male	yes	Infections and infestations	Infections and infestations - other: infection unclear origin	03/04/2015	16/04/2015	Cetuximab	Yes
100018	1946/male	yes	Metabolism and nutrition disorders	Metabolism and nutrition disorders - other: Exsiccose	07/08/2015	13/08/2015	Cetuximab	Yes
100019	1968/male	yes	Nervous systems disorders	Cognitive Disturbance	19/11/2015	19/11/2015	Cetuximab	Yes
100019	1968/male	yes	General disorders and administration site conditions	General disorders and administration site conditions - other: Reduced overall health condition	14/11/2015	30/11/2015	Cetuximab	Yes

Program: L14-3-1-9sae.sas
Table Generation: 26SEP2018 4:00:40 PM

Listing 14.3.1.10 Deaths (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	Treatment	Date of Death	Reason for Death	Specify AE
010003	1945/male	yes	Cetuximab			
010008	1933/male	yes	Control			
010009	1960/male	yes	Cetuximab			
010011	1945/male	yes	Control			
010013	1948/male	yes	Control	14/06/17	progressive disease	
010016	1946/male	yes	Control	03/10/14	Not known	
010018	1948/female	yes	Cetuximab	20/12/14	progressive disease	
010019	1959/female	yes	Control	19/11/14	progressive disease	
010020	1955/female	yes	Control	25/03/16	progressive disease	
010023	1937/male	yes	Cetuximab	08/12/15	progressive disease	
010025	1956/female	yes	Cetuximab	18/12/15	Other reason	renal failure following surgery for gastric ulcer
010027	1952/male	yes	Control	08/12/17		
020001	1941/male	yes	Control	16/04/12	Other reason	sepsis with multi-organ failure
020003	1938/male	yes	Control	29/10/13	progressive disease	
030002	1951/female	yes	Cetuximab	03/02/17		
030004	1944/male	yes	Control	08/05/14	progressive disease	
030006	1936/female	yes	Cetuximab	02/01/14	Other reason	sepsis after EOS
070001	1946/male	yes	Control	03/12/14	progressive disease	
070002	1949/male	yes	Control	19/02/16	progressive disease	
070003	1939/male	yes	Cetuximab	27/06/17		
090001	1951/male	yes	Control	30/07/16	Other reason	pneumonia
100001	1952/male	yes	Cetuximab	18/04/13	progressive disease	
100003	1949/male	yes	Control	05/07/14	progressive disease	
100004	1948/male	yes	Control	28/04/13	Other (serious) adverse event	death nos

For subjects 010003, 010008, 010009 and 010011 death report form information was not collected.
Program: L14-3-1-10deaths.sas
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Listing 14.3.1.10 Deaths (Safety Population)

Unique Subject ID	Year of Birth/ Gender	Safety analysis set	Treatment	Date of Death	Reason for Death	Specify AE
100005	1946/male	yes	Control	06/11/17		
100008	1959/male	yes	Control	27/07/14	progressive disease	
100009	1954/male	yes	Control	29/08/16		
100011	1944/male	yes	Control	24/04/15	progressive disease	
100014	1952/female	yes	Control	15/04/15	progressive disease	
100019	1968/male	yes	Cetuximab	20/06/16	progressive disease	
110001	1942/male	yes	Cetuximab	22/08/14	progressive disease	and other: renal failure, metabolic acidosis ileus paralytic infection unknown
110002	1944/male	yes	Cetuximab	23/04/17		
190001	1953/male	yes	Cetuximab	06/04/17	progressive disease	

For subjects 010003, 010008, 010009 and 010011 death report form information was not collected.
Program: L14-3-1-10deaths.sas
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Systolic BP (mmHg)	Screening	Screening	Observed	n	31	36
				Mean (SD)	127.3 (17.05)	121.6 (15.66)
				Median	130.0	120.0
				Min, Max	100, 180	94, 150
	Cycle-01	Day 01	Observed	n	31	33
				Mean (SD)	128.6 (14.40)	124.5 (16.66)
				Median	130.0	130.0
				Min, Max	100, 151	95, 161
			CFB	n	31	33
				Mean (SD)	1.3 (15.52)	2.6 (10.80)
				Median	0.0	0.0
				Min, Max	-50, 34	-20, 28
		Day 08	Observed	n	27	30
				Mean (SD)	126.3 (16.09)	127.9 (22.89)
				Median	130.0	120.0
				Min, Max	90, 160	90, 196
			CFB	n	27	30
				Mean (SD)	-2.3 (19.39)	7.3 (16.25)
				Median	0.0	8.0
				Min, Max	-50, 30	-22, 53
		Day 15	Observed	n	26	18
				Mean (SD)	117.3 (15.95)	127.5 (21.03)
				Median	117.0	120.0
				Min, Max	83, 161	100, 172

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
Program: t14-3-2-01-vitals.sas
Table Generation: 21SEP2018 11:47:30 AM

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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Systolic BP (mmHg)	Cycle-01	Day 15	CFB	n	26	18
				Mean (SD)	-9.8 (18.53)	11.0 (22.15)
				Median	-2.5	10.0
				Min, Max	-54, 21	-19, 62
		Day 22	Observed	n	24	20
				Mean (SD)	118.9 (13.97)	122.5 (19.99)
				Median	120.0	120.0
				Min, Max	100, 155	75, 166
			CFB	n	24	20
				Mean (SD)	-8.4 (16.42)	3.7 (14.75)
				Median	-2.5	1.0
				Min, Max	-60, 10	-20, 32
	Cycle-02	Day 01	Observed	n	26	26
				Mean (SD)	120.0 (16.17)	119.8 (20.73)
				Median	116.5	120.0
				Min, Max	90, 150	70, 158
			CFB	n	26	26
				Mean (SD)	-7.9 (20.29)	-1.0 (19.16)
				Median	-7.5	0.0
				Min, Max	-50, 30	-31, 54
		Day 08	Observed	n	25	23
				Mean (SD)	116.7 (20.45)	117.4 (16.74)
				Median	110.0	120.0
				Min, Max	78, 160	76, 150

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Systolic BP (mmHg)	Cycle-02	Day 08	CFB	n	25	23
				Mean (SD)	-11.1 (16.72)	-3.9 (18.05)
				Median	-10.0	-3.0
				Min, Max	-42, 30	-30, 46
		Day 15	Observed	n	25	13
				Mean (SD)	116.3 (14.09)	113.8 (17.56)
				Median	110.0	112.0
				Min, Max	100, 145	80, 150
			CFB	n	25	13
				Mean (SD)	-11.9 (19.23)	-6.8 (14.07)
				Median	-10.0	-10.0
				Min, Max	-60, 20	-35, 20
		Day 22	Observed	n	19	15
				Mean (SD)	119.3 (19.13)	115.5 (12.93)
				Median	111.0	120.0
				Min, Max	90, 160	90, 130
			CFB	n	19	15
				Mean (SD)	-8.3 (23.78)	-6.1 (12.93)
				Median	-10.0	0.0
				Min, Max	-50, 40	-27, 10
	Cycle-03	Day 01	Observed	n	16	11
				Mean (SD)	125.3 (15.65)	116.8 (17.79)
				Median	130.0	120.0
				Min, Max	95, 150	90, 151

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Systolic BP (mmHg)	Cycle-03	Day 01	CFB	n	16	11
				Mean (SD)	-2.8 (18.16)	-4.5 (22.73)
				Median	-2.5	-10.0
				Min, Max	-50, 30	-30, 47
		Day 08	Observed	n	16	9
				Mean (SD)	124.4 (10.14)	118.2 (20.43)
				Median	120.0	110.0
				Min, Max	110, 145	95, 160
			CFB	n	16	9
				Mean (SD)	-3.8 (21.41)	-4.0 (23.40)
				Median	0.0	-10.0
				Min, Max	-60, 30	-51, 30
		Day 15	Observed	n	12	5
				Mean (SD)	123.7 (24.22)	115.8 (14.08)
				Median	120.0	110.0
				Min, Max	90, 174	104, 140
			CFB	n	12	5
				Mean (SD)	-5.5 (25.34)	-8.2 (27.41)
				Median	-2.5	-10.0
				Min, Max	-60, 30	-46, 30
		Day 22	Observed	n	14	8
				Mean (SD)	118.9 (14.70)	107.3 (13.49)
				Median	114.5	105.0
				Min, Max	100, 150	90, 130

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Systolic BP (mmHg)	Cycle-03	Day 22	CFB	n	14	8
				Mean (SD)	-10.4 (22.33)	-17.8 (18.80)
				Median	-5.0	-20.0
				Min, Max	-55, 20	-40, 20
	Cycle-04	Day 01	Observed	n	14	10
				Mean (SD)	123.9 (14.54)	118.2 (18.59)
				Median	120.0	122.5
				Min, Max	100, 154	85, 140
			CFB	n	14	10
				Mean (SD)	-6.1 (19.80)	-3.2 (23.53)
				Median	-2.5	-7.5
				Min, Max	-60, 24	-40, 30
		Day 08	Observed	n	9	8
				Mean (SD)	121.1 (9.28)	118.3 (21.02)
				Median	120.0	113.0
				Min, Max	110, 130	100, 160
			CFB	n	9	8
				Mean (SD)	-1.1 (20.28)	-4.3 (29.31)
				Median	0.0	-5.0
				Min, Max	-40, 30	-40, 50
		Day 15	Observed	n	2	3
				Mean (SD)	130.0 (28.28)	103.7 (15.82)
				Median	130.0	100.0
				Min, Max	110, 150	90, 121

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Systolic BP (mmHg)	Cycle-04	Day 15	CFB	n	2	3
				Mean (SD)	15.0 (7.07)	-19.7 (9.50)
				Median	15.0	-20.0
				Min, Max	10, 20	-29, -10
		Day 22	Observed	n	1	3
				Mean (SD)	140.0 (.)	100.7 (9.02)
				Median	140.0	100.0
				Min, Max	140, 140	92, 110
			CFB	n	1	3
				Mean (SD)	10.0 (.)	-22.7 (31.01)
				Median	10.0	-10.0
				Min, Max	10, 10	-58, 0
	End of Treatment	EOT	Observed	n	31	29
				Mean (SD)	123.3 (16.99)	124.3 (19.84)
				Median	120.0	120.0
				Min, Max	94, 160	70, 175
			CFB	n	30	29
				Mean (SD)	-4.6 (23.12)	2.9 (21.70)
				Median	-1.0	0.0
				Min, Max	-55, 50	-40, 50

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Diastolic BP (mmHg)	Screening	Screening	Observed	n	31	36
				Mean (SD)	74.8 (8.12)	73.6 (8.72)
				Median	74.0	70.0
				Min, Max	60, 90	54, 90
	Cycle-01	Day 01	Observed	n	31	33
				Mean (SD)	74.5 (9.48)	74.9 (7.92)
				Median	75.0	77.0
				Min, Max	60, 90	60, 90
			CFB	n	31	33
				Mean (SD)	-0.3 (9.36)	1.6 (6.97)
				Median	0.0	0.0
				Min, Max	-20, 20	-13, 20
		Day 08	Observed	n	27	30
				Mean (SD)	74.7 (9.38)	75.1 (8.93)
				Median	78.0	80.0
				Min, Max	60, 90	50, 90
			CFB	n	27	30
				Mean (SD)	-0.8 (9.39)	1.8 (10.04)
				Median	0.0	0.0
				Min, Max	-20, 11	-23, 21
		Day 15	Observed	n	26	18
				Mean (SD)	72.0 (9.27)	76.6 (8.44)
				Median	71.0	75.0
				Min, Max	57, 90	60, 90

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Diastolic BP (mmHg)	Cycle-01	Day 15	CFB	n	26	18
				Mean (SD)	-2.6 (8.93)	3.6 (10.66)
				Median	0.0	2.0
				Min, Max	-20, 15	-11, 26
		Day 22	Observed	n	24	20
				Mean (SD)	75.6 (9.21)	76.5 (10.44)
				Median	73.0	79.0
				Min, Max	60, 101	60, 98
			CFB	n	24	20
				Mean (SD)	1.5 (8.09)	5.0 (8.47)
				Median	0.0	6.0
				Min, Max	-10, 21	-10, 18
	Cycle-02	Day 01	Observed	n	26	26
				Mean (SD)	74.1 (7.52)	72.6 (12.28)
				Median	72.5	73.0
				Min, Max	60, 90	42, 90
			CFB	n	26	26
				Mean (SD)	-0.5 (7.68)	-0.5 (13.10)
				Median	0.0	-1.0
				Min, Max	-13, 12	-31, 25
		Day 08	Observed	n	25	23
				Mean (SD)	73.0 (8.67)	74.1 (10.02)
				Median	75.0	70.0
				Min, Max	55, 90	57, 90

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Diastolic BP (mmHg)	Cycle-02	Day 08	CFB	n	25	23
				Mean (SD)	-1.4 (9.42)	1.3 (10.70)
				Median	-1.0	0.0
				Min, Max	-20, 20	-13, 23
		Day 15	Observed	n	25	13
				Mean (SD)	70.3 (9.60)	70.8 (11.60)
				Median	70.0	70.0
				Min, Max	54, 90	50, 94
			CFB	n	25	13
				Mean (SD)	-4.1 (13.84)	-2.2 (10.28)
				Median	-5.0	0.0
				Min, Max	-30, 20	-23, 12
		Day 22	Observed	n	19	15
				Mean (SD)	73.2 (11.34)	70.7 (6.94)
				Median	70.0	70.0
				Min, Max	55, 104	60, 83
			CFB	n	19	15
				Mean (SD)	-0.9 (11.89)	-2.1 (7.54)
				Median	0.0	0.0
				Min, Max	-15, 24	-15, 10
	Cycle-03	Day 01	Observed	n	16	11
				Mean (SD)	72.8 (11.25)	70.2 (9.02)
				Median	75.0	70.0
				Min, Max	55, 90	60, 85

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Diastolic BP (mmHg)	Cycle-03	Day 01	CFB	n	16	11
				Mean (SD)	-2.2 (6.82)	-0.2 (9.43)
				Median	0.0	0.0
				Min, Max	-10, 10	-10, 16
		Day 08	Observed	n	16	9
				Mean (SD)	71.9 (8.54)	68.9 (8.21)
				Median	70.0	70.0
				Min, Max	55, 85	55, 80
			CFB	n	16	9
				Mean (SD)	-3.1 (10.78)	-0.6 (9.50)
				Median	0.0	0.0
				Min, Max	-30, 10	-20, 10
		Day 15	Observed	n	12	5
				Mean (SD)	70.8 (12.58)	70.0 (9.35)
				Median	65.0	70.0
				Min, Max	60, 95	60, 85
			CFB	n	12	5
				Mean (SD)	-4.2 (12.22)	-1.0 (10.84)
				Median	0.0	-5.0
				Min, Max	-30, 15	-10, 15
		Day 22	Observed	n	14	8
				Mean (SD)	69.7 (8.88)	61.5 (7.13)
				Median	70.0	60.0
				Min, Max	60, 85	50, 70

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Diastolic BP (mmHg)	Cycle-03	Day 22	CFB	n	14	8
				Mean (SD)	-5.3 (9.82)	-9.1 (12.89)
				Median	0.0	-10.0
				Min, Max	-30, 5	-30, 10
	Cycle-04	Day 01	Observed	n	14	10
				Mean (SD)	72.0 (10.41)	69.6 (9.54)
				Median	70.0	70.0
				Min, Max	60, 90	55, 80
			CFB	n	14	10
				Mean (SD)	-3.7 (8.86)	0.2 (8.84)
				Median	0.0	1.0
				Min, Max	-20, 8	-15, 10
		Day 08	Observed	n	9	8
				Mean (SD)	68.3 (11.18)	66.9 (7.04)
				Median	70.0	67.5
				Min, Max	55, 90	60, 80
			CFB	n	9	8
				Mean (SD)	-5.0 (16.96)	-1.3 (6.41)
				Median	0.0	0.0
				Min, Max	-30, 30	-10, 10
		Day 15	Observed	n	2	3
				Mean (SD)	75.0 (7.07)	67.7 (6.81)
				Median	75.0	70.0
				Min, Max	70, 80	60, 73

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Diastolic BP (mmHg)	Cycle-04	Day 15	CFB	n	2	3
				Mean (SD)	10.0 (0.00)	2.7 (11.02)
				Median	10.0	8.0
				Min, Max	10, 10	-10, 10
		Day 22	Observed	n	1	3
				Mean (SD)	60.0 (.)	65.0 (8.66)
				Median	60.0	70.0
				Min, Max	60, 60	55, 70
			CFB	n	1	3
				Mean (SD)	-10.0 (.)	0.0 (10.00)
				Median	-10.0	0.0
				Min, Max	-10, -10	-10, 10
	End of Treatment	EOT	Observed	n	31	29
				Mean (SD)	74.3 (10.10)	74.1 (9.76)
				Median	80.0	78.0
				Min, Max	54, 90	42, 94
			CFB	n	30	29
				Mean (SD)	-0.7 (11.98)	1.2 (10.44)
				Median	0.0	0.0
				Min, Max	-30, 20	-31, 23

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Heart rate (beats/min)	Screening	Screening	Observed	n	31	36
				Mean (SD)	77.3 (10.63)	76.3 (10.21)
				Median	76.0	76.0
				Min, Max	55, 100	59, 98
	Cycle-01	Day 01	Observed	n	31	33
				Mean (SD)	75.9 (10.46)	75.4 (11.71)
				Median	76.0	76.0
				Min, Max	56, 100	53, 100
			CFB	n	31	33
				Mean (SD)	-1.4 (9.93)	-1.2 (8.65)
				Median	0.0	0.0
				Min, Max	-32, 16	-24, 25
		Day 08	Observed	n	28	29
				Mean (SD)	76.6 (10.49)	76.7 (10.82)
				Median	76.0	76.0
				Min, Max	52, 101	56, 100
			CFB	n	28	29
				Mean (SD)	0.2 (10.65)	1.3 (12.68)
				Median	0.0	0.0
				Min, Max	-22, 16	-28, 32
		Day 15	Observed	n	26	18
				Mean (SD)	79.1 (12.19)	80.4 (14.95)
				Median	80.0	76.5
				Min, Max	56, 104	58, 104

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Heart rate (beats/min)	Cycle-01	Day 15	CFB	n	26	18
				Mean (SD)	2.3 (11.73)	7.1 (12.84)
				Median	2.0	5.0
				Min, Max	-20, 32	-16, 26
		Day 22	Observed	n	24	20
				Mean (SD)	77.8 (10.29)	84.7 (14.45)
				Median	79.5	83.5
				Min, Max	56, 96	58, 112
			CFB	n	24	20
				Mean (SD)	1.4 (10.70)	11.1 (13.14)
				Median	3.0	9.0
				Min, Max	-24, 24	-6, 32
	Cycle-02	Day 01	Observed	n	26	26
				Mean (SD)	81.0 (11.06)	84.0 (16.72)
				Median	80.0	82.5
				Min, Max	52, 116	58, 139
			CFB	n	26	26
				Mean (SD)	4.5 (11.52)	6.7 (16.08)
				Median	8.0	3.0
				Min, Max	-16, 35	-26, 49
		Day 08	Observed	n	25	23
				Mean (SD)	85.0 (15.84)	84.0 (12.80)
				Median	82.0	84.0
				Min, Max	52, 130	60, 108

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Heart rate (beats/min)	Cycle-02	Day 08	CFB	n	25	23
				Mean (SD)	8.2 (13.59)	7.4 (13.61)
				Median	8.0	8.0
				Min, Max	-12, 44	-26, 31
		Day 15	Observed	n	24	13
				Mean (SD)	85.0 (16.04)	85.5 (17.06)
				Median	82.0	84.0
				Min, Max	62, 128	56, 116
			CFB	n	24	13
				Mean (SD)	7.3 (14.08)	9.4 (15.71)
				Median	2.5	8.0
				Min, Max	-12, 40	-12, 48
		Day 22	Observed	n	20	15
				Mean (SD)	80.1 (10.98)	84.1 (13.32)
				Median	79.5	84.0
				Min, Max	58, 108	60, 112
			CFB	n	20	15
				Mean (SD)	3.1 (10.27)	8.7 (8.87)
				Median	5.0	8.0
				Min, Max	-20, 19	-8, 24
	Cycle-03	Day 01	Observed	n	16	11
				Mean (SD)	77.0 (11.00)	82.8 (9.41)
				Median	78.0	84.0
				Min, Max	58, 96	60, 93

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Heart rate (beats/min)	Cycle-03	Day 01	CFB	n	16	11
				Mean (SD)	3.6 (10.56)	5.3 (8.45)
				Median	4.0	4.0
				Min, Max	-16, 20	-6, 20
		Day 08	Observed	n	16	10
				Mean (SD)	73.4 (10.42)	83.6 (8.88)
				Median	72.0	86.0
				Min, Max	56, 96	68, 94
			CFB	n	16	10
				Mean (SD)	0.0 (12.39)	5.5 (10.04)
				Median	-2.0	8.0
				Min, Max	-20, 28	-12, 20
		Day 15	Observed	n	12	6
				Mean (SD)	77.9 (12.09)	88.5 (6.80)
				Median	83.0	89.5
				Min, Max	56, 96	76, 96
			CFB	n	12	6
				Mean (SD)	4.1 (9.73)	11.0 (8.74)
				Median	6.0	10.0
				Min, Max	-12, 22	-2, 24
		Day 22	Observed	n	14	8
				Mean (SD)	78.9 (10.94)	86.1 (12.94)
				Median	80.5	88.0
				Min, Max	60, 92	68, 100

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Heart rate (beats/min)	Cycle-03	Day 22	CFB	n	14	8
				Mean (SD)	4.4 (10.70)	7.5 (14.69)
				Median	4.0	10.0
				Min, Max	-12, 20	-14, 32
	Cycle-04	Day 01	Observed	n	14	10
				Mean (SD)	76.6 (13.82)	82.9 (12.67)
				Median	74.0	80.0
				Min, Max	57, 108	68, 108
			CFB	n	14	10
				Mean (SD)	3.9 (12.19)	7.4 (13.00)
				Median	2.0	5.0
				Min, Max	-12, 34	-8, 32
		Day 08	Observed	n	9	8
				Mean (SD)	73.3 (12.81)	82.4 (10.93)
				Median	72.0	82.0
				Min, Max	52, 92	64, 96
			CFB	n	9	8
				Mean (SD)	-0.2 (12.10)	5.5 (6.74)
				Median	8.0	4.0
				Min, Max	-22, 12	0, 16
		Day 15	Observed	n	2	3
				Mean (SD)	64.0 (19.80)	99.0 (6.56)
				Median	64.0	100.0
				Min, Max	50, 78	92, 105

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.2.1 Descriptive statistics of Vital Signs (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Heart rate (beats/min)	Cycle-04	Day 15	CFB	n	2	3
				Mean (SD)	-11.0 (18.38)	23.3 (10.26)
				Median	-11.0	26.0
				Min, Max	-24, 2	12, 32
		Day 22	Observed	n	1	3
				Mean (SD)	88.0 (.)	102.0 (3.46)
				Median	88.0	100.0
				Min, Max	88, 88	100, 106
			CFB	n	1	3
				Mean (SD)	14.0 (.)	26.3 (6.03)
				Median	14.0	27.0
				Min, Max	14, 14	20, 32
	End of Treatment	EOT	Observed	n	32	29
				Mean (SD)	81.9 (17.75)	83.1 (18.82)
				Median	80.0	80.0
				Min, Max	50, 128	56, 139
			CFB	n	31	29
				Mean (SD)	4.3 (18.66)	6.9 (16.32)
				Median	7.0	4.0
				Min, Max	-40, 47	-24, 49

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.3.1 Descriptive statistics of Physical Examination (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Body weight (kg)	Screening	Screening	Observed	n	32	36
				Mean (SD)	78.0 (18.89)	71.9 (15.18)
				Median	73.5	71.8
				Min, Max	52, 133	50, 121
	Cycle-01	Day 01	Observed	n	30	34
				Mean (SD)	78.3 (19.25)	71.5 (15.91)
				Median	73.4	69.0
				Min, Max	53, 134	50, 121
			CFB	n	30	34
				Mean (SD)	0.0 (1.47)	-0.1 (1.25)
				Median	0.0	0.0
				Min, Max	-3, 4	-3, 3
		Day 08	Observed	n	28	32
				Mean (SD)	78.3 (18.46)	72.0 (16.12)
				Median	73.4	69.1
				Min, Max	55, 130	51, 124
			CFB	n	28	32
				Mean (SD)	-0.8 (2.07)	0.1 (2.51)
				Median	-1.0	0.0
				Min, Max	-6, 4	-6, 5
		Day 15	Observed	n	28	22
				Mean (SD)	77.0 (19.28)	72.8 (16.80)
				Median	71.6	69.8
				Min, Max	52, 130	52, 117

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.3.1 Descriptive statistics of Physical Examination (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Body weight (kg)	Cycle-01	Day 15	CFB	n	28	22
				Mean (SD)	-1.8 (2.13)	-1.4 (2.18)
				Median	-1.7	-1.4
				Min, Max	-6, 4	-6, 3
		Day 22	Observed	n	26	23
				Mean (SD)	75.1 (18.50)	70.4 (13.33)
				Median	68.7	69.5
				Min, Max	51, 127	54, 105
			CFB	n	26	23
				Mean (SD)	-2.2 (2.68)	-1.0 (2.71)
				Median	-2.9	-1.2
				Min, Max	-6, 4	-7, 6
	Cycle-02	Day 01	Observed	n	26	29
				Mean (SD)	75.0 (17.62)	70.7 (15.65)
				Median	68.7	67.0
				Min, Max	56, 124	52, 117
			CFB	n	26	29
				Mean (SD)	-3.3 (3.01)	-1.1 (3.03)
				Median	-3.0	-1.0
				Min, Max	-11, 5	-7, 9
		Day 08	Observed	n	24	25
				Mean (SD)	74.8 (17.50)	71.0 (14.82)
				Median	68.2	68.0
				Min, Max	57, 125	52, 109

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.3.1 Descriptive statistics of Physical Examination (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Body weight (kg)	Cycle-02	Day 08	CFB	n	24	25
				Mean (SD)	-4.2 (3.52)	-1.7 (3.59)
				Median	-4.6	-1.2
				Min, Max	-13, 4	-12, 7
		Day 15	Observed	n	24	13
				Mean (SD)	74.1 (17.98)	67.2 (12.29)
				Median	68.0	67.0
				Min, Max	55, 125	53, 97
			CFB	n	24	13
				Mean (SD)	-4.6 (4.27)	-2.4 (2.85)
				Median	-5.2	-2.0
				Min, Max	-13, 4	-7, 3
		Day 22	Observed	n	17	15
				Mean (SD)	70.1 (11.15)	71.3 (13.22)
				Median	68.5	68.8
				Min, Max	55, 87	55, 99
			CFB	n	17	15
				Mean (SD)	-4.3 (3.64)	-3.2 (2.90)
				Median	-5.2	-3.1
				Min, Max	-10, 4	-8, 3
	Cycle-03	Day 01	Observed	n	15	11
				Mean (SD)	70.8 (19.22)	72.3 (15.84)
				Median	63.5	69.0
				Min, Max	55, 124	54, 99

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.3.1 Descriptive statistics of Physical Examination (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Body weight (kg)	Cycle-03	Day 01	CFB	n	15	11
				Mean (SD)	-4.5 (4.09)	-3.8 (3.68)
				Median	-3.9	-2.5
				Min, Max	-11, 5	-10, 1
		Day 08	Observed	n	13	10
				Mean (SD)	72.3 (20.72)	71.4 (15.13)
				Median	68.7	67.7
				Min, Max	53, 125	55, 99
			CFB	n	13	10
				Mean (SD)	-5.6 (4.61)	-1.0 (4.35)
				Median	-5.0	-1.6
				Min, Max	-12, 4	-9, 7
		Day 15	Observed	n	13	6
				Mean (SD)	71.8 (20.06)	66.4 (14.37)
				Median	68.4	62.5
				Min, Max	53, 122	55, 94
			CFB	n	13	6
				Mean (SD)	-5.6 (4.79)	-3.1 (6.04)
				Median	-6.6	-3.0
				Min, Max	-12, 3	-13, 6
		Day 22	Observed	n	12	8
				Mean (SD)	70.3 (20.90)	70.2 (14.81)
				Median	62.0	65.7
				Min, Max	52, 121	56, 94

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.3.1 Descriptive statistics of Physical Examination (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Body weight (kg)	Cycle-03	Day 22	CFB	n	12	8
				Mean (SD)	-5.7 (4.99)	-3.4 (3.67)
				Median	-6.0	-2.9
				Min, Max	-14, 5	-11, 0
	Cycle-04	Day 01	Observed	n	14	11
				Mean (SD)	71.9 (19.14)	73.7 (16.20)
				Median	65.1	67.0
				Min, Max	54, 123	56, 100
			CFB	n	14	11
				Mean (SD)	-4.3 (5.62)	-1.0 (4.35)
				Median	-4.5	-0.6
				Min, Max	-12, 11	-7, 8
		Day 08	Observed	n	8	7
				Mean (SD)	64.0 (12.41)	69.7 (17.35)
				Median	61.2	66.8
				Min, Max	54, 92	52, 100
			CFB	n	8	7
				Mean (SD)	-1.8 (7.29)	-2.3 (3.54)
				Median	-2.2	-0.6
				Min, Max	-14, 12	-7, 2
		Day 15	Observed	n	2	3
				Mean (SD)	79.8 (16.62)	59.0 (7.02)
				Median	79.8	57.0
				Min, Max	68, 92	53, 67

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.3.1 Descriptive statistics of Physical Examination (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Body weight (kg)	Cycle-04	Day 15	CFB	n	2	3
				Mean (SD)	0.8 (0.35)	-3.2 (3.23)
				Median	0.8	-3.7
				Min, Max	1, 1	-6, 0
		Day 22	Observed	n	1	3
				Mean (SD)	89.5 (.)	59.8 (7.50)
				Median	89.5	58.8
				Min, Max	90, 90	53, 68
			CFB	n	1	3
				Mean (SD)	-1.5 (.)	-2.5 (3.91)
				Median	-1.5	-4.1
				Min, Max	-2, -2	-5, 2
	End of Treatment	EOT	Observed	n	32	29
				Mean (SD)	73.3 (17.79)	69.2 (13.52)
				Median	68.8	67.0
				Min, Max	51, 121	54, 108
			CFB	n	32	29
				Mean (SD)	-4.7 (5.23)	-1.8 (4.46)
				Median	-3.9	-1.0
				Min, Max	-14, 12	-13, 5

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.3.1 Descriptive statistics of Physical Examination (Safety Population)

Parameters	Cycles	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Body height (cm)	Screening	Screening	Observed	n	32	36
				Mean (SD)	171.8 (7.52)	173.8 (7.53)
				Median	170.5	173.5
				Min, Max	159, 192	158, 189
BSA (m²)	Screening	Screening	Observed	n	32	36
				Mean (SD)	1.9 (0.25)	1.8 (0.21)
				Median	1.9	1.8
				Min, Max	2, 3	2, 2

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.4.1 Descriptive statistics of Karnofsky Performance Status (Safety Population)

Parameter	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Karnofsky Performance Status	Screening	Observed	n	32	36
			Mean (SD)	90.6 (7.59)	89.2 (8.74)
			Median	90.0	90.0
			Min, Max	70, 100	70, 100
	Chemocycle 01	Observed	n	30	36
			Mean (SD)	90.0 (7.43)	90.3 (8.78)
			Median	90.0	90.0
			Min, Max	70, 100	70, 100
		CFB	n	30	36
			Mean (SD)	-0.7 (4.50)	1.1 (5.75)
			Median	0.0	0.0
			Min, Max	-10, 10	-20, 20
	Chemocycle 02	Observed	n	26	27
			Mean (SD)	87.3 (10.41)	87.0 (9.53)
			Median	90.0	90.0
			Min, Max	70, 100	70, 100
		CFB	n	26	27
			Mean (SD)	-3.5 (6.89)	-3.3 (7.34)
			Median	0.0	0.0
			Min, Max	-20, 10	-20, 20

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
Program: t14-3-4-01-karnofsky.sas
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Table 14.3.4.1 Descriptive statistics of Karnofsky Performance Status (Safety Population)

Parameter	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Karnofsky Performance Status	Chemocycle 03	Observed	n	16	11
			Mean (SD)	80.9 (10.68)	73.6 (11.20)
			Median	80.0	80.0
			Min, Max	60, 100	50, 90
		CFB	n	16	11
			Mean (SD)	-7.8 (11.69)	-12.7 (11.04)
			Median	-10.0	-10.0
			Min, Max	-30, 10	-30, 0
	Chemocycle 04	Observed	n	14	11
			Mean (SD)	80.0 (11.77)	81.8 (9.82)
			Median	80.0	80.0
			Min, Max	50, 90	70, 100
		CFB	n	14	11
			Mean (SD)	-7.9 (8.93)	-4.5 (12.93)
			Median	-10.0	0.0
			Min, Max	-30, 0	-20, 20

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.4.1 Descriptive statistics of Karnofsky Performance Status (Safety Population)

Parameter	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Karnofsky Performance Status	End of Treatment	Observed	n	30	31
			Mean (SD)	82.3 (12.51)	78.7 (22.62)
			Median	85.0	80.0
			Min, Max	50, 100	10, 100
		CFB	n	30	31
			Mean (SD)	-8.0 (12.15)	-10.3 (20.25)
			Median	-5.0	0.0
			Min, Max	-40, 10	-70, 20
Karnofsky Performance Status, Categorical	Screening	70%	n (%)	1 (3.1)	2 (5.6)
		80%	n (%)	5 (15.6)	9 (25.0)
		90%	n (%)	17 (53.1)	15 (41.7)
		100%	n (%)	9 (28.1)	10 (27.8)
		Total	n (%)	32 (100.0)	36 (100.0)
	Chemocycle 01	70%	n (%)	1 (3.1)	1 (2.8)
		80%	n (%)	5 (15.6)	10 (27.8)
		90%	n (%)	17 (53.1)	12 (33.3)
		100%	n (%)	7 (21.9)	13 (36.1)
		Missing	n (%)	2 (6.3)	0 (0.0)
		Total	n (%)	32 (100.0)	36 (100.0)

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.4.1 Descriptive statistics of Karnofsky Performance Status (Safety Population)

Parameter	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Karnofsky Performance Status, Categorical	Chemocycle 02	70%	n (%)	3 (9.4)	2 (5.6)
		80%	n (%)	9 (28.1)	11 (30.6)
		90%	n (%)	6 (18.8)	7 (19.4)
		100%	n (%)	8 (25.0)	7 (19.4)
		Missing	n (%)	6 (18.8)	9 (25.0)
		Total	n (%)	32 (100.0)	36 (100.0)
	Chemocycle 03	50%	n (%)	0 (0.0)	1 (2.8)
		60%	n (%)	1 (3.1)	1 (2.8)
		70%	n (%)	4 (12.5)	3 (8.3)
		80%	n (%)	4 (12.5)	5 (13.9)
		85%	n (%)	1 (3.1)	0 (0.0)
		90%	n (%)	5 (15.6)	1 (2.8)
		100%	n (%)	1 (3.1)	0 (0.0)
		Missing	n (%)	16 (50.0)	25 (69.4)
		Total	n (%)	32 (100.0)	36 (100.0)
	Chemocycle 04	50%	n (%)	1 (3.1)	0 (0.0)
		70%	n (%)	3 (9.4)	3 (8.3)
		80%	n (%)	4 (12.5)	4 (11.1)
		90%	n (%)	6 (18.8)	3 (8.3)
		100%	n (%)	0 (0.0)	1 (2.8)
		Missing	n (%)	18 (56.3)	25 (69.4)
		Total	n (%)	32 (100.0)	36 (100.0)

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.4.1 Descriptive statistics of Karnofsky Performance Status (Safety Population)

Parameter	Visit	Type	Statistics	Cetuximab (N=32)	Control (N=36)
Karnofsky Performance Status, Categorical	End of Treatment	10%	n (%)	0 (0.0)	1 (2.8)
		30%	n (%)	0 (0.0)	1 (2.8)
		40%	n (%)	0 (0.0)	2 (5.6)
		50%	n (%)	1 (3.1)	0 (0.0)
		60%	n (%)	3 (9.4)	1 (2.8)
		70%	n (%)	2 (6.3)	5 (13.9)
		80%	n (%)	9 (28.1)	6 (16.7)
		90%	n (%)	12 (37.5)	7 (19.4)
		100%	n (%)	3 (9.4)	8 (22.2)
		Missing	n (%)	2 (6.3)	5 (13.9)
		Total	n (%)	32 (100.0)	36 (100.0)

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Global health status	Screening	Observed	n	31	29
			Mean (SD)	61.8 (20.84)	56.0 (24.89)
			Median	66.7	50.0
			Min, Max	16.7, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	23	24
			Mean (SD)	52.9 (22.28)	54.5 (22.25)
			Median	58.3	62.5
			Min, Max	16.7, 83.3	0.0, 100.0
		CFB	n	23	22
			Mean (SD)	-8.3 (15.69)	-2.3 (23.60)
			Median	-8.3	0.0
			Min, Max	-33.3, 25.0	-50.0, 66.7
	End of treatment	Observed	n	23	26
			Mean (SD)	51.4 (25.95)	50.3 (23.51)
			Median	50.0	50.0
			Min, Max	16.7, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	-9.1 (23.96)	-4.7 (33.41)
			Median	0.0	0.0
			Min, Max	-66.7, 50.0	-66.7, 66.7

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Physical functioning	Screening	Observed	n	31	29
			Mean (SD)	82.0 (17.43)	79.0 (20.14)
			Median	86.7	86.7
			Min, Max	46.7, 100.0	26.7, 100.0
	Re-evaluation	Observed	n	24	26
			Mean (SD)	73.1 (23.38)	70.8 (25.79)
			Median	80.0	70.0
			Min, Max	13.3, 100.0	20.0, 100.0
		CFB	n	24	24
			Mean (SD)	-9.8 (23.01)	-9.2 (21.70)
			Median	-5.8	0.0
			Min, Max	-66.7, 16.7	-53.3, 33.3
	End of treatment	Observed	n	23	26
			Mean (SD)	60.3 (30.52)	68.2 (23.42)
			Median	60.0	73.3
			Min, Max	6.7, 100.0	20.0, 100.0
		CFB	n	23	23
			Mean (SD)	-19.2 (27.34)	-13.0 (24.66)
			Median	-13.3	-13.3
			Min, Max	-80.0, 33.3	-60.0, 33.3

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.

NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.

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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Role functioning	Screening	Observed	n	31	29
			Mean (SD)	72.6 (28.72)	70.1 (30.01)
			Median	83.3	66.7
			Min, Max	16.7, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	23	25
			Mean (SD)	55.1 (35.33)	60.0 (35.68)
			Median	66.7	66.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	-18.1 (34.05)	-8.0 (26.53)
			Median	-16.7	0.0
			Min, Max	-100.0, 66.7	-83.3, 50.0
	End of treatment	Observed	n	22	26
			Mean (SD)	45.5 (34.57)	52.6 (29.70)
			Median	33.3	50.0
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	22	23
			Mean (SD)	-22.0 (32.69)	-18.1 (28.39)
			Median	-16.7	-16.7
			Min, Max	-66.7, 33.3	-66.7, 33.3

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.

NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.

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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Emotional functioning	Screening	Observed	n	31	29
			Mean (SD)	66.4 (25.32)	64.9 (22.20)
			Median	66.7	66.7
			Min, Max	0.0, 100.0	8.3, 100.0
	Re-evaluation	Observed	n	24	24
			Mean (SD)	67.9 (23.20)	68.4 (28.34)
			Median	66.7	75.0
			Min, Max	25.0, 100.0	16.7, 100.0
		CFB	n	24	22
			Mean (SD)	-0.5 (23.34)	8.3 (22.86)
			Median	0.0	8.3
			Min, Max	-41.7, 50.0	-25.0, 50.0
	End of treatment	Observed	n	23	26
			Mean (SD)	59.8 (25.33)	64.5 (27.25)
			Median	58.3	62.5
			Min, Max	25.0, 100.0	16.7, 100.0
		CFB	n	23	23
			Mean (SD)	-9.4 (25.54)	3.4 (27.52)
			Median	0.0	0.0
			Min, Max	-66.7, 41.7	-38.9, 58.3

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.

NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/problems depending on the item.

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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Cognitive functioning	Screening	Observed	n	31	29
			Mean (SD)	86.6 (18.47)	84.5 (17.21)
			Median	100.0	83.3
			Min, Max	33.3, 100.0	50.0, 100.0
	Re-evaluation	Observed	n	24	24
			Mean (SD)	83.3 (20.26)	80.6 (24.90)
			Median	83.3	83.3
			Min, Max	33.3, 100.0	16.7, 100.0
		CFB	n	24	22
			Mean (SD)	-3.5 (17.01)	-2.3 (18.75)
			Median	0.0	0.0
			Min, Max	-33.3, 33.3	-50.0, 33.3
	End of treatment	Observed	n	23	26
			Mean (SD)	73.9 (26.03)	76.3 (22.69)
			Median	83.3	83.3
			Min, Max	33.3, 100.0	16.7, 100.0
		CFB	n	23	23
			Mean (SD)	-13.8 (24.95)	-7.2 (21.80)
			Median	-16.7	0.0
			Min, Max	-66.7, 33.3	-66.7, 16.7

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Social functioning	Screening	Observed	n	31	29
			Mean (SD)	70.4 (28.45)	68.4 (32.53)
			Median	66.7	66.7
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	23	24
			Mean (SD)	66.7 (32.57)	61.1 (32.48)
			Median	66.7	66.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	22
			Mean (SD)	-4.3 (36.31)	0.0 (36.73)
			Median	0.0	0.0
			Min, Max	-66.7, 100.0	-66.7, 66.7
	End of treatment	Observed	n	22	26
			Mean (SD)	56.1 (34.71)	61.5 (34.89)
			Median	58.3	66.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	22	23
			Mean (SD)	-12.1 (37.86)	-3.6 (42.03)
			Median	-16.7	0.0
			Min, Max	-100.0, 100.0	-100.0, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Fatigue	Screening	Observed	n	31	29
			Mean (SD)	29.7 (23.90)	35.8 (28.08)
			Median	33.3	33.3
			Min, Max	0.0, 88.9	0.0, 100.0
	Re-evaluation	Observed	n	24	26
			Mean (SD)	48.1 (24.88)	44.4 (31.11)
			Median	44.4	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	24
			Mean (SD)	19.9 (19.10)	5.3 (25.56)
			Median	22.2	8.3
			Min, Max	-11.1, 55.6	-55.6, 55.6
	End of treatment	Observed	n	23	26
			Mean (SD)	52.7 (31.11)	48.5 (24.92)
			Median	55.6	52.8
			Min, Max	0.0, 88.9	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	21.7 (24.50)	15.5 (33.92)
			Median	22.2	11.1
			Min, Max	-33.3, 66.7	-55.6, 72.2

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Nausea and vomiting	Screening	Observed	n	31	29
			Mean (SD)	11.3 (19.90)	7.5 (17.59)
			Median	0.0	0.0
			Min, Max	0.0, 66.7	0.0, 66.7
	Re-evaluation	Observed	n	24	26
			Mean (SD)	25.0 (30.69)	24.4 (32.40)
			Median	16.7	16.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	24
			Mean (SD)	18.1 (28.20)	16.0 (26.68)
			Median	16.7	0.0
			Min, Max	-16.7, 83.3	-16.7, 83.3
	End of treatment	Observed	n	23	26
			Mean (SD)	31.9 (32.53)	25.6 (33.41)
			Median	16.7	16.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	23.2 (30.46)	21.7 (29.06)
			Median	16.7	16.7
			Min, Max	-16.7, 100.0	-16.7, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Pain	Screening	Observed	n	31	30
			Mean (SD)	32.8 (30.88)	28.3 (30.37)
			Median	33.3	16.7
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	26
			Mean (SD)	33.3 (34.40)	27.6 (30.53)
			Median	33.3	16.7
			Min, Max	0.0, 100.0	0.0, 83.3
		CFB	n	24	25
			Mean (SD)	3.5 (26.00)	0.7 (27.42)
			Median	0.0	0.0
			Min, Max	-33.3, 83.3	-33.3, 83.3
	End of treatment	Observed	n	23	26
			Mean (SD)	35.5 (32.30)	37.2 (36.61)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	24
			Mean (SD)	-2.2 (27.66)	2.1 (37.85)
			Median	0.0	0.0
			Min, Max	-50.0, 66.7	-66.7, 83.3

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Dyspnoea	Screening	Observed	n	31	29
			Mean (SD)	17.2 (29.65)	17.2 (27.63)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	26
			Mean (SD)	20.8 (27.47)	15.4 (27.05)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 66.7
		CFB	n	24	24
			Mean (SD)	9.7 (28.62)	-2.8 (32.48)
			Median	0.0	0.0
			Min, Max	-66.7, 66.7	-100.0, 66.7
	End of treatment	Observed	n	23	26
			Mean (SD)	24.6 (33.66)	29.5 (28.79)
			Median	0.0	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	10.1 (23.43)	11.6 (39.71)
			Median	0.0	0.0
			Min, Max	-33.3, 66.7	-66.7, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/problems depending on the item.
Program: t14-3-5-1-qol30.sas
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Insomnia	Screening	Observed	n	31	29
			Mean (SD)	30.1 (30.25)	28.7 (35.33)
			Median	33.3	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	26
			Mean (SD)	33.3 (34.05)	42.3 (37.19)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	24
			Mean (SD)	4.2 (38.46)	15.3 (46.08)
			Median	0.0	0.0
			Min, Max	-66.7, 100.0	-66.7, 100.0
	End of treatment	Observed	n	23	26
			Mean (SD)	21.7 (25.84)	41.0 (35.66)
			Median	0.0	33.3
			Min, Max	0.0, 66.7	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	-10.1 (35.44)	14.5 (41.23)
			Median	0.0	0.0
			Min, Max	-66.7, 66.7	-66.7, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Appetite loss	Screening	Observed	n	31	29
			Mean (SD)	22.6 (29.04)	32.2 (37.25)
			Median	0.0	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	25
			Mean (SD)	43.1 (34.72)	46.7 (41.94)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	23
			Mean (SD)	19.4 (48.07)	20.3 (43.51)
			Median	33.3	0.0
			Min, Max	-100.0, 100.0	-66.7, 100.0
	End of treatment	Observed	n	23	26
			Mean (SD)	50.7 (40.04)	52.6 (41.28)
			Median	33.3	66.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	23.2 (43.15)	31.9 (50.73)
			Median	0.0	33.3
			Min, Max	-33.3, 100.0	-100.0, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Constipation	Screening	Observed	n	31	29
			Mean (SD)	15.1 (30.84)	18.4 (31.61)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	24
			Mean (SD)	33.3 (34.05)	31.9 (34.72)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	22
			Mean (SD)	20.8 (42.63)	16.7 (43.34)
			Median	0.0	0.0
			Min, Max	-100.0, 100.0	-100.0, 100.0
	End of treatment	Observed	n	23	26
			Mean (SD)	26.1 (33.27)	23.1 (29.47)
			Median	0.0	16.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	13.0 (29.71)	-1.4 (39.54)
			Median	0.0	0.0
			Min, Max	-33.3, 100.0	-100.0, 66.7

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Diarrhoea	Screening	Observed	n	31	29
			Mean (SD)	5.4 (19.43)	6.9 (13.74)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 33.3
	Re-evaluation	Observed	n	24	24
			Mean (SD)	11.1 (25.38)	13.9 (25.85)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	22
			Mean (SD)	9.7 (26.88)	6.1 (16.70)
			Median	0.0	0.0
			Min, Max	-33.3, 100.0	0.0, 66.7
	End of treatment	Observed	n	22	26
			Mean (SD)	16.7 (22.42)	9.0 (22.23)
			Median	0.0	0.0
			Min, Max	0.0, 66.7	0.0, 100.0
		CFB	n	22	23
			Mean (SD)	15.2 (24.62)	2.9 (19.88)
			Median	0.0	0.0
			Min, Max	-33.3, 66.7	-33.3, 66.7

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.1 Descriptive statistics for EORTC QLQ-C30 global health status, functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Financial difficulties	Screening	Observed	n	31	29
			Mean (SD)	21.5 (33.94)	26.4 (34.94)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	24
			Mean (SD)	20.8 (30.79)	27.8 (36.34)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	22
			Mean (SD)	-1.4 (33.30)	-3.0 (27.04)
			Median	0.0	0.0
			Min, Max	-66.7, 100.0	-66.7, 66.7
	End of treatment	Observed	n	23	26
			Mean (SD)	26.1 (31.71)	25.6 (30.27)
			Median	0.0	16.7
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	0.0 (36.24)	-5.8 (38.47)
			Median	0.0	0.0
			Min, Max	-100.0, 66.7	-100.0, 33.3

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.

NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/problems depending on the item.

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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Eating	Screening	Observed	n	31	28
			Mean (SD)	37.9 (30.72)	45.2 (28.73)
			Median	33.3	58.3
			Min, Max	0.0, 91.7	0.0, 91.7
	Re-evaluation	Observed	n	24	24
			Mean (SD)	45.1 (28.33)	45.3 (27.35)
			Median	50.0	43.1
			Min, Max	0.0, 91.7	8.3, 83.3
		CFB	n	24	22
			Mean (SD)	9.0 (20.84)	0.5 (32.14)
			Median	8.3	4.2
			Min, Max	-33.3, 41.7	-58.3, 75.0
	End of treatment	Observed	n	23	26
			Mean (SD)	42.0 (28.15)	42.4 (26.87)
			Median	41.7	43.1
			Min, Max	0.0, 100.0	0.0, 91.7
		CFB	n	23	23
			Mean (SD)	4.0 (34.07)	1.9 (36.20)
			Median	0.0	0.0
			Min, Max	-50.0, 91.7	-75.0, 66.7

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Reflux	Screening	Observed	n	31	28
			Mean (SD)	21.0 (27.21)	21.4 (27.54)
			Median	16.7	16.7
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	22	25
			Mean (SD)	34.1 (34.30)	22.7 (28.82)
			Median	33.3	16.7
			Min, Max	0.0, 100.0	0.0, 83.3
		CFB	n	22	23
			Mean (SD)	17.4 (31.90)	0.7 (36.05)
			Median	8.3	0.0
			Min, Max	-33.3, 100.0	-100.0, 83.3
	End of treatment	Observed	n	23	26
			Mean (SD)	28.3 (27.26)	21.2 (26.90)
			Median	33.3	16.7
			Min, Max	0.0, 100.0	0.0, 83.3
		CFB	n	23	23
			Mean (SD)	11.6 (28.62)	-1.4 (35.86)
			Median	0.0	0.0
			Min, Max	-33.3, 66.7	-100.0, 66.7

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.

NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.

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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Pain	Screening	Observed	n	31	28
			Mean (SD)	25.8 (22.66)	31.5 (25.17)
			Median	22.2	27.8
			Min, Max	0.0, 77.8	0.0, 100.0
	Re-evaluation	Observed	n	23	25
			Mean (SD)	33.3 (30.70)	32.4 (25.84)
			Median	22.2	33.3
			Min, Max	0.0, 100.0	0.0, 88.9
		CFB	n	23	23
			Mean (SD)	9.7 (27.07)	1.7 (27.70)
			Median	0.0	0.0
			Min, Max	-22.2, 100.0	-55.6, 55.6
	End of treatment	Observed	n	23	26
			Mean (SD)	29.5 (24.98)	27.4 (27.26)
			Median	22.2	22.2
			Min, Max	0.0, 100.0	0.0, 88.9
		CFB	n	23	23
			Mean (SD)	2.9 (18.42)	-6.5 (35.24)
			Median	0.0	0.0
			Min, Max	-22.2, 44.4	-100.0, 55.6

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Trouble swallowing saliva	Screening	Observed	n	31	28
			Mean (SD)	33.3 (41.28)	16.7 (27.96)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	25
			Mean (SD)	29.2 (33.06)	32.0 (35.33)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	23
			Mean (SD)	-6.9 (41.68)	13.0 (34.44)
			Median	0.0	0.0
			Min, Max	-100.0, 66.7	-66.7, 66.7
	End of treatment	Observed	n	23	26
			Mean (SD)	31.9 (32.53)	26.9 (35.30)
			Median	33.3	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	-2.9 (41.33)	4.3 (30.66)
			Median	0.0	0.0
			Min, Max	-100.0, 66.7	-66.7, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Choked when swallowing	Screening	Observed	n	31	28
			Mean (SD)	18.3 (28.33)	17.9 (24.82)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 66.7
	Re-evaluation	Observed	n	24	24
			Mean (SD)	22.2 (30.56)	20.8 (25.66)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 66.7
		CFB	n	24	22
			Mean (SD)	5.6 (28.94)	6.1 (28.43)
			Median	0.0	0.0
			Min, Max	-66.7, 66.7	-66.7, 66.7
	End of treatment	Observed	n	23	26
			Mean (SD)	18.8 (22.08)	11.5 (20.96)
			Median	0.0	0.0
			Min, Max	0.0, 66.7	0.0, 66.7
		CFB	n	23	23
			Mean (SD)	4.3 (35.25)	-5.8 (29.56)
			Median	0.0	0.0
			Min, Max	-66.7, 66.7	-66.7, 66.7

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Dry mouth	Screening	Observed	n	31	27
			Mean (SD)	19.4 (26.91)	21.0 (30.87)
			Median	0.0	0.0
			Min, Max	0.0, 66.7	0.0, 100.0
	Re-evaluation	Observed	n	24	24
			Mean (SD)	33.3 (31.08)	33.3 (35.44)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	24	21
			Mean (SD)	18.1 (35.41)	4.8 (30.34)
			Median	0.0	0.0
			Min, Max	-33.3, 100.0	-66.7, 33.3
	End of treatment	Observed	n	23	26
			Mean (SD)	42.0 (36.54)	28.2 (32.24)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	22
			Mean (SD)	21.7 (38.41)	1.5 (41.76)
			Median	0.0	0.0
			Min, Max	-33.3, 100.0	-100.0, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Trouble with taste	Screening	Observed	n	31	27
			Mean (SD)	9.7 (21.42)	8.6 (14.89)
			Median	0.0	0.0
			Min, Max	0.0, 66.7	0.0, 33.3
	Re-evaluation	Observed	n	23	24
			Mean (SD)	43.5 (32.47)	29.2 (37.19)
			Median	33.3	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	22
			Mean (SD)	34.8 (32.53)	18.2 (38.11)
			Median	33.3	0.0
			Min, Max	0.0, 100.0	-33.3, 100.0
	End of treatment	Observed	n	23	26
			Mean (SD)	44.9 (40.96)	37.2 (40.36)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	22
			Mean (SD)	33.3 (46.06)	27.3 (39.36)
			Median	33.3	0.0
			Min, Max	-66.7, 100.0	-33.3, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.

NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.

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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Trouble with coughing	Screening	Observed	n	31	28
			Mean (SD)	21.5 (33.94)	15.5 (21.24)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 66.7
	Re-evaluation	Observed	n	23	25
			Mean (SD)	30.4 (33.20)	30.7 (34.59)
			Median	33.3	33.3
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	7.2 (38.87)	15.9 (28.19)
			Median	0.0	0.0
			Min, Max	-100.0, 66.7	-33.3, 66.7
	End of treatment	Observed	n	23	26
			Mean (SD)	23.2 (25.49)	29.5 (31.73)
			Median	33.3	33.3
			Min, Max	0.0, 66.7	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	-1.4 (34.05)	15.9 (28.19)
			Median	0.0	0.0
			Min, Max	-66.7, 66.7	-33.3, 100.0

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.

NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.

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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Trouble with coughing	Screening	Observed	n	31	28
			Mean (SD)	10.8 (23.39)	13.1 (33.13)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	23	25
			Mean (SD)	20.3 (24.08)	16.0 (29.06)
			Median	0.0	0.0
			Min, Max	0.0, 66.7	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	10.1 (32.47)	1.4 (21.27)
			Median	0.0	0.0
			Min, Max	-100.0, 66.7	-66.7, 33.3
	End of treatment	Observed	n	23	26
			Mean (SD)	17.4 (24.35)	16.7 (31.62)
			Median	0.0	0.0
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	10.1 (29.19)	0.0 (14.21)
			Median	0.0	0.0
			Min, Max	-66.7, 100.0	-33.3, 33.3

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
Program: t14-3-5-2-qol18.sas
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Table 14.3.5.2 Descriptive statistics for EORTC QLQ-OES18 functional and symptom scales (Safety Population)

Scale	Visit	Type	Statistic	Cetuximab (N= 32) N (%)	Control (N= 36) N (%)
Dysphagia (function scale)	Screening	Observed	n	30	28
			Mean (SD)	48.5 (32.16)	44.8 (31.64)
			Median	44.4	44.4
			Min, Max	0.0, 100.0	0.0, 100.0
	Re-evaluation	Observed	n	24	25
			Mean (SD)	54.6 (32.09)	47.6 (34.17)
			Median	61.1	44.4
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	23	23
			Mean (SD)	0.5 (30.24)	0.0 (24.85)
			Median	0.0	0.0
			Min, Max	-44.4, 66.7	-66.7, 55.6
	End of treatment	Observed	n	22	26
			Mean (SD)	44.9 (31.33)	44.0 (33.33)
			Median	38.9	38.9
			Min, Max	0.0, 100.0	0.0, 100.0
		CFB	n	22	23
			Mean (SD)	-10.1 (33.41)	0.0 (35.93)
			Median	-16.7	0.0
			Min, Max	-66.7, 55.6	-66.7, 55.6

Abbreviations: CFB = change from baseline, Min = minimum, Max = maximum, SD = standard deviation.
NOTE: The scores were scaled to 0-100, higher score representing higher level of QoL, higher level of functioning, or higher level of symptomatology/ problems depending on the item.
Program: t14-3-5-2-qol18.sas
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Table 14.3.6.1: Creatinine [mg/dl]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	68	32	36
	Mean	0.81	0.78	0.83
	SD	0.16	0.14	0.18
	Median	0.79	0.77	0.81
	Min; max	0.53; 1.35	0.53; 1.15	0.6; 1.35
	n – Normal	63 (92.6)	31 (96.9)	32 (88.9)
	n – abnormal, CNR	5 (7.4)	1 (3.1)	4 (11.1)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	61	28	33
	Mean	0.78	0.77	0.79
	SD	0.17	0.16	0.18
	Median	0.76	0.76	0.8
	Min, max	0.48; 1.35	0.5; 1.1	0.48; 1.35
	n – Normal	53 (86.9)	26 (92.9)	27 (81.8)
	n – abnormal, CNR	8 (13.1)	2 (7.1)	6 (18.2)
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	57	27	30
	Mean	0.79	0.75	0.83
	SD	0.23	0.19	0.26
	Median	0.76	0.75	0.79
	Min, max	0.38; 1.67	0.38; 1.27	0.44; 1.67
	n – Normal	45 (78.9)	21 (77.8)	24 (80.0)
	n – abnormal, CNR	11 (19.3)	6 (22.2)	5 (16.7)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (7.0)	0	1 (3.3)
Cycle 3 Day 1	n	28	16	12
	Mean	0.72	0.66	0.80
	SD	0.21	0.18	0.22
	Median	0.69	0.66	0.79
	Min, max	0.44; 1.42	0.44; 1.14	0.57; 1.42
	n – Normal	21 (77.8)	11 (68,8)	10 (83.3)
	n – abnormal, CNR	7 (25.0)	5 (31.3)	2 (16.7)
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	25	14	11
	Mean	0.77	0.67	0.89
	SD	0.27	0.25	0.26
	Median	0.78	0.63	0.81
	Min, max	0.43; 1.58	0.43; 1.37	0.6; 1.58
	n – Normal	17 (68.0)	8 (57.1)	9 (81.8)
	n – abnormal, CNR	7 (28.0)	5 (35.7)	2 (18.2)
	n – abnormal, CR	1 (4.0)	1 (7.1)	0
EOT	n	62	31	31
	Mean	0.86	0.80	0.92
	SD	0.33	0.32	0.34
	Median	0.80	0.72	0.81
	Min, max	0.36; 2	0.36; 2	0.37; 1.88
	n – Normal	45 (72.6)	23 (74.2)	22 (71.0)
	n – abnormal, CNR	15 (24.2)	7 (22.6)	8 (25.8)
	n – abnormal, CR	2 (3.2)	1 (3.2)	1 (3.2)

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.2: Bilirubine [mg/dl]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	66	31	35
	Mean	0.51	0.52	0.50
	SD	0.26	0.20	0.32
	Median	0.46	0.5	0.46
	Min; max	0.12; 1.81	0.2; 0.98	0.12; 1.81
	n – Normal	65 (98.5)	31 (100.0)	34 (97.1)
	n – abnormal, CNR	1 (1.5)	0	1 (2.9)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	58	28	30
	Mean	0.46	0.50	0.43
	SD	0.17	0.16	0.17
	Median	0.44	0.50	0.43
	Min, max	0.12; 0.87	0.21; 0.81	0.12; 0.87
	n – Normal	58 (100.0)	28 (100.0)	30 (100.0)
	n – abnormal, CNR	0	0	0
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	50	24	26
	Mean	0.39	0.38	0.39
	SD	0.19	0.15	0.22
	Median	0.35	0.35	0.35
	Min, max	0.12; 1.2	0.18; 0.85	0.12; 1.2
	n – Normal	48 (96.0)	23 (95.8)	25 (96.2)
	n – abnormal, CNR	2 (4.0)	1 (4.2)	1 (3.8)
	n – abnormal, CR	0	0	0
Cycle 3 Day 1	n	24	16	8
	Mean	0.39	0.40	0.36
	SD	0.19	0.20	0.17
	Median	0.35	0.34	0.37
	Min, max	0.12; 0.89	0.18; 0.89	0.12; 0.59
	n – Normal	24 (100.0)	16 (100.0)	8 (100.0)
	n – abnormal, CNR	0	0	0
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	25	14	11
	Mean	0.38	0.35	0.42
	SD	0.22	0.08	0.33
	Median	0.35	0.36	0.3
	Min, max	0.18; 1.3	0.22; 0.5	0.18; 1.3
	n – Normal	25 (100.0)	14 (100.0)	11 (100.0)
	n – abnormal, CNR	0	0	0
	n – abnormal, CR	0	0	0
EOT	n	58	28	30
	Mean	0.48	0.53	0.44
	SD	0.26	0.26	0.27
	Median	0.40	0.46	0.39
	Min, max	0.1; 1.47	0.23; 1.47	0.1; 1.2
	n – Normal	53 (91.4)	27 (96.4)	26 (86.7)
	n – abnormal, CNR	4 (6.9)	1 (3.6)	3 (10.0)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (1.7)	0	1 (3.3)

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.3: SGOT/AST [U/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	68	32	36
	Mean	21.81	24.00	19.86
	SD	8.88	11.08	5.83
	Median	19	20	19
	Min; max	9; 57	11; 57	9; 37
	n – Normal	61 (89.7)	26 (81.3)	35 (97.2)
	n – abnormal, CNR	6 (8.8)	5 (15.6)	1 (2.8)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (1.5)	1 (3.1)	0
Cycle 1 Day 1	n	62	29	33
	Mean	21.79	23.97	19.88
	SD	6.76	7.86	4.99
	Median	20.5	24	19
	Min, max	9; 40	11; 40	9; 31
	n – Normal	60 (96.8)	27 (93.1)	33 (100.0)
	n – abnormal, CNR	2 (3.2)	2 (6.9)	0
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	53	25	28
	Mean	19.65	21.80	20.14
	SD	10.71	7.95	5.13
	Median	17	20	20
	Min, max	5; 57	10; 37	11; 33
	n – Normal	51 (96.2)	23 (92.0)	28 (100.0)
	n – abnormal, CNR	2 (3.8)	2 (8.0)	0
	n – abnormal, CR	0	0	0
Cycle 3 Day 1	n	26	15	11
	Mean	20.31	22.00	18.00
	SD	9.67	11.93	4.94
	Median	17	16	18
	Min, max	8; 48	8; 48	12; 30
	n – Normal	23 (88.5)	12 (80.0)	11 (100.0)
	n – abnormal, CNR	3 (11.5)	3 (20.0)	0
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	25	14	11
	Mean	18.36	17.29	19.73
	SD	6.39	5.78	7.13
	Median	17	16.5	19
	Min, max	10; 32	10; 30	11; 32
	n – Normal	25 (100.0)	14 (100.0)	11 (100.0)
	n – abnormal, CNR	0	0	0
	n – abnormal, CR	0	0	0
EOT	n	59	29	30
	Mean	24.71	21.00	28.30
	SD	20.54	7.65	27.57
	Median	21	21	20.5
	Min, max	9; 162	9; 42	11; 162
	n – Normal	53 (89.8)	27 (93.1)	26 (86.7)
	n – abnormal, CNR	6 (10.2)	2 (6.9)	4 (13.3)
	n – abnormal, CR	0	0	0

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.4: SGPT/ALT [U/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	68	32	36
	Mean	21.96	25.56	18.75
	SD	13.70	16.92	9.14
	Median	17.5	17.5	17
	Min; max	5; 68	5; 68	8; 50
	n – Normal	62 (91.2)	26 (81.3)	36 (100.0)
	n – abnormal, CNR	5 (7.4)	5 (15.6)	0
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (1.5)	1 (3.1)	0
Cycle 1 Day 1	n	61	28	33
	Mean	24.82	31.86	18.85
	SD	15.27	18.65	7.98
	Median	21	24	17
	Min, max	8; 69	11; 69	8; 39
	n – Normal	52 (85.2)	19 (67.9)	33 (100.0)
	n – abnormal, CNR	9 (14.8)	9 (32.1)	0
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	52	24	28
	Mean	19.65	22.92	16.86
	SD	10.71	12.97	7.46
	Median	17	21	17
	Min, max	5; 57	6; 57	5; 34
	n – Normal	48 (92.3)	20 (83.3)	28 (100.0)
	n – abnormal, CNR	4 (7.7)	4 (16.7)	0
	n – abnormal, CR	0	0	0
Cycle 3 Day 1	n	26	15	11
	Mean	17.38	20.20	13.55
	SD	11.28	13.63	5.43
	Median	13	18	12
	Min, max	6; 57	6; 57	6; 24
	n – Normal	22 (84.6)	11 (73.3)	11 (100.0)
	n – abnormal, CNR	4 (15.4)	4 (26.7)	0
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	25	14	11
	Mean	14.28	14.21	14.36
	SD	5.91	5.70	6.44
	Median	12	12.5	12
	Min, max	6; 28	6; 22	6; 28
	n – Normal	23 (92.0)	12 (85.7)	11 (100.0)
	n – abnormal, CNR	2 (8.0)	2 (14.3)	0
	n – abnormal, CR	0	0	0
EOT	n	59	28	31
	Mean	21.73	20.25	23.06
	SD	15.75	10.62	19.35
	Median	18	20	18
	Min, max	5; 92	6; 51	5; 92
	n – Normal	53 (89.8)	25 (89.3)	28 (90.3)
	n – abnormal, CNR	6 (10.2)	3 (10.7)	3 (9.7)
	n – abnormal, CR	0	0	0

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.5: LDH [U/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	63	30	33
	Mean	191.03	191.67	190.45
	SD	50.33	41.48	57.85
	Median	186	191.5	180
	Min; max	91; 364	96; 168	91; 364
	n – Normal	56 (88.9)	29 (96.7)	27 (81.8)
	n – abnormal, CNR	7 (11.1)	1 (3.3)	6 (18.2)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	61	28	33
	Mean	186.28	189.54	183.52
	SD	49.58	42.75	55.23
	Median	182	183.5	176
	Min, max	91; 377	96; 279	91; 377
	n – Normal	54 (88.5)	25 (89.3)	29 (87.9)
	n – abnormal, CNR	6 (9.8)	3 (10.7)	3 (9.1)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (1.6)	0	1 (3.0)
Cycle 2 Day 1	n	51	24	27
	Mean	191.39	197.33	167.22
	SD	44.19	43.91	40.09
	Median	175	203	166
	Min, max	85; 279	113; 279	85; 235
	n – Normal	49 (96.1)	22 (91.7)	27 (100.0)
	n – abnormal, CNR	2 (3.9)	2 (8.3)	0
	n – abnormal, CR	0	0	0
Cycle 3 Day 1	n	24	14	10
	Mean	199.08	205.93	189.50
	SD	58.10	39.94	78.40
	Median	190	204	145.5
	Min, max	126; 351	148; 281	126; 351
	n – Normal	19 (79.2)	12 (85.7)	7 (70.0)
	n – abnormal, CNR	5 (20.8)	2 (14.3)	3 (30.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	25	14	11
	Mean	179.92	190.93	165.91
	SD	47.41	56.44	29.45
	Median	170	192.5	157
	Min, max	103; 310	103; 310	129; 221
	n – Normal	22 (88.0)	12 (85.7)	10 (90.9)
	n – abnormal, CNR	3 (12.0)	2 (14.3)	1 (9.1)
	n – abnormal, CR	0	0	0
EOT	n	54	25	29
	Mean	189.02	205.36	191.69
	SD	56.30	45.08	64.56
	Median	197.5	201	194
	Min, max	71; 333	103; 297	71; 333
	n – Normal	45 (83.3)	21 (84.0)	24 (82.8)
	n – abnormal, CNR	9 (16.7)	4 (16.0)	5 (17.2)
	n – abnormal, CR	0	0	0

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.6: Alkaline Phosphatase [U/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	66	31	35
	Mean	80.03	78.26	81.60
	SD	25.92	26.73	25.47
	Median	72.5	72	76
	Min; max	53; 163	53; 161	53; 163
	n – Normal	58 (87.9)	27 (87.2)	31 (88.6)
	n – abnormal, CNR	8 (21.1)	4 (12.9)	4 (11.4)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	59	28	31
	Mean	81.12	78.21	83.74
	SD	30.20	27.25	32.87
	Median	72	68.5	73
	Min, max	52; 197	52; 152	52; 197
	n – Normal	52 (88.1)	25 (89.3)	27 (87.1)
	n – abnormal, CNR	7 (11.9)	3 (10.7)	4 (12.9)
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	51	25	26
	Mean	80.59	84.08	77.23
	SD	29.07	30.92	27.36
	Median	73	73	69
	Min, max	51; 198	58; 198	51; 168
	n – Normal	46 (90.2)	23 (92.0)	23 (88.5)
	n – abnormal, CNR	5 (9.8)	2 (8.0)	3 (11.5)
	n – abnormal, CR	0	0	0
Cycle 3 Day 1	n	25	15	10
	Mean	92.00	93.67	89.50
	SD	42.93	50.52	30.52
	Median	79	79	78.5
	Min, max	54; 266	54; 266	64; 153
	n – Normal	21 (84.0)	13 (86.7	8 (80.0)
	n – abnormal, CNR	4 (16.0)	2 (13.3)	2 (20.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	24	13	11
	Mean	88.58	81.69	96.73
	SD	31.34	24.05	37.83
	Median	77	73	84
	Min, max	56; 178	56; 137	58; 178
	n – Normal	20 (83.3)	12 (92.3)	8 (72.7)
	n – abnormal, CNR	4 (16.7)	1 (7.7)	3 (27.3)
	n – abnormal, CR	0	0	0
EOT	n	53	25	28
	Mean	94.36	89.64	98.57
	SD	57.81	58.41	58.01
	Median	76	76	75
	Min, max	48; 351	48; 351	51; 326
	n – Normal	44 (83.0)	22 (88.0)	22 (78.6)
	n – abnormal, CNR	8 (15.1)	3 (12.0)	5 (17.9)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (18.9)	0	1 (3.6)

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.7: Sodium [mmol/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	67	31	36
	Mean	138.03	137.97	138.09
	SD	5.20	6.82	3.33
	Median	139	139	139
	Min; max	107; 147	107; 147	131; 144
	n – Normal	59 (88.1)	28 (90.3)	31 (86.1)
	n – abnormal, CNR	8 (11.9)	3 (9.7)	5 (13.9)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	63	30	33
	Mean	138.24	138.73	137.79
	SD	3.62	4.27	2.90
	Median	138	138	138
	Min, max	127; 147	127; 147	131; 143
	n – Normal	54 (85.7)	25 (83.3)	29 (87.9)
	n – abnormal, CNR	9 (14.3)	5 (16.7)	4 (12.1)
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	56	26	30
	Mean	137.50	137.65	137.36
	SD	3.73	4.02	3.53
	Median	138	139	137.5
	Min, max	128; 144	131; 143	128; 144
	n – Normal	43 (76.8)	18 (69.2)	25 (83.3)
	n – abnormal, CNR	12 (21.4)	8 (30.8)	4 (13.3)
	n – abnormal, CR	1 (1.8)	0	1 (3.3)
Cycle 3 Day 1	n	28	16	12
	Mean	136.76	136.69	136.87
	SD	4.40	4.98	3.70
	Median	138	138.5	137.5
	Min, max	126; 143	126; 143	129; 142
	n – Normal	20 (71.4)	11 (68.8)	9 (75.0)
	n – abnormal, CNR	7 (25.0)	4 (25.0)	3 (25.0)
	n – abnormal, CR	1 (3.6)	1 (6.3)	0
Cycle 4 Day 1	n	25	14	11
	Mean	137.20	136.86	137.65
	SD	3.94	4.19	3.76
	Median	138	137	139
	Min, max	127; 145	127; 145	129; 141
	n – Normal	19 (76.0)	11 (78.6)	8 (72.7)
	n – abnormal, CNR	6 (24.0)	3 (21.4)	3 (27.3)
	n – abnormal, CR	0	0	0
EOT	n	64	31	33
	Mean	136.86	136.39	137.31
	SD	3.62	3.76	3.48
	Median	137.5	137	138
	Min, max	124; 144	124; 142	129; 144
	n – Normal	48 (75.0)	23 (74.2)	25 (75.8)
	n – abnormal, CNR	16 (25.0)	8 (25.8)	8 (24.2)
	n – abnormal, CR	0	0	0

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Table 14.3.6.8: Potassium [mmol/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	67	31	36
	Mean	4.17	4.13	4.21
	SD	0.43	0.37	0.48
	Median	4.14	4.1	4.2
	Min; max	3.0; 5.3	3.4; 4.9	3.0; 5.3
	n – Normal	60 (89.6)	28 (90.3)	32 (88.9)
	n – abnormal, CNR	7 (10.4)	3 (9.7)	4 (11.1)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	63	30	33
	Mean	4.13	4.12	4.15
	SD	0.49	0.46	0.51
	Median	4.11	4.09	4.2
	Min, max	3.1; 5.4	3.3; 5.4	3.1; 5.3
	n – Normal	53 (84.1)	24 (80.0)	29 (78.9)
	n – abnormal, CNR	8 (12.7)	5 (16.7)	3 (9.1)
	n – abnormal, CR	1 (1.6)	1 (3.3)	0
	Evaluation ND	1 (1.6)	0	1 (3.0)
Cycle 2 Day 1	n	56	26	30
	Mean	4.05	4.01	4.09
	SD	0.51	0.59	0.44
	Median	4.09	4.06	4.09
	Min, max	2.7; 5.2	2.7; 5.1	3.4; 5.2
	n – Normal	46 (82.1)	18 (69.2)	28 (93.3)
	n – abnormal, CNR	7 (12.5)	5 (19.2)	2 (26.7)
	n – abnormal, CR	3 (5.4)	3 (11.5)	0
Cycle 3 Day 1	n	28	16	12
	Mean	4.04	3.83	4.32
	SD	0.50	0.49	0.36
	Median	4.04	3.76	4.38
	Min, max	2.95; 4.9	2.95; 4.9	3.7; 4.9
	n – Normal	26 (92.9)	14 (87.5)	12 (100.0)
	n – abnormal, CNR	0	0	0
	n – abnormal, CR	2 (7.1)	2 (12.5)	0
Cycle 4 Day 1	n	25	14	11
	Mean	4.07	3.95	4.21
	SD	0.38	0.39	0.31
	Median	4.11	3.95	4.24
	Min, max	3.4; 4.7	3.4; 4.7	3.6; 4.7
	n – Normal	24 (96.0)	13 (92.9)	11 (100.0)
	n – abnormal, CNR	1 (4.0)	1 (7.1)	0
	n – abnormal, CR	0	0	0
EOT	n	64	31	33
	Mean	3.97	3.92	4.02
	SD	0.46	0.49	0.43
	Median	4	3.96	4.07
	Min, max	3.0; 4.9	3.0; 4.9	3.0; 4.74
	n – Normal	53 (82.8)	24 (77.4)	29 (87.9)
	n – abnormal, CNR	8 (12.5)	6 (19.4)	2 (6.1)
	n – abnormal, CR	3 (4.7)	1 (3.2)	2 (6.1)

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Table14.3.6.9: Calcium [mmol/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	67	31	36
	Mean	2.39	2.38	2.40
	SD	0.10	0.08	0.11
	Median	2.39	2.38	2.39
	Min; max	2.17; 2.8	2.17; 2.56	2.18; 2.8
	n – Normal	63 (94.0)	30 (96.8)	33 (91.7)
	n – abnormal, CNR	4 (6.0)	1 (3.2)	3 (8.3)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	63	30	33
	Mean	2.35	2.34	2.35
	SD	0.11	0.11	0.11
	Median	2.36	2.36	2.33
	Min, max	1.99; 2.6	1.99; 2.52	2.11; 2.6
	n – Normal	59 (93.7)	29 (96.7)	30 (90.9)
	n – abnormal, CNR	2 (3.2)	0	2 (6.1)
	n – abnormal, CR	1 (1.6)	1 (3.3)	0
	Evaluation ND	1 (1.6)	0	1 (3.0)
Cycle 2 Day 1	n	54	24	30
	Mean	2.29	2.28	2.29
	SD	0.15	0.11	0.17
	Median	2.3	2.305	2.3
	Min, max	1.64; 2.63	2.08; 2.49	1.64; 2.63
	n – Normal	46 (85.2)	20 (83.3)	26 (86.7)
	n – abnormal, CNR	8 (14.8)	4 (16.7)	4 (13.3)
	n – abnormal, CR	0	0	0
Cycle 3 Day 1	n	28	16	12
	Mean	2.26	2.22	2.31
	SD	0.12	0.13	0.10
	Median	2.27	2.255	2.3
	Min, max	1.96; 2.52	1.96; 2.43	2.17; 2.52
	n – Normal	23 (82.1)	12 (75.0)	11 (91.7)
	n – abnormal, CNR	5 (17.9)	4 (25.0)	1 (8.3)
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	25	14	11
	Mean	2.27	2.21	2.34
	SD	0.13	0.13	0.10
	Median	2.27	2.225	2.32
	Min, max	1.94; 2.55	1.94; 2.4	2.22; 2.55
	n – Normal	20 (80.0)	9 (64.3)	11 (100.0)
	n – abnormal, CNR	5 (20.0)	5 (35.7)	0
	n – abnormal, CR	0	0	0
EOT	n	62	30	32
	Mean	2.23	2.19	2.27
	SD	0.19	0.19	0.17
	Median	2.27	2.23	2.30
	Min, max	1.58; 2.6	1.58; 2.47	1.64; 2.6
	n – Normal	48 (77.4)	21 (70.0)	27 (84.4)
	n – abnormal, CNR	11 (17.7)	7 (23.3)	4 (12.5)
	n – abnormal, CR	2 (3.2)	2 (6.7)	0
	Evaluation ND	1 (1.6)	0	1 (3.1)

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Table 14.3.6.10: Magnesium [mmol/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	61	30	31
	Mean	0.82	0.81	0.82
	SD	0.09	0.09	0.10
	Median	0.83	0.82	0.84
	Min; max	0.53; 1.05	0.57; 0.94	0.53; 1.05
	n – Normal	54 (88.5)	27 (90.0)	27 (87.1)
	n – abnormal, CNR	5 (8.2)	2 (6.7)	3 (9.7)
	n – abnormal, CR	0	0	0
	Evaluation ND	2 (3.3)	1 (3.3)	1 (3.2)
Cycle 1 Day 1	n	55	26	29
	Mean	0.82	0.83	0.81
	SD	0.10	0.11	0.10
	Median	0.82	0.83	0.83
	Min, max	0.53; 1.11	0.63: 1.11	0.53; 0.98
	n – Normal	51 (92.7)	24 (92.3)	27 (93.1)
	n – abnormal, CNR	4 (7.3)	2 (7.7)	2 (6.9)
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	48	24	24
	Mean	0.71	0.66	0.77
	SD	0.12	0.10	0.10
	Median	0.72	0.68	0.78
	Min, max	0.43; 0.93	0.44; 0.84	0.43; 0.93
	n – Normal	32 (66.7)	11 (54.8)	21 (87.5)
	n – abnormal, CNR	15 (31.3)	12 (50.0)	3 (12.5)
	n – abnormal, CR	1 (2.1)	1 (4.2)	0
Cycle 3 Day 1	n	23	16	7
	Mean	0.66	0.60	0.79
	SD	0.12	0.08	0.11
	Median	0.64	0.63	0.79
	Min, max	0.37; 0.97	0.37; 0.68	0.62; 0.97
	n – Normal	9 (39.1)	3 (18.8)	6 (85.7)
	n – abnormal, CNR	12 (52.2)	11 (68.8)	1 (14.3)
	n – abnormal, CR	2 (8.7)	2 (12.5)	0
Cycle 4 Day 1	n	23	13	10
	Mean	0.66	0.61	0.72
	SD	0.10	0.08	0.09
	Median	0.66	0.62	0.71
	Min, max	0.5; 0.84	0.5; 0.75	0.56; 0.84
	n – Normal	11 (47.8)	3 (23.1)	8 (80.0)
	n – abnormal, CNR	11 (47.8)	9 (69.2)	2 (20.0)
	n – abnormal, CR	1 (4.3)	1 (7.7)	0
EOT	n	47	24	23
	Mean	0.67	0.63	0.72
	SD	0.13	0.14	0.11
	Median	0.67	0.63	0.73
	Min, max	0.34; 0.9	0.34; 0.9	0.43; 0.88
	n – Normal	25 (53.2)	8 (33.3)	17 (73.9)
	n – abnormal, CNR	20 (42.6)	14 (58.3)	6 (26.1)
	n – abnormal, CR	2 (4.3)	2 (8.3)	0

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Table 14.3.6.11: Gamma-GT [U/l]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	67	31	36
	Mean	42.99	52.55	34.75
	SD	40.88	56.48	16.30
	Median	34	36	31.5
	Min; max	7; 295	14; 295	7; 81
	n – Normal	57 (85.1)	25 (80.6)	32 (88.9)
	n – abnormal, CNR	10 (14.9)	6 (19.4)	4 (11.1)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	57	26	31
	Mean	49.32	59.73	40.58
	SD	57.79	78.30	30.88
	Median	34	34.5	33
	Min, max	12; 356	18; 256	12; 188
	n – Normal	46 (80.7)	20 (76.9)	26 (83.9)
	n – abnormal, CNR	8 (14.0)	5 (19.2)	3 (9.7)
	n – abnormal, CR	1 (1.8)	1 (3.8)	0
	Evaluation ND	2 (3.5)	0	2 (6.5)
Cycle 2 Day 1	n	52	25	27
	Mean	51.19	67.16	36.41
	SD	58.44	79.20	20.87
	Median	35	36	31
	Min, max	13; 293	16; 293	13; 84
	n – Normal	42 (80.8)	19 (76.0)	23 (85.2)
	n – abnormal, CNR	9 (17.3)	5 (20.0)	4 (14.8)
	n – abnormal, CR	1 (1.9)	1 (4.0)	0
Cycle 3 Day 1	n	24	15	9
	Mean	81.88	105.33	69.44
	SD	118.89	143.43	61.06
	Median	61.5	64	54
	Min, max	16; 609	16; 609	21; 217
	n – Normal	11 (45.8)	6 (40.0)	5 (55.6)
	n – abnormal, CNR	13 (54.2)	9 (60.0)	4 (44.4)
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	24	13	11
	Mean	75.92	64.31	89.64
	SD	72.11	51.36	91.72
	Median	61	59	63
	Min, max	24; 336	24; 221	24; 336
	n – Normal	12 (50.0)	7 (53.8)	5 (45.5)
	n – abnormal, CNR	12 (50.0)	6 (46.2)	6 (54.5)
	n – abnormal, CR	0	0	0
EOT	n	58	27	31
	Mean	77.14	71.93	81.68
	SD	78.40	55.36	94.74
	Median	56.5	60	47
	Min, max	13; 437	16; 165	13; 437
	n – Normal	32 (55.2)	13 (48.1)	19 (61.3)
	n – abnormal, CNR	25 (43.1)	14 (51.9)	11 (35.5)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (1.7)	0	1 (3.2)

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Table 14.3.6.12: Haemoglobin [g/dl]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	68	32	36
	Mean	13.54	13.64	13.46
	SD	1.58	1.32	1.78
	Median	13.6	13.6	13.4
	Min; max	9.1; 18.8	10.5; 16.4	9.1; 18.8
	n – normal	42 (61.8)	22 (68.8)	20 (55.6)
	n – abnormal, CNR	26 (38.2)	10 (31.3)	16 (44.4)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	63	30	33
	Mean	13.29	13.46	13.13
	SD	1.70	1.52	1.85
	Median	13.4	13.7	13.1
	Min, max	9.1; 18.8	9.3; 15.8	9.1; 18.8
	n – normal	37 (58.7)	19 (63.3)	18 (54.5)
	n – abnormal, CNR	26 (41.3)	11 (36.7)	15 (45.5)
	n – abnormal, CR	0	0	0
Cycle 1 Day 8	n	63	29	34
	Mean	13.35	13.65	13.10
	SD	1.96	1.65	2.17
	Median	13.6	13.9	12.7
	Min, max	7.9; 17.8	9.9; 16.7	7.9; 17.8
	n – normal	33 (52.4)	20 (69.0)	13 (38.2)
	n – abnormal, CNR	29 (46.0)	9 (31.0)	20 (58.8)
	n – abnormal, CR	1 (1.6)	0	1 (2.9)
Cycle 1 Day 15	n	59	29	30
	Mean	12.47	13.03	11.93
	SD	2.11	1.81	2.26
	Median	12.7	12.8	12.5
	Min, max	6.1; 15.9	8.2; 15.9	6.1; 15.8
	n – normal	29 (49.2)	18 (62.1)	11 (36.7)
	n – abnormal, CNR	27 (54.8)	11 (37.9)	16 (53.3)
	n – abnormal, CR	3 (5.1)	0	3 (10.0)
Cycle 1 Day 22	n	55	28	27
	Mean	12.27	12.39	12.15
	SD	1.53	1.45	1.63
	Median	12.9	12.85	12.9
	Min, max	8.6; 14.9	8.7; 14.9	8.6; 14.2
	n – normal	19 (34.5)	13 (46.4)	6 (22.2)
	n – abnormal, CNR	35 (63.6)	14 (50.0)	21 (77.8)
	n – abnormal, CR	1 (1.8)	1 (3.6)	0
Cycle 2 Day 1	n	57	27	30
	Mean	12.37	12.56	12.19
	SD	1.55	1.64	1.46
	Median	12.5	12.9	12.2
	Min, max	9.3; 15.9	9.5; 15.9	9.3; 15
	n – normal	21 (36.8)	13 (48.1)	8 (26.7)
	n – abnormal, CNR	35 (61.4)	13 (48.1)	22 (73.3)
	n – abnormal, CR	1 (1.8)	1 (3.7)	0
Cycle 2 Day 8	n	53	26	27
	Mean	12.50	12.68	12.32

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Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	SD	1.76	1.88	1.66
	Median	12.2	12.6	12
	Min, max	9.1; 15.9	9.2; 15.9	9.1; 15.8
	n – normal	23 (43.4)	13 (50.0)	10 (37.0)
	n – abnormal, CNR	30 (56.6)	13 (50.0)	17 (63.0)
	n – abnormal, CR	0	0	0
Cycle 2 Day 15	n	46	26	20
	Mean	11.58	11.58	11.59
	SD	1.73	1.75	1.76
	Median	11.75	11.3	12.25
	Min, max	7.6; 14.9	8.9; 14.9	7.6; 14.3
	n – normal	11 (23.9)	8 (30.8)	3 (15.0)
	n – abnormal, CNR	34 (73.9)	18 (69.2)	16 (80.0)
	n – abnormal, CR	1 (2.2)	0	1 (5.0)
Cycle 2 Day 22	n	43	23	20
	Mean	10.90	10.93	10.86
	SD	1.69	1.77	1.64
	Median	10.9	10.7	11.3
	Min, max	8; 14	8.6; 14	8; 14
	n – normal	8 (18.6)	6 (26.1)	2 (10.0)
	n – abnormal, CNR	33 (76.7)	16 (69.6)	17 (85.0)
	n – abnormal, CR	2 (4.7)	1 (4.3)	1 (5.0)
Cycle 3 Day 1	n	28	16	12
	Mean	10.89	11.29	10.37
	SD	1.40	1.39	1.30
	Median	10.9	11.4	10.1
	Min, max	8.6; 13.3	8.8; 13.3	8.6; 12.5
	n – normal	4 (14.3)	2 (12.5)	2 (16.7)
	n – abnormal, CNR	22 (78.6)	13 (81.3)	9 (75.0)
	n – abnormal, CR	2 (7.1)	1 (6.3)	1 (8.3)
Cycle 3 Day 8	n	26	15	11
	Mean	10.68	10.68	10.69
	SD	1.48	1.34	1.72
	Median	10.5	10.6	10.1
	Min, max	8.5; 13.6	8.5; 13.5	8.9; 13.6
	n – normal	6 (23.1)	3 (20.0)	3 (27.3)
	n – abnormal, CNR	19 (73.1)	11 (73.3)	8 (72.7)
	n – abnormal, CR	1 (3.8)	1 (6.7)	0
Cycle 3 Day 15	n	24	15	9
	Mean	10.57	10.72	10.31
	SD	1.54	1.62	1.47
	Median	10.2	10.9	10.1
	Min, max	8.2; 13.3	8.4; 13.3	8.2; 12.6
	n – normal	6 (25.0)	5 (33.3)	1 (11.1)
	n – abnormal, CNR	17 (70.1)	9 (60.0)	8 (88.9)
	n – abnormal, CR	1 (4.2)	1 (6.7)	0
Cycle 3 Day 22	n	27	16	11
	Mean	10.71	10.84	10.53
	SD	1.16	1.13	1.23
	Median	10.3	10.7	10.1
	Min, max	8.7; 12.6	9; 12.4	8.7; 12.6
	n – normal	4 (14.8)	2 (12.5)	2 (18.2)

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Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	n – abnormal, CNR	21 (77.8)	13 (81.3)	8 (72.7)
	n – abnormal, CR	2 (7.4)	1 (6.3)	1 (9.1)
Cycle 4 Day 1	n	25	14	11
	Mean	10.77	10.99	10.50
	SD	1.19	1.16	1.22
	Median	10.5	10.9	10.3
	Min, max	8.7: 12.8	9.3; 12.8	8.7; 12.3
	n – normal	2 (8.0)	1 (7.1)	1 (9.1)
	n – abnormal, CNR	21 (84.0)	12 (85.7)	9 (81.8)
	n – abnormal, CR	2 (8.0)	1 (7.1)	1 (9.1)
Cycle 4 Day 8	n	23	13	10
	Mean	11.28	11.62	10.85
	SD	1.55	1.39	1.70
	Median	11.2	12.3	10.35
	Min, max	9; 13.7	9.4; 13.1	9; 13.7
	n – normal	7 (30.4)	5 (38.5)	2 (20.0)
	n – abnormal, CNR	16 (69.6)	8 (61.5)	8 (80.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 15	n	13	9	4
	Mean	11.20	11.34	10.88
	SD	1.20	1.25	1.17
	Median	11.7	11.7	11.05
	Min, max	8.8; 12.8	8.8; 12.8	9.5; 11.9
	n – normal	1 (7.7)	1 (11.1)	0
	n – abnormal, CNR	12 (92.3)	8 (88.9)	4 (100.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 22	n	9	3	6
	Mean	10.66	10.53	10.72
	SD	1.67	2.05	1.66
	Median	10.5	10.5	10.9
	Min, max	8.5; 12.6	8.5; 12.6	8.7; 12.6
	n – normal	1 (11.1)	0	1 (16.7)
	n – abnormal, CNR	8 (88.9)	3 (100.0)	5 (83.3)
	n – abnormal, CR	0	0	0
EOT	n	66	32	34
	Mean	11.50	11.73	11.29
	SD	1.75	1.68	1.82
	Median	11.65	12	11.35
	Min, max	8.6; 15.8	8.8; 14.4	8.6; 15.8
	n – normal	16 (24.2)	10 (31.3)	6 (17.6)
	n – abnormal, CNR	45 (68.2)	20 (62.5)	25 (73.5)
	n – abnormal, CR	3 (4.5)	2 (6.3)	1 (2.9)
	Evaluation ND	2 (3.0)	0	2 (5.9)

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table14.3.6.13: Erythrocytes [/pl]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	68	32	36
	Mean	4.39	4.43	4.35
	SD	0.47	0.41	0.51
	Median	4.42	4.46	4.34
	Min; max	2.71; 5.32	3.26; 5.1	2.71; 5.32
	n – normal	50 (73.5)	25 (78.1)	25 (69.4)
	n – abnormal, CNR	18 (26.5)	7 (21.9)	11 (30.6)
	n – abnormal, CR	0	0	0
Cycle 1 Day 1	n	63	30	33
	Mean	4.32	4.38	4.26
	SD	0.47	0.42	0.51
	Median	4.32	4.39	4.28
	Min, max	2.71; 5.32	3.29; 5.07	2.71; 5.32
	n – normal	41 (65.1)	23 (76.7)	18 (54.5)
	n – abnormal, CNR	22 (34.9)	7 (23.3)	15 (45.5)
	n – abnormal, CR	0	0	0
Cycle 1 Day 8	n	63	29	34
	Mean	4.35	4.41	4.29
	SD	0.57	0.47	0.64
	Median	4.41	4.51	4.22
	Min, max	2.38; 5.46	3.23; 5.24	2.38; 5.46
	n – normal	41 (65.1)	21 (72.4)	20 (58.8)
	n – abnormal, CNR	21 (33.3)	8 (27.6)	13 (38.2)
	n – abnormal, CR	1 (1.6)	0	1 (2.9)
Cycle 1 Day 15	n	59	29	30
	Mean	4.03	4.21	3.86
	SD	0.67	0.61	0.70
	Median	4.08	4.15	3.98
	Min, max	2; 5.62	2.75; 5.62	2; 4.71
	n – normal	25 (42.4)	14 (48.3)	11 (36.7)
	n – abnormal, CNR	31 (52.5)	15 (51.7)	16 (53.3)
	n – abnormal, CR	3 (5.1)	0	3 (10.0)
Cycle 1 Day 22	n	55	28	27
	Mean	3.98	4.02	3.93
	SD	0.48	0.46	0.51
	Median	4.1	4.17	4.01
	Min, max	2.81; 4.74	3.04; 4.74	2.81; 4.69
	n – normal	23 (41.8)	13 (46.4)	10 (37.0)
	n – abnormal, CNR	31 (56.4)	14 (50.0)	17 (63.0)
	n – abnormal, CR	1 (1.8)	1 (3.6)	0
Cycle 2 Day 1	n	57	27	30
	Mean	4.14	4.04	4.23
	SD	1.34	0.56	1.77
	Median	3.96	4	3.96
	Min, max	2.78; 13.32	3; 5.28	2.78; 13.32
	n – normal	18 (31.6)	12 (44.4)	6 (20.0)
	n – abnormal, CNR	38 (66.7)	14 (51.9)	24 (80.0)
	n – abnormal, CR	1 (1.8)	1 (3.7)	0
Cycle 2 Day 8	n	53	26	27
	Mean	4.03	4.09	3.97

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Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	SD	0.61	0.67	0.55
	Median	3.95	4.20	3.91
	Min, max	2.8; 5.37	2.8; 5.37	2.8; 5.34
	n – normal	20 (37.7)	11 (42.3)	9 (33.3)
	n – abnormal, CNR	33 (62.3)	15 (57.7)	18 (66.7)
	n – abnormal, CR	0	0	0
Cycle 2 Day 15	n	46	26	20
	Mean	3.07	3.73	3.67
	SD	0.56	0.58	0.54
	Median	3.76	3.63	3.78
	Min, max	2.56; 5.03	2.91; 5.03	2.56; 4.5
	n – normal	12 (26.1)	8 (30.8)	4 (20.0)
	n – abnormal, CNR	33 (71.7)	18 (69.2)	15 (75.0)
	n – abnormal, CR	1 (2.2)	0	1 (5.0)
Cycle 2 Day 22	n	43	23	20
	Mean	3.44	3.48	3.38
	SD	0.54	0.56	0.52
	Median	3.35	3.35	3.41
	Min, max	2.53; 4.69	2.7; 4.69	2.53; 4.5
	n – normal	5 (11.6)	4 (17.4)	1 (5.0)
	n – abnormal, CNR	36 (83.7)	18 (78.3)	18 (90.0)
	n – abnormal, CR	2 (4.7)	1 (4.3)	1 (5.0)
Cycle 3 Day 1	n	28	16	12
	Mean	3.42	3.54	3.26
	SD	0.48	0.47	0.46
	Median	3.44	3.57	3.12
	Min, max	2.6; 4.3	2.79; 4.3	2.6; 4.01
	n – normal	3 (10.7)	2 (12.5)	1 (8.3)
	n – abnormal, CNR	24 (85.7)	13 (81.3)	11 (91.7)
	n – abnormal, CR	1 (3.6)	1 (6.3)	0
Cycle 3 Day 8	n	26	15	11
	Mean	3.38	3.40	3.35
	SD	0.44	0.36	0.55
	Median	3.4	3.4	3.08
	Min, max	2.59; 4.23	2.59; 3.94	2.75; 4.23
	n – normal	2 (7.7)	1 (6.7)	1 (9.1)
	n – abnormal, CNR	24 (92.3)	14 (93.3)	10 (90.9)
	n – abnormal, CR	0	0	0
Cycle 3 Day 15	n	24	15	9
	Mean	3.26	3.29	3.22
	SD	0.48	0.51	0.44
	Median	3.3	3.32	3.16
	Min, max	2.37; 4.18	2.37; 4.18	2.7; 4.09
	n – normal	3 (12.5)	2 (13.3)	1 (11.1)
	n – abnormal, CNR	21 (87.5)	13 (86.7)	8 (88.9)
	n – abnormal, CR	0	0	0
Cycle 3 Day 22	n	27	16	11
	Mean	3.24	3.31	3.15
	SD	0.39	0.36	0.44
	Median	3.23	3.34	3.03
	Min, max	2.36; 4.06	2.59; 3.9	2.36; 4.06
	n – normal	1 (3.7)	0	1 (9.1)

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Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	n – abnormal, CNR	24 (88.9)	15 (93.8)	9 (81.8)
	n – abnormal, CR	2 (7.4)	1 (6.3)	1 (9.1)
Cycle 4 Day 1	n	25	14	11
	Mean	3.25	3.32	3.16
	SD	0.38	0.39	0.36
	Median	3.2	3.39	3.1
	Min, max	2.51; 3.98	2.51; 3.97	2.7; 3.98
	n – normal	1 (4.0)	0	1 (9.1)
	n – abnormal, CNR	22 (91.7)	13 (92.9)	9 (81.8)
	n – abnormal, CR	2 (8.0)	1 (7.1)	1 (9.1)
Cycle 4 Day 8	n	23	13	10
	Mean	3.41	3.56	3.22
	SD	0.53	0.49	0.53
	Median	3.41	3.56	3.07
	Min, max	2.43; 4.42	2.54; 4.27	2.7; 4.42
	n – normal	4 (17.4)	3 (23.1)	1 (10.0)
	n – abnormal, CNR	19 (82.6)	10 (76.9)	9 (90.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 15	n	13	9	4
	Mean	3.30	3.39	3.09
	SD	0.42	0.46	0.25
	Median	3.34	3.53	3.05
	Min, max	2.3; 3.8	2.3; 3.8	2.87; 3.4
	n – normal	1 (7.7)	1 (11.1)	0
	n – abnormal, CNR	12 (92.3)	8 (88.9)	4 (100.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 22	n	9	3	6
	Mean	3.10	3.04	3.13
	SD	0.48	0.71	0.41
	Median	3.21	3.4	3.05
	Min, max	2.23; 3.71	2.23; 3.5	2.63; 3.71
	n – normal	0	0	0
	n – abnormal, CNR	9 (100.0)	3 (100.0)	6 (100.0)
	n – abnormal, CR	0	0	0
EOT	n	66	32	34
	Mean	3.64	3.70	3.59
	SD	0.63	0.63	0.65
	Median	3.63	3.68	3.54
	Min, max	2.4; 5.34	2.4; 4.77	2.63; 5.34
	n – normal	14 (21.2)	8 (25.0)	6 (17.6)
	n – abnormal, CNR	49 (74.2)	23 (71.9)	26 (76.5)
	n – abnormal, CR	2 (3.0)	1 (3.1)	1 (2.9)
	Evaluation ND	1 (1.5)	0	0

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.14: Platelets [/nl]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	68	32	36
	Mean	286.51	266.94	303.92
	SD	89.09	74.39	98.14
	Median	274	266	289
	Min; max	114; 565	114; 415	168; 565
	n – normal	53 (77.9)	25 (78.1)	28 (77.8)
	n – abnormal, CNR	14 (20.6)	6 (18.8)	8 (22.2)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (1.5)	1 (3.1)	0
Cycle 1 Day 1	n	63	30	33
	Mean	281.25	247.13	312.27
	SD	89.74	59.45	101.58
	Median	270	252	296
	Min, max	134; 565	134; 371	168; 565
	n – normal	52 (82.5)	27 (90.0)	25 (75.8)
	n – abnormal, CNR	9 (14.3)	3 (10.0)	6 (18.2)
	n – abnormal, CR	0	0	0
	Evaluation ND	2 (3.2)	0	2 (6.1)
Cycle 1 Day 8	n	63	29	34
	Mean	238.52	227.48	247.94
	SD	83.97	80.51	86.88
	Median	221	213	233
	Min, max	55; 465	55; 423	109; 465
	n – normal	49 (77.8)	23 (79.3)	26 (76.5)
	n – abnormal, CNR	14 (22.2)	6 (20.7)	8 (23.5)
	n – abnormal, CR	0	0	0
Cycle 1 Day 15	n	59	29	30
	Mean	150.17	163.52	137.27
	SD	63.32	62.76	62.17
	Median	141	171	124
	Min, max	7; 318	62; 318	7; 274
	n – normal	28 (47.5)	17 (58.6)	11 (36.7)
	n – abnormal, CNR	30 (51.0)	12 (41.4)	18 (60.0)
	n – abnormal, CR	1 (1.7)	0	1 (3.3)
Cycle 1 Day 22	n	55	28	27
	Mean	186.16	171.39	201.48
	SD	83.61	53.63	105.13
	Median	164	156	181
	Min, max	63; 497	99; 307	63; 497
	n – normal	33 (60.0)	16 (57.1)	17 (63.0)
	n – abnormal, CNR	22 (40.0)	12 (42.9)	10 (37.0)
	n – abnormal, CR	0	0	0
Cycle 2 Day 1	n	57	27	30
	Mean	244.68	226.48	261.07
	SD	94.76	77.74	106.47
	Median	231	218	247
	Min, max	87; 603	87; 365	137; 603
	n – normal	43 (75.4)	22 (81.5)	21 (70.0)
	n – abnormal, CNR	13 (22.8)	4 (14.8)	9 (30.0)
	n – abnormal, CR	1 (1.8)	1 (3.7)	0

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Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Cycle 2 Day 8	n	53	26	27
	Mean	215.79	188.73	241.85
	SD	98.52	74.04	112.71
	Median	218	193	231
	Min, max	24; 521	48: 392	24; 521
	n – normal	31 (58.5)	14 (53.8)	17 (63.0)
	n – abnormal, CNR	19 (35.8)	10 (38.5)	9 (33.3)
	n – abnormal, CR	3 (5.7)	2 (7.7)	1 (3.7)
Cycle 2 Day 15	n	46	26	20
	Mean	120.41	113.15	129.85
	SD	53.32	45.31	62.19
	Median	119	110	124
	Min, max	26; 282	35; 226	26; 282
	n – normal	11 (23.9)	5 (19.2)	6 (30.0)
	n – abnormal, CNR	32 (69.6)	19 (73.1)	13 (65.0)
	n – abnormal, CR	3 (6.5)	2 (7.7)	1 (5.0)
Cycle 2 Day 22	n	43	23	20
	Mean	174.09	174.43	173.70
	SD	66.36	71.13	62.25
	Median	155	146	166
	Min, max	41; 299	41; 299	81; 273
	n – normal	24 (55.8)	11 (47.8)	13 (65.0)
	n – abnormal, CNR	17 (39.5)	10 (43.5)	7 (35.0)
	n – abnormal, CR	2 (4.7)	2 (8.7)	0
Cycle 3 Day 1	n	28	16	12
	Mean	293.86	269.38	326.50
	SD	126.94	87.706	164.41
	Median	281	280	297
	Min, max	103; 642	103; 406	129; 642
	n – normal	19 (67.9)	13 (81.3)	6 (50.0)
	n – abnormal, CNR	9 (32.1)	3 (18.8)	6 (50.0)
	n – abnormal, CR	0	0	0
Cycle 3 Day 8	n	26	15	11
	Mean	252.04	224.73	289.27
	SD	116.52	88.62	142.50
	Median	222	202	270
	Min, max	76; 639	76; 404	118; 639
	n – normal	19 (73.1)	11 (73.3)	8 (72.7)
	n – abnormal, CNR	7 (26.9)	4 (26.7)	3 (27.3)
	n – abnormal, CR	0	0	0
Cycle 3 Day 15	n	24	15	9
	Mean	188.00	168.40	220.67
	SD	98.88	51.49	146.79
	Median	176.5	179	174
	Min, max	72; 578	72: 231	102; 587
	n – normal	15 (62.5)	9 (60.0)	6 (66.7)
	n – abnormal, CNR	9 (37.5)	6 (40.0)	3 (33.3)
	n – abnormal, CR	0	0	0
Cycle 3 Day 22	n	27	16	11
	Mean	189.56	188.81	190.64
	SD	64.36	64.85	66.79
	Median	186	188	186

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Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	Min, max	82; 329	82; 329	105; 328
	n – normal	20 (74.1)	12 (75.0)	8 (72.7)
	n – abnormal, CNR	7 (25.9)	4 (25.0)	3 (27.3)
	n – abnormal, CR	0	0	0
Cycle 4 Day 1	n	25	14	11
	Mean	214.36	219.86	207.36
	SD	76.03	82.56	70.12
	Median	207	207	207
	Min, max	117; 406	117; 406	128; 382
	n – normal	18 (72.0)	10 (71.4)	8 (72.7)
	n – abnormal, CNR	7 (28.0)	4 (28.6)	3 (27.3)
	n – abnormal, CR	0	0	0
Cycle 4 Day 8	n	23	13	10
	Mean	198.83	220.15	171.10
	SD	64.97	72.49	42.42
	Median	196	209	177
	Min, max	95; 347	109; 347	95; 232
	n – normal	19 (82.6)	11 (84.6)	8 (80.0)
	n – abnormal, CNR	4 (17.4)	2 (15.4)	2 (20.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 15	n	13	9	4
	Mean	163.23	162.44	165.00
	SD	57.38	63.90	47.69
	Median	149	140	176
	Min, max	90; 269	90; 269	101; 207
	n – normal	7 (53.8)	4 (44.4)	3 (75.0)
	n – abnormal, CNR	6 (46.2)	5 (55.6)	1 (25.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 22	n	9	3	6
	Mean	192.67	230.67	173.67
	SD	102.87	153.76	78.58
	Median	158	241	153
	Min, max	66; 379	72; 379	66; 282
	n – normal	3 (33.3)	1 (33.3)	2 (33.3)
	n – abnormal, CNR	6 (66.7)	2 (66.7)	4 (66.7)
	n – abnormal, CR	0	0	0
EOT	n	66	32	34
	Mean	228.77	207.53	248.76
	SD	128.53	128.16	127.51
	Median	217	211	231
	Min, max	35; 748	35; 748	66; 635
	n – normal	38 (57.6)	19 (59.4)	19 (55.9)
	n – abnormal, CNR	28 (42.4)	13 (40.7)	15 (44.1)
	n – abnormal, CR	0	0	0

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.15: Leucocytes [/nl]

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	68	32	36
	Mean	8.65	7.81	9.40
	SD	3.00	1.99	3.53
	Median	7.67	7.58	8.26
	Min; max	3.37; 19.6	3.37; 12.5	4.55; 19.6
	n – normal	52 (76.5)	27 (84.4)	25 (69.4)
	n – abnormal, CNR	15 (22.1)	5 (15.7)	10 (27.8)
	n – abnormal, CR	1 (1.5)	0	1 (2.8)
Cycle 1 Day 1	n	63	30	33
	Mean	8.72	8.05	9.34
	SD	3.09	2.58	3.41
	Median	7.91	7.36	8.4
	Min, max	4.55; 19.68	4.86; 16.03	4.55; 19.68
	n – normal	49 (77.8)	25 (83.3)	24 (72.7)
	n – abnormal, CNR	12 (19.0)	5 (16.7)	7 (21.2)
	n – abnormal, CR	1 (1.6)	0	1 (3.0)
	Evaluation ND	1 (1.6)	0	1 (3.0)
Cycle 1 Day 8	n	63	29	34
	Mean	7.39	7.66	7.17
	SD	2.84	2.41	3.18
	Median	6.64	7.46	6.01
	Min, max	2.65; 19.9	2.65; 13.1	1.33; 19.9
	n – normal	52 (82.5)	23 (79.3)	29 (85.3)
	n – abnormal, CNR	11 (17.4)	6 (20.7)	5 (14.7)
	n – abnormal, CR	0	0	0
Cycle 1 Day 15	n	59	29	30
	Mean	5.31	5.84	4.79
	SD	2.54	3.08	1.79
	Median	5.1	5.61	4.81
	Min, max	0.23; 12.4	0.57; 12.4	0.23; 8.25
	n – normal	38 (64.4)	16 (55.2)	22 (73.3)
	n – abnormal, CNR	16 (27.1)	10 (34.5)	6 (20.0)
	n – abnormal, CR	3 (5.1)	2 (6.9)	1 (3.3)
	Evaluation ND	2 (3.4)	1 (3.4)	1 (3.3)
Cycle 1 Day 22	n	55	28	27
	Mean	3.83	4.03	3.61
	SD	1.81	1.66	1.95
	Median	3.85	3.94	3.06
	Min, max	1.29; 9.13	1.7; 8.42	1.29; 9.13
	n – normal	24 (43.6)	13 (46.4)	11 (40.7)
	n – abnormal, CNR	30 (54.5)	14 (50.0)	16 (59.3)
	n – abnormal, CR	1 (1.8)	1 (3.6)	0
Cycle 2 Day 1	n	57	27	30
	Mean	5.09	5.27	4.92
	SD	2.27	2.22	2.34
	Median	4.3	5.06	4.28
	Min, max	2.24; 11.01	2.58; 10.6	2.24; 11.01
	n – normal	38 (66.7)	19 (70.4)	19 (63.3)
	n – abnormal, CNR	19 (33.3)	8 (29.6)	11 (36.7)
	n – abnormal, CR	0	0	0

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Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Cycle 2 Day 8	n	53	26	27
	Mean	5.58	4.92	6.22
	SD	2.77	2.19	3.14
	Median	5	4.70	5.83
	Min, max	0.29; 13.97	0.29; 10.89	1.82; 13.97
	n – normal	37 (69.8)	18 (69.2)	19 (70.4)
	n – abnormal, CNR	15 (28.3)	7 (26.9)	8 (29.6)
	n – abnormal, CR	1 (1.9)	1 (3.8)	0
Cycle 2 Day 15	n	46	26	20
	Mean	4.18	4.05	4.35
	SD	2.01	1.84	2.25
	Median	3.63	3.465	3.75
	Min, max	0.75; 9.85	1.75; 8.49	0.75; 9.85
	n – normal	20 (43.5)	10 (38.5)	10 (50.0)
	n – abnormal, CNR	23 (50.0)	15 (57.7)	8 (40.0)
	n – abnormal, CR	3 (6.5)	1 (3.8)	2 (10.0)
Cycle 2 Day 22	n	43	23	20
	Mean	3.50	3.49	3.50
	SD	1.90	1.49	2.32
	Median	2.93	2.93	2.84
	Min, max	1.7; 12.49	1.7; 8.41	2.08; 12.49
	n – normal	11 (25.6)	7 (30.4)	4 (20.0)
	n – abnormal, CNR	31 (72.1)	16 (69.6)	15 (75.0)
	n – abnormal, CR	1 (2.3)	0	1 (5.0)
Cycle 3 Day 1	n	28	16	12
	Mean	6.20	5.75	6.80
	SD	2.76	2.43	2.15
	Median	5	5	5.77
	Min, max	3.02; 12.9	3.02; 10.1	3.4; 12.9
	n – normal	20 (71.4)	10 (62.5)	10 (83.3)
	n – abnormal, CNR	7 (25.0)	6 (37.5)	1 (8.3)
	n – abnormal, CR	1 (3.6)	0	1 (8.3)
Cycle 3 Day 8	n	26	15	11
	Mean	6.42	5.45	7.75
	SD	2.91	1.94	3.54
	Median	5.52	4.81	6.43
	Min, max	3.2; 14.78	3.38; 10.3	3.2; 14.78
	n – normal	19 (73.0)	12 (80.0)	7 (63.6)
	n – abnormal, CNR	7 (26.9)	3 (20.0)	4 (36.4)
	n – abnormal, CR	0	0	0
Cycle 3 Day 15	n	24	15	9
	Mean	5.59	4.84	6.84
	SD	2.28	1.83	2.50
	Median	5.04	4.2	6.54
	Min, max	1.77; 11	1.77; 8.1	3.7; 11
	n – normal	17 (70.8)	11 (73.3)	6 (66.7)
	n – abnormal, CNR	6 (25.0)	4 (26.7)	2 (22.2)
	n – abnormal, CR	1 (4.1)	0	1 (11.1)
Cycle 3 Day 22	n	27	16	11
	Mean	4.07	3.74	4.55
	SD	1.60	1.20	2.03
	Median	3.78	3.62	3.86

Visit	Statistic	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	Min, max	2.02; 7.93	2.02; 6.7	2.5; 7.93
	n – normal	12 (44.4)	7 (43.8)	5 (45.5)
	n – abnormal, CNR	14 (51.9)	8 (50.0)	6 (54.5)
	n – abnormal, CR	1 (3.7)	1 (6.3)	0
Cycle 4 Day 1	n	25	14	11
	Mean	4.99	4.92	5.08
	SD	2.13	2.65	1.33
	Median	4.48	3.67	4.76
	Min, max	2.66; 12.4	2.66; 12.4	3.4; 7.12
	n – normal	15 (60.0)	5 (35.7)	10 (90.1)
	n – abnormal, CNR	10 (40.0)	9 (64.3)	1 (9.1)
	n – abnormal, CR	0	0	0
Cycle 4 Day 8	n	23	13	10
	Mean	5.18	5.19	5.16
	SD	2.19	1.65	2.84
	Median	5.2	5.3	4.37
	Min, max	2.01; 11.96	2.01; 8.32	2.1; 11.96
	n – normal	16 (69.6)	10 (76.9)	6 (60.0)
	n – abnormal, CNR	7 (30.4)	3 (23.1)	4 (40.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 15	n	13	9	4
	Mean	4.23	4.33	4.01
	SD	1.37	1.47	1.26
	Median	3.8	3.99	3.65
	Min, max	2.32; 7.22	2.32; 7.22	2.91; 5.81
	n – normal	6 (46.2)	5 (55.6)	1 (25.0)
	n – abnormal, CNR	7 (53.8)	4 (44.4)	3 (75.0)
	n – abnormal, CR	0	0	0
Cycle 4 Day 22	n	9	3	6
	Mean	3.85	4.20	3.68
	SD	1.30	1.05	1.46
	Median	4.2	4.3	3.7
	Min, max	1.5; 5.53	3.11; 5.2	1.5; 5.53
	n – normal	6 (66.7)	2 (66.7)	4 (66.7)
	n – abnormal, CNR	3 (33.3)	1 (33.3)	2 (33.3)
	n – abnormal, CR	0	0	0
EOT	n	66	32	34
	Mean	5.86	5.62	6.08
	SD	2.86	2.34	3.29
	Median	5.36	5.19	5.68
	Min, max	1.97; 19.6	1.97; 11.12	2.3; 19.6
	n – normal	49 (74.2)	24 (75.0)	25 (73.5)
	n – abnormal, CNR	16 (24.2)	8 (25.0)	8 (23.5)
	n – abnormal, CR	1 (1.5)	0	1 (2.9)

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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Table 14.3.6.16: Neutrophils [/nl]

Visit	Statistic	Total (N=66) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Screening	n	65	32	33
	Mean	5.91	5.06	6.74
	SD	2.62	1.53	3.17
	Median	5.1	4.90	5.77
	Min; max	2.21; 16.21	2.21; 8.95	2.68; 16.21
	n – normal	55 (84.6)	30 (93.8)	25 (75.8)
	n – abnormal, CNR	9 (13.8)	2 (6.3)	7 (21.2)
	n – abnormal, CR	1 (1.5)	0	1 (3.0)
Cycle 1 Day 1	n	57	27	30
	Mean	5.91	5.32	6.44
	SD	2.36	1.92	2.62
	Median	5.3	4.71	5.90
	Min, max	2.68; 15.03	3.22; 11.51	2.68; 15.03
	n – normal	47 (82.5)	25 (92.6)	21 (70.0)
	n – abnormal, CNR	9 (15.8)	2 (7.4)	7 (23.3)
	n – abnormal, CR	1 (1.8)	0	1 (3.3)
Cycle 1 Day 8	n	45	23	22
	Mean	5.47	5.87	5.05
	SD	2.23	2.13	2.31
	Median	5.13	5.9	4.29
	Min, max	2.06; 13	2.06; 11.7	2.61; 13
	n – normal	29 (64.4)	16 (69.6)	13 (59.1)
	n – abnormal, CNR	16 (35.6)	7 (30.4)	9 (40.9)
	n – abnormal, CR	0	0	0
Cycle 1 Day 15	n	41	21	20
	Mean	4.20	4.34	4.05
	SD	2.16	2.72	1.42
	Median	3.84	3.84	3.88
	Min, max	0.23; 9.90	0.23; 9.90	1.48; 7.51
	n – normal	24 (58.5)	12 (57.1)	12 (60.0)
	n – abnormal, CNR	14 (34.1)	7 (33.3)	7 (35.0)
	n – abnormal, CR	3 (7.3)	2 (9.5)	1 (5.0)
Cycle 1 Day 22	n	46	24	22
	Mean	2.66	2.97	2.33
	SD	1.65	1.70	1.55
	Median	2.5	2.675	2.08
	Min, max	0.47; 7.22	0.80; 7.22	0.47; 6.31
	n – normal	26 (56.5)	13 (54.2)	13 (59.1)
	n – abnormal, CNR	15 (32.6)	9 (37.5)	6 (27.3)
	n – abnormal, CR	4 (8.7)	1 (4.2)	3 (13.6)
	Evaluation ND	1 (2.2)	1 (4.2)	0
Cycle 2 Day 1	n	51	25	26
	Mean	3.65	3.81	3.51
	SD	2.02	2.13	1.94
	Median	2.9	3.1	2.88
	Min, max	1.62; 9.39	1.74; 9.39	1.62; 9.30
	n – normal	39 (76.5)	18 (72.0)	21 (80.8)
	n – abnormal, CNR	12 (23.5)	7 (28.0)	5 (19.2)
	n – abnormal, CR	0	0	0
Cycle 2 Day 8	n	34	16	18

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Visit	Statistic	Total (N=66) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
....	Mean	4.79	4.73	4.84
	SD	2.19	2.13	2.29
	Median	4.39	4.11	4.50
	Min, max	2.1; 12.4	2.1; 10.13	2.16; 12.4
	n – normal	19 (55.9)	7 (43.8)	12 (66.7)
	n – abnormal, CNR	15 (44.1)	9 (56.3)	6 (33.3)
	n – abnormal, CR	0	0	0
Cycle 2 Day 15	n	33	18	15
	Mean	3.38	3.13	3.67
	SD	2.01	1.71	2.34
	Median	2.78	2.57	3.08
	Min, max	0.4; 9.04	0.4; 7.08	0.49; 9.04
	n – normal	25 (75.8)	15 (83.3)	10 (66.7)
	n – abnormal, CNR	6 (18.2)	3 (16.7)	3 (20.0)
	n – abnormal, CR	2 (6.1)	0	2 (13.3)
Cycle 2 Day 22	n	19	11	8
	Mean	2.56	2.02	3.32
	SD	2.30	0.80	3.40
	Median	1.97	1.78	2.26
	Min, max	1.06; 11.52	1.36; 4.09	1.06; 11.52
	n – normal	10 (52.6)	5 (45.5)	5 (62.5)
	n – abnormal, CNR	7 (36.8)	5 (45.5)	2 (25.0)
	n – abnormal, CR	2 (10.5)	1 (9.1)	1 (12.5)
Cycle 3 Day 1	n	22	14	8
	Mean	4.20	3.79	4.91
	SD	2.22	1.98	2.57
	Median	3.54	3.03	4.15
	Min, max	1.9; 10.2	1.9; 8.53	2.44; 10.2
	n – normal	20 (90.9)	13 (92.9)	7 (87.5)
	n – abnormal, CNR	1 (4.5)	1 (7.1)	0
	n – abnormal, CR	1 (4.5)	0	1 (12.5)
Cycle 3 Day 8	n	17	11	6
	Mean	4.74	4.18	5.77
	SD	2.80	1.79	4.09
	Median	3.77	3.58	4.58
	Min, max	2.4; 13.45	2.4; 8.1	2.42; 13.45
	n – normal	15 (88.2)	10 (90.9)	5 (83.3)
	n – abnormal, CNR	1 (5.9)	0	1 (16.7)
	n – abnormal, CR	0	0	0
	Evaluation ND	1 (5.9)	1 (9.1)	0
Cycle 3 Day 15	n	9	12	7
	Mean	4.0	3.52	4.82
	SD	1.89	1.46	2.35
	Median	3.49	3.14	3.74
	Min, max	1.86; 7.97	1.86; 6.5	2.67; 7.97
	n – normal	15 (78.9)	11 (91.7)	4 (57.1)
	n – abnormal, CNR	3 (15.8)	1 (8.3)	2 (28.6)
	n – abnormal, CR	1 (5.3)	0	1 (14.3)
Cycle 3 Day 22	n	24	14	10
	Mean	2.68	2.42	3.05
	SD	1.31	1.00	1.63
	Median	2.4	2.39	2.61

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Visit	Statistic	Total (N=66) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	Min, max	0.88; 5.45	0.88; 5.25	1.21; 5.45
	n – normal	19 (79.2)	13 (92.9)	6 (60.0)
	n – abnormal, CNR	4 (16.7)	0	4 (40.0)
	n – abnormal, CR	1 (4.2)	1 (7.1)	0
Cycle 4 Day 1	n	23	12	11
	Mean	3.72	3.79	3.65
	SD	2.05	2.68	1.18
	Median	3.1	2.69	3.56
	Min, max	1.67; 11	1.67; 11	2.2; 5.52
	n – normal	21 (91.3)	10 (83.3)	11 (100.0)
	n – abnormal, CNR	2 (8.7)	2 (16.7)	0
	n – abnormal, CR	0	0	0
Cycle 4 Day 8	n	11	5	6
	Mean	3.94	4.26	3.68
	SD	1.77	2.12	1.58
	Median	4	4.43	3.8
	Min, max	1.1; 6.98	1.2; 6.98	1.1; 5.65
	n – normal	9 (81.8)	4 (80.0)	5 (83.3)
	n – abnormal, CNR	2 (18.2)	1 (20.0)	1 (16.7)
	n – abnormal, CR	0	0	0
Cycle 4 Day 15	n	8	4	4
	Mean	3.59	4.40	2.78
	SD	1.21	1.75	1.05
	Median	3.87	4.2	2.36
	Min, max	2.07; 5.45	3.74; 5.45	2.07; 4.32
	n – normal	8 (100.0)	4 (100.0)	4 (100.0)
	n – abnormal, CNR	0	0	0
	n – abnormal, CR	0	0	0
Cycle 4 Day 22	n	7	2	5
	Mean	2.33	3.02	2.06
	SD	1.042	0.97	1.03
	Median	2.3	3.015	2.11
	Min, max	0.76; 3.7	2.33; 3.7	0.76; 3.57
	n – normal	7 (100.0)	2 (100.0)	5 (100.0)
	n – abnormal, CNR	0	0	0
	n – abnormal, CR	0	0	0
EOT	n	46	20	26
	Mean	4.46	4.37	4.52
	SD	2.54	2.27	2.77
	Median	3.73	3.60	4.07
	Min, max	0.92; 14.7	1.2; 9.39	0.92; 14.7
	n – normal	31 (67.4)	14 (70.0)	17 (65.4)
	n – abnormal, CNR	14 (30.4)	6 (30.0)	8 (30.8)
	n – abnormal, CR	1 (2.2)	0	1 (3.8)

CNR: Clinically not relevant, CR: Clinically relevant, ND: not done

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14.3.7   Exposure

Table 14.3.7-1: Exposure to cetuximab

		Statistics	Arm A (N=32) n (%)	Specification/Comment
Day 1	400 mg/m² administered		31 (96.9)	
	Other dose administered		1 (3.1)	200 mg/m²
	Total dose [mg]	Mean	733.18	
		SD	139.27	
		Median	741.6	
		Min; max	320; 1016	
	Dose modification	No	26 (81.3)	
		Discontinued	4 (12.5)	Documented for 2 patients[1], two further patient discontinued cetuximab treatment due to an allergic reaction
		Reduced	1 (3.1)	
		Delayed	1 (3.1)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	4 (12.5)	
		Skin toxicity	0	
		Other	2 (6.3)	Organisational (2)
Day 8	250 mg/m² administered		28 (87.5)	
	Other dose administered		0	
	Total dose [mg]	Mean	473.56	
		SD	60.60	
		Median	469.95	
		Min; max	388; 635	
	Dose modification	No	27 (96.4)	
		Discontinued	0	
		Reduced	0	
		Delayed	1 (3.7)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	1 (3.7)	Organisational (1)
Day 15	250 mg/m² administered		28 (87.5)	

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		Statistics	Arm A (N=32) n (%)	Specification/Comment
	Other dose administered		0	
	Total dose [mg]	Mean	472.64	
		SD	61.06	
		Median	464.45	
		Min; max	385; 635	
	Dose modification	No	26 (92.9)	
		Discontinued	1 (3.6)[1]	
		Reduced	0	
		Delayed	1 (3.6)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	2 (7.1)	Esophageal bleeding (1), unknown (1)[1]
Day 22	250 mg/m² administered		27 (84.4)	
	Other dose administered		0	
	Total dose [mg]	Mean	474.39	
		SD	60.13	
		Median	471.9	
		Min; max	393; 635	
	Dose modification	No	27 (100.0)	
		Discontinued	0	
		Reduced	0	
		Delayed	0	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	0	
Day 29	250 mg/m² administered		27 (84.4)	
	Other dose administered		0	
	Total dose [mg]	Mean	471.41	
		SD	61.48	
		Median	457	
		Min; max	392; 635	
	Dose modification	No	22 (81.5)	
		Discontinued	1 (3.7)[1]	

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		Statistics	Arm A (N=32) n (%)	Specification/Comment
		Reduced	1 (3.7)	
		Delayed	2 (7.4)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	4 (14.8)	End of study (1), weight loss (1), organisational (1), unknown (1 disc)[1]
Day 36	250 mg/m² administered		25 (78.1)	
	Other dose administered		1 (3.1)	0
	Total dose [mg]	Mean	462.65	
		SD	57.54	
		Median	445	
		Min; max	395; 635	
	Dose modification	No	18 (69.2)	
		Discontinued	6 (23.1)[1]	
		Reduced	1 (3.8)	
		Delayed	1 (3.8)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	8 (30.8)	SAE (1), weight loss (1), unknown (6 disc)[1]
Day 43	250 mg/m² administered		20 (62.5)	
	Other dose administered		0	
	Total dose [mg]	Mean	459.11	
		SD	47.52	
		Median	445	
		Min; max	398; 585	
	Dose modification	No	14 (70.0)	
		Discontinued	4 (20.0)	No cetuximab administered for cycle (1), unknown (3)[1]
		Reduced	0	
		Delayed	2 (10.0)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	

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		Statistics	Arm A (N=32) n (%)	Specification/Comment
	Other		5 (25.0)[1]	Cetuximab-induced pneumoitis (1 disc.), organisational (1), SAE (1), unknown (3 disc)[1]
Day 50	250 mg/m² administered		16 (50.0)	
	Other dose administered		0	
	Total dose [mg]	Mean	451.66	
		SD	51.22	
		Median	431.6	
		Min; max	395; 585	
	Dose modification	No	14 (87.5)	
		Discontinued	1 (6.3)	No cetuximab administered for cycle
		Reduced	0	
		Delayed	2 (12.5)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	1 (6.3)	
		Other	2 (12.5)	SAE (1 disc.), Nausea/vomiting (1)
Day 57	250 mg/m² administered		15 (46.9)	
	Other dose administered		0	
	Total dose [mg]	Mean	448	
		SD	48.76	
		Median	433	
		Min; max	399; 580	
	Dose modification	No	13 (86.7)	
		Discontinued	0	
		Reduced	0	
		Delayed	2 (13.3)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	2 (13.3)	AE leucopenia (1), infection (1)
Day 64	250 mg/m² administered		15 (46.9)	
	Other dose administered		0	
	Total dose [mg]	Mean	445.76	
		SD	53.69	

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		Statistics	Arm A (N=32) n (%)	Specification/Comment
		Median	431.1	
		Min; max	384; 580	
	Dose modification	No	13 (86.7)	
		Discontinued	0	
		Reduced	0	
		Delayed	2 (13.3)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	2 (13.3)	SAE leucopenia (1), infection (1)
Day 71	250 mg/m² administered		15 (46.9)	
	Other dose administered		0	
	Total dose [mg]	Mean	445.49	
		SD	51.15	
		Median	430.5	
		Min; max	391; 580	
	Dose modification	No	10 (66.7)	
		Discontinued	1 (6.7)[1]	
		Reduced	0	
		Delayed	4 (26.7)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	5 (33.3)	Patient's wish (1), organisational (2), panaritium (1), unknown (1 disc)[1]
Day 78	250 mg/m² administered		14 (43.8)	
	Other dose administered		0	
	Total dose [mg]	Mean	445.74	
		SD	53.41	
		Median	427.1	
		Min; max	393; 585	
	Dose modification	No	13 (92.9)	
		Discontinued	1 (7.1)	No cetuximab administered for cycle
		Reduced	0	
		Delayed	0	

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		Statistics	Arm A (N=32) n (%)	Specification/Comment
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	1 (3.1)	discontinued
		Other	0	
Day 85	250 mg/m² administered		13 (40.6)[1]	One further patient was documented as "no cetuximab administered for cycle, indicated as "discontinued" on day 78
	Other dose administered		0	
	Total dose [mg]	Mean	443.77	
		SD	55.12	
		Median	427.1	
		Min; max	386; 580	
	Dose modification	No	13 (100.0)[1]	
		Discontinued	0	
		Reduced	0	
		Delayed	0	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	
		Skin toxicity	0	
		Other	0	
Day 92	250 mg/m² administered		13 (40.6)[1]	One further patient was documented as "no cetuximab administered for cycle, indicated as "discontinued" on day 78
	Other dose administered		0	
	Total dose [mg]	Mean	443.99	
		SD	55.08	
		Median	427.1	
		Min; max	383; 580	
	Dose modification	No	12 (92.3)	
		Discontinued	0	
		Reduced	0	
		Delayed	1 (3.1)	
	Reason for dose modification	Allergic/ hypersensitivity reaction	0	

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	Statistics	Arm A (N=32) n (%)	Specification/Comment
	Skin toxicity	0	0
	Other	1 (3.1)	Patient's wish (1)

SD: Standard deviation

[1] Table based on CRF page "Exposure", but was revised with further information given in the CRF, but not consistently documented on CRF page "exposure".

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Table 14.3.7-2: Exposure to cisplatin (mg)

		Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Cycle 1	Dose 1	n (%)	65 (95.6)	29 (90.6)	36 (100.0)
		mean	37.14	37.92	36.51
		SD	3.96	4.69	3.20
		median	37.4	37.7	37
		min, max	30.5; 50	30.5; 50	30.6; 43
	Dose 2	n (%)	65 (95.6)	29 (90.6)	36 (100.0)
		mean	37.17	37.96	36.54
		SD	3.97	4.68	3.21
		median	37.4	37.7	37
		min, max	30; 50	30.4; 50	30; 43
	Dose 3	n (%)	65 (95.6)	29 (90.6)	36 (100.0)
		mean	37.26	37.91	36.72
		SD	3.90	4.69	3.05
		median	37.55	37.7	37
		min, max	30.8; 50	30.9; 50	30.8; 43
	Dose 4	n (%)	64 (94.1)	29 (90.6)	35 (97.2)
		mean	37.26	37.89	36.73
		SD	3.97	4.73	3.16
		median	37.6	37.7	37.3
		min, max	30.4; 50	30.4; 50	30.5; 43
	Median total dose cycle 1		37.5	37.7	37
		No dose modification	54 (79.4)	25 (78.1)	29 (80.6)
		Dose reduced	3 (4.4)	1 (3.1)	2 (5.6)
		Reason for reduction	Toxicity (3)	Toxicity (1)	Toxicity (2)
		Dose delayed	8 (11.8)	3 (9.4)	5 (13.9)
		Reason for delay	Holiday (1), organisational (3), toxicity (1), administration (1), unclear renal function (1), organisation/MRSA (1)	Organisational (2), unclear renal function (1)	Holiday (1), Organisational (1), toxicity (1), administration (1), organisation/MRSA (1)
Cycle 2	Dose 1	n (%)	56 (83.3)	28 (87.5)	28 (77.8)
		mean	36.76	37.04	36.47
		SD	4.56	5.57	3.29

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		Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
		median	37	36.95	37
		min, max	23.7; 50	23.7; 50	30.61; 42.5
	Dose 2	n (%)	55 (80.9)	27 (84.4)	28 (77.8)
		mean	36.90	37.50	36.33
		SD	4.24	5.05	3.26
		median	36.9	37	36.7
		min, max	28; 50	28; 50	30.81; 42.5
	Dose 3	n (%)	54 (79.4)	27 (84.4)	27 (75.0)
		mean	36.88	37.47	36.29
		SD	4.32	5.08	3.40
		median	36.95	37	36.9
		min, max	28; 50	28; 50	30.52; 42.5
	Dose 4	n (%)	54 (79.4)	27 (84.4)	27 (75.0)
		mean	36.93	37.51	36.34
		SD	4.27	5.03	3.34
		median	37	37	37
		min, max	28; 50	28; 50	31.06; 42.5
	Median total dose cycle 2		36.98	37	36.95
		No dose modification	40 (58.8)	20 (62.5)	20 (55.6)
		Dose reduced	7 (10.3)	3 (9.4)	4 (11.1)
		Reason for reduction	Toxicity (6), weight loss (1),	Toxicity (2), weight loss (1)	Toxicity (4)
		Dose delayed	11 (16.2)	5 (15.6)	6 (16.7)
		Reason for delay	Organisation (3), toxicity (6), patient's request (1), unknown (1)	Organisation (2), toxicity (2), patient's request (1)	Organisation (1), toxicity (4), unknown (1)
Cycle 3	Dose 1	n (%)	27 (39.7)	16 (50.0)	11 (30.6)
		mean	45.33	40.13	52.90
		SD	30.27	18.76	41.80
		median	36.6	25.55	37.2
		min, max	23.8; 164	23.8; 108	25.2; 164
	Dose 2	n (%)	27 (39.7)	16 (50.0)	11 (30.6)
		mean	45.79	40.63	52.83
		SD	30.78	19.32	41.85

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		Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
		median	36.7	36.4	37.2
		min, max	23.6; 176	23.6; 108	24.7; 164
	Dose 3	n (%)	27 (39.7)	16 (50.0)	11 (30.6)
		mean	45.83	40.72	52.80
		SD	30.75	19.25	41.86
		median	36.7	36.4	37.2
		min, max	24.4; 164	24.4; 108	25.3; 164
	Dose 4	n (%)	26 (38.2)	15 (46.9)	11 (30.6)
		mean	50.26	41.76	61.09
		SD	33.51	19.18	44.57
		median	37.2	36.5	38.6
		min, max	31.08; 164	31.7; 107	31.08; 164
Median total dose cycle 3			36.7	36.4	37.2
		No dose modification	12 (17.6)	7 (21.9)	5 (13.9)
		Dose reduced	6 (8.9)	3 (9-4)	3 (8.3)
		Reason for reduction	Toxicity (6)	Toxicity (3)	Toxicity (3)
		Dose delayed	11 (16.2)	6 (18.8)	5 (13.9)
		Reason for delay	General state and elevated CRP (1), organization (4), holiday (1), toxicity (5)	Organisation (2), toxicity (3), holiday (1)	General state and elevated CRP (1), organisation (2), toxicity (2)
Cycle 4	Dose 1	n (%)	22 (32.4)	12 (37.5)	10 (31.3)
		mean	38.53	35.8	41.80
		SD	12.82	3.24	18.68
		median	36.9	35.5	38.4
		min, max	25.3; 93	31; 40	25.3; 93
	Dose 2	n (%)	22 (32.4)	12 (37.5)	10 (31.3)
		mean	38.51	35.85	41.70
		SD	12.83	3.20	18.73
		median	36.9	25.5	38.4
		min, max	25.5; 93	30.9; 40	25.5; 93
	Dose 3	n (%)	22 (32.4)	12 (37.5)	10 (31.3)
		mean	38.51	35.83	41.72
		SD	12.83	3.21	18.72

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	Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	median	36.9	35.5	38.4
	min, max	25.4; 93	31; 40	25.4; 93
Dose 4	n (%)	22 (32.4)	12 (37.5)	10 (31.3)
	mean	38.45	35.79	41.64
	SD	12.86	3.26	18.77
	median	36.9	35.5	38.4
	min, max	25.5; 93	31; 40	25.5; 93
Median total dose cycle 4		36.9	35.5	38.4
	No dose modification	13 (19.1)	8 (25.0)	5 (13.9)
	Dose reduced	3 (3.3)	1 (3.1)	2 (5.6)
	Reason for reduction	Toxicity (2), precaution (1)	Toxicity (1)	Toxicity (1), precaution (1)
	Dose delayed	9 (13.2)	5 (15.6)	4 (11.1)
	Reason for delay	Organisation (4), Toxicity (4), general state (1)	Organisation (2), toxicity (3)	Organisation (2), toxicity (1), general state (1)

SD: Standard deviation

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Table 14.3.7-3: Exposure to 5-FU [mg]

		Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Cycle 1	Dose 1	n (%)	65 (95.6)	29 (90.6)	36 (100.0)
		mean	1859.42	1899.30	1827.28
		SD	197.32	231.09	161.54
		median	1870	1887	1850
		min, max	1518; 2500	1560; 2500	1518; 2150
	Dose 2	n (%)	65 (95.6)	29 (90.6)	36 (100.0)
		mean	1859.15	1896.86	1828.77
		SD	199.30	233.66	163.80
		median	1870	1887	1850
		min, max	1499; 2500	1546; 2500	1499; 2150
	Dose 3	n (%)	65 (95.6)	29 (90.6)	36 (100.0)
		mean	1862.04	1898.34	1832.80
		SD	196.71	232.42	159.89
		median	1870	1887	1850
		min, max	1494; 2500	1560; 2500	1494; 2150
	Dose 4	n (%)	63 (92.6)	28 (87.5)	35 (97.2)
		mean	1856.63	1882.67	1835.80
		SD	188.49	218.10	161.26
		median	1870	1878.5	1850
		min, max	1489; 2500	1560; 2500	1489; 2150
	Median total dose cycle 1		1870	1887	1850
		No dose modification	55 (80.9)	25 (78.1)	30 (83.3)
		Dose reduced	2 (2.9)	1 (3.1)	1 (2.8)
		Reason for reduction	Toxicity (2)	Toxicity (1)	Toxicity (1)
		Dose delayed	8 (11.8)	3 (9.4)	5 (13.9)
		Reason for delay	Administration (1), unclear renal function (1), organisation/MRSA (1), organisation (2), toxicity (2), holiday (1)	Organisation (2), unclear renal function (1)	Administration (1), organization/MRSA (1), organisation (1), toxicity (1), holiday (1)
Cycle 2	Dose 1	n (%)	53 (77.9)	26 (81.3)	27 (75.0)
		mean	1832.98	1831.60	1834.30

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		Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
		SD	211.37	259.02	157.63
		median	1844	1805	1850
		min, max	1240; 2500	1240; 2500	1571.22; 2125
	Dose 2	n (%)	52 (76.5)	25 (78.1)	27 (75.0)
		mean	1841.94	1855.07	1829.78
		SD	197.59	233.68	160.80
		median	1844	1830	1850
		min, max	1500; 2500	1500; 2500	1853.73; 2125
	Dose 3	n (%)	51 (75.0)	25 (78.1)	26 (72.2)
		mean	1841.89	1852.67	1831.53
		SD	200.68	235.43	164.63
		median	1844	1830	1857.5
		min, max	1500; 2500	1500; 2500	1577.96; 2125
	Dose 4	n (%)	50 (73.5)	25 (78.1)	25 (69.4)
		mean	1843.03	1854.67	1831.39
		SD	202.48	234.18	169.06
		median	1847	1830	1851
		min, max	1500; 2500	1500; 2500	1547.64; 2125
Median total dose cycle 2			1844	1830	1850.5
		No dose modification	41 (60.3)	20 (62.5)	21 (58.3)
		Dose reduced	7 (10.3)	3 (9.4)	4 (11.1)
		Reason for reduction	Toxicity (7)	Toxicity (3)	Toxicity (4)
		Dose delayed	11 (16.2)	6 (18.8)	5 (13.9)
		Reason for delay	Toxicity (5), SAE (1), organisation (3), patient's request (1), unknown (1)	Toxicity (2), SAE (1), organisation (2), patient's request (1)	Toxicity (3), organization (1), unknown (1)
Cycle 3	Dose 1	n (%)	25 (36.8)	15 (46.9)	10 (27.8)
		mean	1324.21	1300.13	1360.32
		SD	177.91	173.24	187.89
		median	1350	1275	1421.25
		min, max	825; 1567.5	825; 1525	986; 1567.5
	Dose 2	n (%)	25 (36.8)	15 (46.9)	10 (27.8)
		mean	1326.13	1302.47	1361.62

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		Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
		SD	175.49	171.29	184.81
		median	1350	1275	1421.25
		min, max	825; 1567.5	825; 1525	1000; 1567.5
	Dose 3	n (%)	25 (36.8)	15 (46.9)	10 (27.8)
		mean	1325.13	1299.33	1363.82
		SD	175.71	174.03	180.14
		median	1350	1275	1421.25
		min, max	825; 1567.5	825; 1525	1020; 1567.5
	Dose 4	n (%)	24 (35.3)	14	10 (27.8)
		mean	1346.64	1336.5	1360.83
		SD	143.03	112.65	183.20
		median	1357.5	1288.75	1421.25
		min, max	1024; 1567.5	1208; 1525	1024; 1567.5
	Median total dose cycle 3		1350	1275	1421.25
		No dose modification	15 (22.1)	9 (28.1)	6 (16.7)
		Dose reduced	4 (5.9)	2 (6.3)	2 (5.6)
		Reason for reduction	Toxicity (4)	Toxicity (2)	Toxicity (1)
		Dose delayed	9 (13.2)	5 (15.6)	4 (11.1)
		Reason for delay	Toxicity (4), organisation (3), holiday (1), general state and elevated CRP (1)	Toxicity (3), holiday (1), organization (1)	Toxicity (1), organization (2), general state and elevated CRP (1)
Cycle 4	Dose 1	n (%)	22 (23.4)	12 (37.5)	10 (27.8)
		mean	1360.18	1349.60	1372.88
		SD	145.16	117.03	179.15
		median	1383.75	1332.75	1440
		min, max	1036; 1575	1183; 1515	1036; 1575
	Dose 2	n (%)	22 (23.4)	12 (37.5)	10 (27.8)
		mean	1360.25	1352.80	1369.18
		SD	148.01	114.33	187.02
		median	1383.75	1332.75	1440
		min, max	1000; 1575	1185; 1515	1000; 1575
	Dose 3	n (%)	22 (23.4)	12 (37.5)	10 (27.8)
		mean	1363.63	1352.88	1376.52

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	Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
	SD	141.13	113.83	174.06
	median	1383.75	1332.75	1440
	min, max	1046; 1575	1196; 1515	1046; 1575
Dose 4	n (%)	22 (23.4)	12 (37.5)	10 (27.8)
	mean	1362.30	1350.18	1376.83
	SD	143.01	117.40	174.48
	median	1383.75	1332.75	1440
	min, max	1039; 1575	1183; 1515	1039; 1575
Median total dose cycle 4		1383.75	1332.75	1440
	No dose modification	15 (22.1)	8 (25.0)	7 (19.4)
	Dose reduced	1 (1.5)	1 (15.6)	0
	Reason for reduction	Toxicity (1)	Toxicity (1)	NA
	Dose delayed	8 (11.8)	5 (15.6)	3 (8.3)
	Reason for delay	Organisation (3), toxicity (4), general state (1)	Organisation (2), toxicity (3)	Organisation (1), general state (1), toxicity (1)

SD: Standard deviation, NA: not applicable

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Table 14.3.7-4: Exposure to radiotherapy

	Statistics	Total (N=68) n (%)	Arm A (N=32) n (%)	Arm B (N=36) n (%)
Total dose (Gy)	n (%)	65 (95.6)	29 (90.6)	36 (100.0)
	mean	51.70	54.81	49.19
	SD	9.76	6.46	11.24
	median	55.8	59.4	45.2
	min, max	9; 61.2	45; 59.4	9; 61.2
No interruption	n (%)	43 (63.2)	22 (68.8)	21 (58.3)
Interruption	n (%)	22 (32.4)	7 (21.9)	15 (41.7)
Interruption for more than 7 days	n (%)	7 (5.9)	3 (9.4)	4 (11.1)
Reason for interruption		- Organisation (3) - Toxicity (10) - Patient's compliance (1) - Heart attack (1) - Holiday (2) - Irradiation unit breakdown (1) - Technical problem (1) - Death (1) - Haematologic event and lung infection (1) - Unknown (1)	- Organisation (1) - Toxicity (6)	- Organisation (2) - Toxicity (4) - Patient's compliance (1) - Heart attack (1) - Holiday (2) - Irradiation unit breakdown (1) - Technical problem (1) - Death (1) - Haematologic event and lung infection (1) - Unknown (1)
Stop of radiotherapy after 45 Gy due to resectability	n (%)	25 (36.8)	8 (25.0)	17 (26.2)
Full radiotherapy with 59.4 Gy		30 (44.1)	18 (56.3)	12 (33.3)

SD: standard deviation

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16 APPENDICES

16.1 Study information

16.1.1 Protocol and protocol amendments

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16.1.2 Sample CRF

16.1.3 List of ethics committees

Site	Address	Local Ethics Committee	Local Authority
01	Universitätsklinikum Schleswig-Holstein Campus Lübeck Klinik für Strahlentherapie Ratzeburger Allee 160 23538 Lübeck	Ethik-Kommission der Medizinischen Fakultät der Universität zu Lübeck Ratzeburger Allee 160, Haus 21 23538 Lübeck	Landesamt für soziale Dienste Schleswig-Holstein Dezernat 31 Arzneimittelüberwachung Adolf-Westphal-Str. 4 24143 Kiel
02	Klinikum der Universität München Campus Großhadern Klinik für Strahlentherapie und Radioonkologie Marchionistr. 15 81377 München	Ethik-Kommission der Medizinischen Fakultät der LMU München Pettenkoferstr. 8a 80336 München	Regierung von Oberbayern Zentrale Arzneimittelüberwachung Bayern Sachgebiet 53.2 ZAB; Pharmazie 80538 München
03	Radiologische Universitätsklinik Abt. Radioonkologie und Strahlentherapie Im Neuenheimer Feld 400 69120 Heidelberg	Ethikkommission der Medizinischen Fakultät Heidelberg Universitätsklinikum Heidelberg Alte Glockengießerei 11/1 69115 Heidelberg	Regierungspräsidium Karlsruhe Referat 25 Markgrafenstr. 46 76133 Karlsruhe
04	Hämatologisch-onkologische Praxis Altona Mörkenstr. 47 22767 Hamburg	Ethik-Kommission der Ärztekammer Hamburg Humboldtstrasse 67a 22083 Hamburg	Behörde für Gesundheit und Verbraucherschutz der Freien und Hansestadt Hamburg Fachabteilung V 14 Patientenschutz und Sicherheit in der Medizin Billstr. 80 20539 Hamburg
05	Friedrich-Ebert-Krankenhaus Neumünster Kliniken für Innere Medizin Klinik für Hämatologie, Onkologie und Nephrologie Friesenstr. 11 24534 Neumünster	Ethik-Kommission bei der Ärztekammer Schleswig-Holstein Bismarckallee 8-12 23795 Bad Segeberg	Landesamt für soziale Dienste Schleswig-Holstein Dezernat 31 Arzneimittelüberwachung Adolf-Westphal-Str. 4 24143 Kiel
06	Universitätsklinikum Rostock (AÖR) Klinik und Poliklink für Strahlentherapie Südring 75 18059 Rostock	Ethikkommission an der Medizinischen Fakultät der Universität Rostock St.-Georg-Strasse 108 18055 Rostock	Landesamt für Gesundheit und Soziales Mecklenburg-Vorpommern Arzneimittelüberwachungs und –prüfstelle Wismarsche Str. 298 19055 Schwerin
07	Klinikum der Stadt Wolfsburg Medizinische Klinik II Sauerbruchstr. 7 38440 Wolfsburg	Ethik-Kommission der Ärztekammer Niedersachsen Berliner Allee 20 30175 Hannover	Staatliches Gewerbeaufsichtsamt Braunschweig Inspektorat Braunschweig Petzvalstr. 18 38104 Braunschweig
08	Klinikum der Universität Regensburg Klinik und Poliklinik für Strahlentherapie Franz-Josef-Strauß-Allee 11	Ethikkommission der Medizinischen Fakultät Universitätsklinikum Regensburg Franz-Josef-Strauß-Allee 11	Regierung von Oberbayern Zentrale Arzneimittelüberwachung Bayern

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Site	Address	Local Ethics Committee	Local Authority
	93053 Regensburg	93053 Regensburg	Sachgebiet 53.2 ZAB; Pharmazie 80538 München
09	Universitätsklinikum Leipzig Klinik für Strahlentherapie und Radioonkologie Stephanstr. 9a 04103 Leipzig	Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig Institut für klinische Pharmakologie Härtelstrasse 16-18 04107 Leipzig	Landesdirektion Leipzig Referat 24 Veterinärwesen und Lebensmittelüberwachung, Pharmazie Braunstr. 2 04107 Leipzig
10	Johannes-Gutenberg-Universität Universitätsmedizin Mainz I.Medizinische Klinik und Poliklinik Langenbeckstr. 1 55131 Mainz	Ethik-Kommission der Landesärztekammer Rheinland-Pfalz Deutschhausplatz 3 55116 Mainz	Landesamt für Soziales, Jugend und Versorgung Rheinland-Pfalz Referat 55 Arzneimittel, Tierarzneimittel Baedeker Str. 2-10 56073 Koblenz
11	Universitätsklinikum Hamburg-Eppendorf Onkologisches Zentrum Klinik für Strahlentherapie und Radioonkologie Martinistr. 52 20246 Hamburg	Ethik-Kommission der Ärztekammer Hamburg Humboldtstrasse 67a 22083 Hamburg	Behörde für Gesundheit und Verbraucherschutz der Freien und Hansestadt Hamburg Fachabteilung V 14 Patientenschutz und Sicherheit in der Medizin Billstr. 80 20539 Hamburg
13	Eberhard-Karls-Universität Universitätsklinikum Tübingen MVZ Radioonkologie Hoppe-Seyler-Str. 3 72076 Tübingen	Ethik-Kommission der Medizinischen Fakultät und am Universitätsklinikum Tübingen Gartenstrasse 47 72074 Tübingen	Regierungspräsidium Tübingen Referat 25 Übrige pharmazeutische Bereiche Konrad-Adenauer-Str. 20 72072 Tübingen
14	Friedrich-Alexander-Universität Erlangen-Nürnberg Strahlenklinik Universitätsstr. 27 91054 Erlangen	Ethik-Kommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg Krankenhausstraße 12 91054 Erlangen	Regierung von Oberbayern Zentrale Arzneimittelüberwachung Bayern Sachgebiet 53.2 ZAB; Pharmazie 80538 München
15	Otto-von-Guericke-Universität Magdeburg Medizinische Fakultät Klinik für Strahlentherapie Leipziger Str. 44 39120 Magdeburg	Ethikkommission der Otto-von Guericke-Universität Magdeburg Leipziger Strasse 44 39120 Magdeburg	Landesverwaltungsamt Sachsen-Anhalt Referat 604 Bereich 604.c - Pharmazie Ernst-Karnieth-Str. 2 06112 Halle/Saale
18	Klinikum Stuttgart – Katharinenhospital (KH) Klinik für Radioonkologie und Strahlentherapie (MVZ) Kriegsbergstr. 60 70174 Stuttgart	Ethik-Kommission der Ärztekammer Hamburg Humboldtstrasse 67a 22083 Hamburg	Regierungspräsidium Stuttgart Referat 102 Ärztliche und pharmazeutische Angelegenheiten Ruppmannstr. 21 70565 Stuttgart

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Site	Address	Local Ethics Committee	Local Authority
19	Städtisches Klinikum Magdeburg Krankenhaus Olvenstedt Klinik für Allgemein- und Viszeralchirurgie Binkenallee 30 39130 Magdeburg	Sächsische Landesärztekammer Körperschaft öffentlichen Rechts Ethikkommission Postfach 100465 01074 Dresden	Landesverwaltungsamt Sachsen-Anhalt Referat 604 Bereich 604.c - Pharmazie Ernst-Karnieth-Str. 2 06112 Halle/Saale

16.1.4 List of sites

Site	Address	Participation
01	Universitätsklinikum Schleswig-Holstein Campus Lübeck Klinik für Strahlentherapie Ratzeburger Allee 160 23538 Lübeck	**Aug 2011 – Sep2018**
02	Klinikum der Universität München Campus Großhadern Klinik für Strahlentherapie und Radioonkologie Marchionistr. 15 81377 München	**Aug 2011 – Sep2018**
03	Radiologische Universitätsklinik Abt. Radioonkologie und Strahlentherapie Im Neuenheimer Feld 400 69120 Heidelberg	**Aug 2011 – Sep2018**
04	Hämatologisch-onkologische Praxis Altona Mörkenstr. 47 22767 Hamburg	**Aug 2011 - Mar 2015**
05	Friedrich-Ebert-Krankenhaus Neumünster Kliniken für Innere Medizin Klinik für Hämatologie, Onkologie und Nephrologie Friesenstr. 11 24534 Neumünster	**Aug 2011 - Mar 2015**
06	Universitätsklinikum Rostock (AÖR) Klinik und Poliklink für Strahlentherapie Südring 75 18059 Rostock	**Aug 2011 - Mar 2015**
07	Klinikum der Stadt Wolfsburg Medizinische Klinik II Sauerbruchstr. 7 38440 Wolfsburg	**Aug 2011 – Sep2018**
08	Klinikum der Universität Regensburg Klinik und Poliklinik für Strahlentherapie Franz-Josef-Strauß-Allee 11 93053 Regensburg	**Aug 2011 - Mar 2015**
09	Universitätsklinikum Leipzig Klinik für Strahlentherapie und Radioonkologie Stephanstr. 9a 04103 Leipzig	**Aug 2011 – Sep2018**
10	Johannes-Gutenberg-Universität Universitätsmedizin Mainz I.Medizinische Klinik und Poliklinik Langenbeckstr. 1 55131 Mainz	**Aug 2011 – Sep2018**
11	Universitätsklinikum Hamburg-Eppendorf Onkologisches Zentrum Klinik für Strahlentherapie und Radioonkologie Martinistr. 52 20246 Hamburg	**Aug 2011 – Sep2018**
13	Eberhard-Karls-Universität Universitätsklinikum Tübingen MVZ Radioonkologie Hoppe-Seyler-Str. 3 72076 Tübingen	**Sep 2011 – Sep2018**
14	Friedrich-Alexander-Universität Erlangen-Nürnberg	**Jun 2012 – Sep2018**

Site	Address	Participation
	Strahlenklinik Universitätsstr. 27 91054 Erlangen	
15	Otto-von-Guericke-Universität Magdeburg Medizinische Fakultät Klinik für Strahlentherapie Leipziger Str. 44 39120 Magdeburg	**Jun 2012 - Mar 2015**
18	Klinikum Stuttgart – Katharinenhospital (KH) Klinik für Radioonkologie und Strahlentherapie (MVZ) Kriegsbergstr. 60 70174 Stuttgart	**Feb 2013 – Sep2018**
19	Städtisches Klinikum Magdeburg Krankenhaus Olvenstedt Klinik für Allgemein- und Viszeralchirurgie Binkenallee 30 39130 Magdeburg	**Dec 2012 – Sep2018**

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16.1.5 Signature LKP

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16.1.6 List of patients receiving test drug(s)/investigational product(s) from specific batches where more than one batch was used

Patient number	Batch numbers
010001	133830, 136027, 133830, 139009, 139173
010002	NA
010003	133830, 136027, 139009, 139173
010004	NA
010005	NA
010006	133830, 139173, 144522, 147896
010007	NA
010008	NA
010009	133830, 143387, 149194, 155278, 156955, 155279, 158076
010010	143387, 151894, 155278, 155279, 156955, 156956, 158076, 159897
010011	NA
010012	151894, 156955, 156956, 159897, 162453
010013	NA
010014	NK
010015	151894, 156096, 157910, 162623, 165096, 168928, 169297
010016	NA
010017	NA
010018	168928, 171167, 180826, 181784
010019	NA
010020	NA
010021	NA
010022	NA
010023	180826
010024	194547, 180826, 198653, 200141, 203620
010025	198315, 198653, 200141, 203620
010026	NA
010027	NA
010028	190638, 204776, 208199, 212882, 214365
010029	NA
010030	215178, 212883, 219365
020001	NA
020002	NA
020003	NA
020004	NA
030001	140088, 142385, 149325, 152290, 152901
030002	149325, 152901, 152902, 155279
030003	149325, 151894, 155279, 156956, 156967, 164486, 165613
030004	NA
030005	151894, 156967, 165613
030006	NA
030007	165613, 186104, 189686
030008	NA
070001	NA
070002	NA
070003	214367, 218143
090001	NA
100001	140088, 142990
100002	NA
100003	NA
100004	NA

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Patient number	Batch numbers
100005	NA
100006	NA
100007	NA
100008	NA
100009	NA
100010	142990, 149194, 168928, 168960
100011	NA
100012	NA
100013	149194, 168928, 168960
100014	NA
100015	168960, 186104, 190466
100016	168960, 186104, 190466
100017	NA
100018	186104, 190446, 190466, 193827
100019	193827, 203620
100020	186104, 193827, 197075, 203620, 204776
100021	NA
110001	139198, 140227, 149699, 149782
110002	187406, 189683, 208119, 212882
130001	NN
130002	NA
130003	NA
140001	173980
190001	NA

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16.1.7 Randomisation scheme and codes

16.2 Patient data listings

16.2.1 Study information listings

16.2.2 Efficacy data listings

16.2.3 Safety data listings

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16.2.4 Listing of individual laboratory measurements by patient, if required by regulatory authorities

Not included, will be shown on request of the competent authority.