Clinical Study Protocol

Study protocol No.	**LEOPARD-II**
EudraCT No.	**2010-023427-18**
Title	Definitive radiochemotherapy with 5-FU / cisplatin plus/minus cetuximab in unresectable locally advanced esophageal cancer: a phase II study
Study phase	II
Coordinating Investigator	Dirk Rades, MD (LKP according to §40 AMG) Department of Radiation Oncology
Sponsor	University Hospital Schleswig-Holstein, Campus Luebeck, Ratzeburger Allee 160, 23538 Luebeck
Date/Version	**Version final 3.0 2016.10.06**

Abbreviations

5-FU	5-fluorouracil
ADR	adverse drug reaction
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	desoxyribonucleic acid
DLT	dose limiting toxicity
EC	Ethic's 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
ICH	International Conference on Harmonisation
IgG	immunglobulin 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	quartal 3, quartal 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

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APPENDICES

1 Synopsis

Study number	Definitive radiochemotherapy with 5-FU / cisplatin plus/minus cetuximab in unresectable locally advanced esophageal cancer: a phase II study
EudraCT number	2010-023427-18
Acronym	LEOPARD-II
Sponsor	University Hospital Schleswig-Holstein, Campus Luebeck, Ratzeburger Allee 160, 23538 Lübeck
Principal investigator	Dirk Rades, MD, University Hospital Schleswig-Holstein, Campus Luebeck, Department of Radiation Oncology, Ratzeburger Allee 160, 23538 Lübeck
Study phase	Phase II
Study center(s)/country(ies)	Approximately 15 German Centers
Planned study period (first enrollment-last subject out)	**Start of Enrolment (FPI): Q3 / 2011**
	End of Enrolment (LPI): Q4 / 2016
	End of Treatment period (LP off treatment): Q1 / 2017
	End of Follow-up period (LP off study): Q1 / 2019
Study objectives	**Primary objective:** 2-year overall survival (OS)
	Secondary objectives: • 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 4.0) • Overall response rate (RECIST Version 1.1) • Quality of Life (EORTC QLQ-C30 and QLQ OES18) In addition the following parameters will be assessed irrespective of a specific time point: • OS • PFS • MFS
Study design and plan	This is an open-label, randomized Phase II study in patients with unresectable esophageal cancer
Planned number of patients	**Total number of patients:** 72-78 patients
	Number of patients per center: 9-15
	Number of patients per treatment arm: 33-36 patients

Schedule of visits and assessments	**Within 4 weeks prior to treatment start** • Written informed consent • Medical History • Clinical staging (endoscopy incl. biopsy) • Endoscopic ultrasound • Tumor Assessment CT/MRI chest and abdomen • ECG and LVEF • FEV_1 • Evaluation by a surgeon with respect to resectability • Tissue immunohistochemistry **Within 7 days prior to treatment start** • Height, weight, vital signs • Karnofsky-Performance Status • Hematology (leucocytes, neutrophils, platelets, erythrocytes, hemoglobin) • Clinical Chemistry (sodium, potassium, calcium, magnesium, creatinine, bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, γ-GT) • Pregnancy test in women of child-bearing potential • Serum sample (10 ml) and whole blood sample (10 ml) for EGFR and ligands determination (if patient agrees to participate in translational study) **<u>Evaluations during radio-immunochemotherapy:</u>** **Weekly:** • Vital signs • Weight • Hematology (leucocytes, neutrophils, platelets, erythrocytes, hemoglobin) • Clinical signs and symptoms, toxicity according to the NCI-CTC version 4.0 • DC-MRT: at day 7 (+/-2) or day 14 (+/-2) of the first cycle (in selected centers) **Every 4 weeks:** • Karnofsky-Performance Status • Biochemistry (sodium, potassium, calcium, magnesium, creatinine, bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, γ-GT) **After 4-4.5 weeks (36-41.4 Gy):** • Endoscopy (incl. biopsy, if patient agrees to participate in translational study) • Endoscopic ultrasound (optional) • Tumor assessment (CT/MRI chest and abdomen) • serum sample (10 ml) for EGFR and ligands determination (if patient agrees to participate in translational study)

	• Re-evaluation by a surgeon with respect to resectability* **: If resectability has been achieved, radiochemotherapy +/- cetuximab is stopped after 45 Gy, and the patient is referred to surgery. If resectability has not been achieved, radiochemotherapy +/- cetuximab is continued.* **End of Treatment (planned after 14 weeks):** At the end of study treatment or at the time of premature withdrawal for any reason the following assessments will be performed: • Vital signs • Karnofsky-performance status • Hematology (leucocytes, neutrophils, platelets, erythrocytes, hemoglobin) • Clinical Chemistry (sodium, potassium, calcium, magnesium, creatinine, bilirubin, SGOT, SGPT, LDH, alkaline Phosphatase, γ-GT) • Clinical signs and symptoms, toxicity according to the NCI-CTC version 4.0 • Endoscopy (incl. biopsy, if patient agrees to participate in translational study) • Endoscopic ultrasound (optional) • Tumor Assessment (CT/MRI chest and abdomen) • serum sample (10 ml) for EGFR and ligands determination (if patient agrees to participate in translational study) **Follow up period:** • Evaluation of toxicity • Treatment outcome • Endoscopic ultrasound (optional) • Tumor Assessment (CT/MRI chest and abdomen)
Diagnosis	Initially unresectable esophageal cancer

Criteria for inclusion	• 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 (please define in CRF).* • KPS ≥ 70 • Women of child-bearing potential must 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, hemoglobin $\geq$ 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 Cockroft-Gault equation) • No known allergy against chimeric antibodies • Effective contraception for both male and female patients if the risk of conception exists

Criteria for exclusion	• 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
Investigational therapy: dose/mode of administration/ dosing schedule	**Product:** 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). **Dosing schedule:** Initial dose of 400 mg/m^2 (day 1), followed by weekly doses of 250 mg/m^2 for a total of 14 weeks. **Mode of administration:** intravenous infusion

Concomitant anti-tumor therapy: dose/mode of administration/ dosing schedule	**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. 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 course (i.e. on days 8-11, 36-39, 71-74 and 99-102) Radiotherapy: 59.4 Gy (33 fractions of 1.8 Gy) will 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 will be administered to the loco-regional lymph nodes. If resectability has been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy will be stopped at 45 Gy and patient will 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 course (i.e. on days 1-4, 29-32, 64-67 and 92-95) Radiotherapy: 59.4 Gy (33 fractions of 1.8 Gy) will 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 will be administered to the loco-regional lymph nodes. If resectability has been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy will be stopped at 45 Gy and patient will undergo surgery.
Planned treatment duration per subject	The planned treatment duration per patient is 14 weeks. The planned duration of radio-immunochemotherapy is 6.5 to 7 weeks. Patients will be withdrawn at any time during the study if they develop unacceptable toxicities or if they withdraw the consent to participate in the trial. Ongoing adverse events related to study treatment will be followed for 6 weeks (skin toxicities until outcome is known) after end of treatment.
Primary target variable	2-year overall survival (OS)
Secondary efficacy target variables	• 1-year OS • 1-year and 2-year PFS • 1-year and 2-year LC • 1-year and 2-year MFS • Overall response rate (RECIST Version 1.1)

Tolerability/safety variable(s)	Toxicity (NCI-CTC 4.0)
Pharmacokinetics	Not applicable
Pharmacodynamics, -genomics and/or -genetics	Not applicable
Quality of life and pharmacoeconomics	Quality of Life (EORTC QLQ-C30 and QLQ OES18)
Other assessments	Not applicable
Data Safety Monitoring Board	A Data Safety Monitoring Board (DSMB) will be implemented to formally review safety data when 20 patients and again when 67 patients (50% of the entire cohort) are randomized and have completed 4 weeks of treatment. The DSMB will focus on safety and survival data only. In addition, the DSMB will be provided with regular reports every 6 months summarizing the same safety information used for the formal review. The key safety parameters to be monitored will be • Overall incidence of patients with any CTCAE-grade III/IV adverse event • Incidence of Serious Adverse Events (SAEs) In case of significant excess toxicity associated with the experimental arm, the DSMB may decide together with the Sponsor to stop the trial early due to safety concerns.

Statistical methods	**Treatment outcome:** Loco-regional control is defined as absence of loco-regional progression based on findings of endoscopy, endoscopic ultrasound, and computed tomography. OS, PFS, MFS and LC are calculated for both treatment groups and for several potential prognostic factors with the Kaplan-Meier method and measured from the day of randomization . Such potential prognostic factors are: age (≤60 vs. >60 years), Karnofsky performance status (100%-80% vs. 70%), tumor location (upper third vs. middle third vs. lower third), tumor length (<7 cm vs. ≥7 cm, according to endoscopy), 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 hemoglobin before radiotherapy (<12 vs. 12-14 vs. > 14 g/dl). Differences between the Kaplan-Meier curves are evaluated with the log-rank test. Results are considered significant if $P < 0.05$. Potential prognostic factors found to be significant in the univariate analysis, are evaluated in a multivariate analysis performed with the Cox proportional hazard model. Stratification at randomization according to : Histology (SCC vs. adeno) KPS (100%-80% vs. 70%) Stage (T1-3 N0-1 vs. T4 and/or N2 and/or M1a) **Toxicity:** Both treatment groups are compared for toxicity using the Chi-square test.

Sample size calculation and explanation	This is an explorative randomized study with 2 parallel groups. Using a standard single-stage phase II design by FLEMING (1981), n = 62 patients evaluable for efficacy have to be recruited. As a similar number of patients is to be recruited to the standard arm, a total number of 124 patients is required. The standard treatment control group serves 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 potentially drop outs 67 patients per arm will be recruited. The OS rate after 2 years is chosen as primary efficacy endpoint. The estimation of the efficacy rate of 40% of the reference group is based on the findings of several studies *(Bedenne 2007, Herskovic 1992, Minsky 2002, Stahl 2005, Al-Sarraf 1997, Cooper 1999).* Therefore, the respective experimental therapy arm would be rated as insufficiently active, if the observed OS rate at 2 years is 40 % or lower. On the other hand, the experimental therapy would be considered to be a very 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. Probability to accept the experimental therapy as promising (> 45% OS rate) with respect to efficacy, in spite of a true OS rate of ≤ 40%: 5% (type I error). Probability to reject the experimental therapy as not sufficiently efficient (≤ 40%), although the true OS rate is promising (> 45%): 20% (type II error, corresponding to a power of 80%). The final conclusion of this trial will depend on the definite 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.
End of the study	The end of study is reached when the last patient has completed the 2-year Follow-up period.

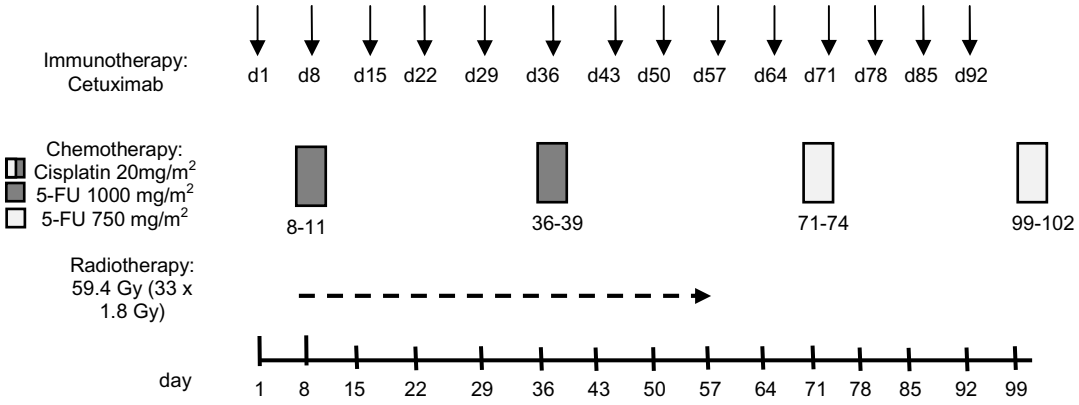
Schedule of Assessments

	Screening		Radio-immunochemotherapy				
Evaluation	**Day -28 to 0**	**Day -7 to 0**	**weekly**	**every 4 weeks**	**after 4-4.5 weeks**	**End of Treatment**	**Follow-Up** (every 3 month)[8]
Written informed consent	X						
Medical history	X						
Clinical staging (endoscopy incl. biopsy)	X				X	X	
Endoscopic ultrasound	X				X	X	X
Tumor 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

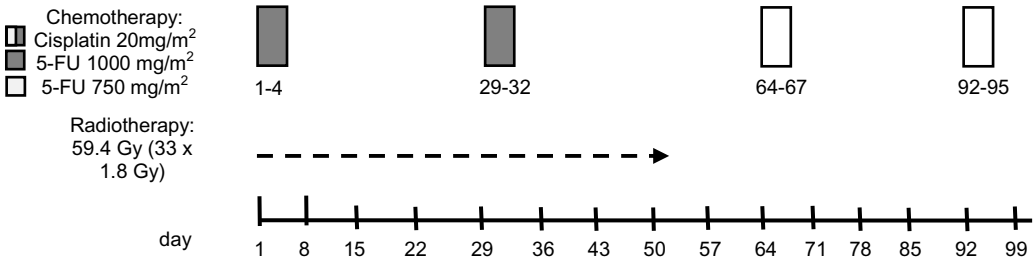
1: vital signs weekly during radio-immunochemotherapy: prior, during and after each cetuximab-infusion
2: Hematology includes: leucocytes, neutrophils, platelets, erythrocytes, hemoglobin
3: Clinical chemistry includes: sodium, potassium, calcium, magnesium, creatinine, bilirubine, SGOT, SGPT, LDH, alkaline 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 agrees 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 will be assessed using the EORTC QLQ-30 questionnaire and the esophagus-specific EORTC QLQ-OES18 module
8: The first follow-up assessment will be performed 3 months after the end of treatment assessment. Follow-up assessments will terminate 2 years after the last patient has completed end of treatment (incl.biopsy, if patient agrees to participate in translational study).

Study Design Flow Chart

Arm A



Arm B



2 Introduction and study background

2.1 Disease background

Esophageal cancer is a highly aggressive neoplasm, a disease of which more than 90% of patients positively diagnosed die of [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].
Although esophageal squamous cell carcinoma cases have steadily declined, the incidence of gastroesophageal junction adenocarcinoma has increased 4%-10% per year among U.S. men since 1976, more rapidly than for any other cancer type, and parallels rises in population trends in obesity and reflux disease [3, 4].
With advances in surgical techniques and treatment, the prognosis of esophageal cancer has slowly improved over the past three decades. However, the 5-year overall survival rate (14%) remains poor, even in comparison with the dismal survival rates (4%) from the 1970s [5]. Underlying reasons for this disappointingly low survival rate are beyond others 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 [6].
Clearly, additional strategies are needed to improve our systemic treatment options. Over the past decade, the field of drug development has been transformed with the identification of and ability to direct treatment at specific molecular targets.

2.2 Current 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.

Treatment decisions are often individualized with respect to the patient's stage and underlying co-morbidities. For patients with bulky advanced tumors unlikely to be cured surgically, upfront chemoradiation is often preferred. With sufficient tumor downstaging, preoperative chemoradiation can be followed by salvage surgery, especially for those patients with residual disease [7]. Preoperative chemoradiation has yet to show a significant improvement in overall survival compared with surgery alone in a prospective randomized trial, although there is a trend of higher survival rates (40%–60%) in those with pathologic complete responses (pCRs) at surgery [8, 9].

Metastatic or unresectable esophageal cancer is found at presentation in more than 50% of patients and remains incurable. Chemotherapy is considered palliative, improving quality of life and dysphagia in 60%–80% of patients [10–12]. Typical clinical and radiographic responses last for fewer than 4 months, with a median overall survival time of 8–10 months. Although a survival benefit has yet to be demonstrated with chemotherapy in advanced esophageal cancer, clinical trials in metastatic gastric cancer have consistently shown a survival benefit with chemotherapy compared with best supportive care alone [13].

One current research focus has been the development of more active and tolerable preoperative cisplatin-containing chemoradiation regimens. Standard chemotherapy regimens with paclitaxel or irinotecan have being studied, as well as those with newer targeted agents.

Chemotherapy can be given as a single agent or in combination, usually in a cisplatin-containing regimen. Active agents include cisplatin, 5-FU, the taxanes, irinotecan, mitomycin C, etoposide and vinorelbine. Response rates for single agents range from 15%–30% [13].

Combination regimens, usually containing cisplatin, tend to produce higher response rates (30%–57%), with occasional patients achieving complete responses (0%–11%) [10–12, 14–17]. However, with the combination regimens, the median survival time remains less than 10 months. Recent randomized trials have indicated that adding a third agent to the combination of 5-FU and cisplatin, either epirubicin or docetaxel modestly improve response rates, time to progression, and survival with greater therapy-related toxicity [18, 19].

2.3 Novel targeted therapies for esophageal cancer

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 tumor 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 [20–23]. EGFR blockade through monoclonal antibodies (Cetuximab, Matuzumab and Panitumumab) and tyrosine kinase inhibitors (gefitinib, erlotinib) has translated into promising evidence of clinical benefit in clinical trials [2].
EGFR-targeted agents are generally well tolerated and are typically not associated with the severe adverse events often seen with cytotoxic chemotherapy.
Other strategies involve *ras*-mediated signal transduction using inhibitors of farnesyl transferase to block the post-translational modification of the *ras* oncogene. Inhibitors of vascular growth factor (bevacizumab) and vascular growth factor receptors (PTK787/ZK222584) and matrix metalloproteinase target the effects of the host environment and are currently also subjects in clinical trials as an adjunct to more traditional cytotoxic therapies [3]. Evidence suggests that novel agents can be administered alone or in combination with standard therapies such as 5-FU or radiation with little additional toxicity. These ongoing and future research efforts will clarify the optimal use and survival benefit of targeted therapies for patients with esophageal cancer.

2.3.1 Epidermal growth factor receptor

The EGFR is a transmembrane glycoprotein, which is commonly expressed, in many normal human tissues. It was one of several growth factors and their receptors, which were found to be encoded by proto-oncogenes. It is a member of the tyrosine kinase family of growth factor receptors, and is over-expressed in many human tumor types. The EGFR, when situated in the transmembrane position, has an extracellular domain, which provides a ligand-binding site for epidermal growth factor (EGF) and transforming growth factor alpha (TGFα). The intracellular domain of EGFR is activated upon ligand binding, which triggers the EGF-mediated tyrosine kinase signal transduction pathway and cascades many cellular operations concerning cell growth and division.

Analyses performed in vitro, using cell lines with a high degree of EGFR expression have shown a proliferation of cells in culture, probably due to activation via an autocrine pathway. In contrast, EGFR antagonists, which block the ligand-binding site, have been developed in order to inhibit proliferation of EGFR-expressing cells.

Table 1 indicates the prevalence of EGFR expression in some common tumor types.

Table 1: Prevalence of EGFR expression in common tumor types

Tumor Type	Percentage of EGFR Expression
Esophagus carcinoma	92%
Squamous cell carcinoma of the head and neck (SCCHN)	90%
Pancreatic carcinoma	89%
Colorectal carcinoma (CRC)	82%
Prostate carcinoma	65%
Bladder carcinoma	65%
Epithelial ovarian carcinoma	60%
Cervical carcinoma	60%
Renal cell carcinoma	50%
Non-small cell lung carcinoma (NSCLC)	50%

2.3.2 Cetuximab

A novel targeted therapy, cetuximab (ERBITUX®) has recently been introduced in the United States, European Union, Switzerland, Mexico and Argentina, and is in the regulatory approval procedure in many other countries. 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 has 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, squamous cell carcinoma of the head and neck and non-small cell lung cancer, with cetuximab given either in combination studies with chemotherapy and radiotherapy or as monotherapy. The main side effects of cetuximab monotherapy are hypersensitivity- and acne-like skin reactions.

2.3.2.1 Cetuximab in chemotherapy

Over the past years, cetuximab has shown promising results in colorectal and head and neck cancer trials. For metastatic colon cancer patients who previously failed irinotecan, cetuximab plus irinotecan produced a response rate of 23%, and as a single agent, the response rate was 9%–11% [25, 26]. The median time to progression was significantly greater in the irinotecan/cetuximab group than in the cetuximab monotherapy group (4.1 months versus 1.5 months, $p < .001$). However, there was no significant difference in overall survival (8.6 months versus 6.9 months, $p = .45$) [25]. These results suggest that the addition of cetuximab helps overcome irinotecan resistance. Patients enrolled in these trials were required to have immunohistochemical (IHC) evidence of positive EGFR expression. Recent studies illustrate that EGFR-negative tumors have the potential to respond to cetuximab and that IHC techniques do not have a predictive value [27]. However, acneiform skin rash consistently correlates with response and survival [25, 28].

In head and neck cancer, several phase II studies have evaluated the combination of cetuximab with platinum-based regimens in pretreated patients with recurrent or metastatic head and neck cancer, with a control rate (complete response [CR] + partial response [PR] + stable disease [SD]) in the range of 29%–66%. In the randomized Eastern Cooperative Oncology Group phase III trial, there was a significant difference in response rate between cisplatin plus cetuximab and cisplatin alone (22.6% versus 9.3%, $p = .05$). While there was a

trend favoring the combination arm in terms of progression-free and overall survival, this underpowered study did not reach statistical significance [29].

Given these encouraging results from the colorectal and head and neck cancer trials, there is active clinical research in esophageal cancer patients with antibody inhibition of the EGFR. Overexpression of EGFR via IHC analysis occurs in 30%–90% of esophageal cancer cases and correlates with poor prognosis [20, 22, 24, 30, 31]. In a retrospective review of 38 patients with resected gastroesophageal adenocarcinoma, Wilkinson et al. demonstrated that poorly differentiated adenocarcinomas of the esophagus demonstrated higher EGFR expression than low-grade tumors based on IHC analysis (57% versus 13%, p = .02). The median overall survival times were 35 months for EGFR-negative patients and 16 months for EGFR-positive patients [30]. Kitagawa and colleagues showed that the cumulative survival rate for patients with *EGFR* gene amplification in their primary tumors was significantly lower than that for patients without amplification (p < .001). A significant correlation was also observed between extensive lymph node involvement at the time of surgery and *EGFR* gene amplification (p < .05) [23].

In two phase I studies, EGFR-directed antibodies have 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 a durable, 6-month PR [32]. In addition, a phase I trial with ABX-EGF, a fully human IgG2 EGFR mAb, reported stable disease for 7 months in one esophageal cancer patient [33]. Preclinical and these early clinical studies suggest potential activity and minimal toxicities with EGFR antibodies for esophageal cancer.

Lorenzen et al. [34] reported a randomized 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.

2.3.2.2 Cetuximab in combination with radiotherapy

Preclinical studies have shown, that Cetuximab enhances the radiosensitivity of EGFR-expressing tumor cells in vitro and in tumor xenografts [35, 36] and the repopulation of epithelial tumor cells after exposure to radiation is related to the activation and expression of EGFR [37, 38]. Cetuximab also enhanced the efficacy of docetaxel chemoradiotherapy in human adenocarcinoma xenografts [39].

So far, cetuximab in combination with radiotherapy has mainly been investigated in head and neck cancer.

Radiation or radiochemotherapy are the standard treatment options for locally advanced, unresectable head and neck cancer. However, with conventional radiotherapy, the relapse-free survival is still disappointing and the majority of patients die from locoregional recurrence. Several attempts have therefore been made to improve the outcome of these patients. In a dose-finding phase I study performed by Robert et al [40], 16 patients with advanced head and neck cancer were treated with conventional or hyperfractionated radiotherapy together with cetuximab. The monoclonal antibody was delivered at a loading dose of 100 to 500 mg/m^2, followed by weekly infusions of 100 to 250 mg/m^2 for 7 to 8 weeks. 15 patients were evaluable for response and all achieved an objective response (13 complete and 2 partial remissions). The median time to progression was 8 months and the 2-year survival rate was 65%. The treatment was well tolerated with asthenia, fever, nausea and skin toxicities being the most common adverse experiences. The recommended dose for cetuximab was defined with a loading dose of 400 to 500 mg/m^2 and a maintenance dose of 250 mg/m^2. Cetuximab was further evaluated in a randomized phase III study which

assessed radiation alone for 6 to 7 weeks compared with radiation plus weekly cetuximab in 424 patients with locoregionally advanced head and neck cancer [41]. The addition of cetuximab to radiotherapy resulted in statistically significant prolongation of overall survival (54 months versus 28 months, p=0.02). Again, the immunoradiotherapy was well tolerated with most of the side effects related to the high dose radiation. Grade 3 to 4 infusion reactions were observed in 3% of the patients treated with cetuximab.
Su et al. [42] observed in a phase II study very promising overall survival data of a combination of Cetuximab with Cisplatin (100 mg/m^2 d1 and 22) concurrent to radiotherapy with concurrent boost. 76% of the patients were alive after three years with a locoregional control rate of 71% and progression free survival after 3 years of 56%. However, frequent typical radiochemotherapy-associated toxicities were observed with 2 deaths on therapy (pneumonia and unknown cause) and 3 severe adverse events (myocardial infarction, bacteremia, arrhythmia). These events led to early study closure after 22 of 25 planned patients.
Based on this study the RTOG started a phase III trial evaluating the addition of cetuximab to Cisplatin concurrent to radiotherapy (RTOG 0522). Recruitment of over 900 patients were closed as planned without reporting of safety issues.

Several phase I and II studies evaluating cetuximab in combination with chemoradiotherapy for patients with esophageal carcinoma have reported first data on congresses. Safran et al. [43] observed esophagitis rates (12% grade 3 and 3 % grade 4) in 60 patients treated with cetuximab and paclitaxel, carboplatin, and 50.4 Gy radiation comparable to treatment schedules without cetuximab. 70% of the patients had a complete clinical response after chemoradiation. 28 patients were treated preoperatively with 3 cycles cisplatin, docetaxel, and cetuximab followed by 45 Gy radiation combined with weekly cisplatin (25 mg/m^2) and cetuximab in a Phase IB/II trial [44]. After 7 patients without limiting toxicities, weekly docetaxel (20 mg/m^2) was added to the chemoimmunoradiation. There were no deaths 30 days post surgery and no treatment-related death after a follow-up of 1 year. Complete or near pathologic regression was found in 68% of the patients. R0 resection was performed in 25 patients and 1-year overall survival was 86%.

2.3.2.3 Cetuximab general safety information

Adverse event data are available for 3339 patients treated with cetuximab alone or in combination with chemotherapy and/or radiation therapy from investigational trials across all indications conducted by ImClone, BMS, Merck KGaA, Investigator sponsored Trials (IST), Cooperative Groups and the National Cancer Institute (NCI). As most of the trials were conducted under different settings and in combination with various cytostatic therapies, adverse reaction rates cannot be validly pooled and quoted as mean rates. Nethertheless, they constitute a basis for identifying approximate adverse event rates associated with the administration of Cetuximab.
Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia). The majority of skin reactions develop within the first three weeks of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed [45]. Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. In the event of Grade 3 or 4 skin reactions the patients should be referred for dermatological advice.
The incidence of radiation dermatitis of any grade was comparable between the treatment groups in a phase 3 SCCHN trial in patients receiving either cetuximab in combination with RT (86%) or RT alone (90%) [46].
Other side effects observed in patients receiving cetuximab monotherapy include asthenia, dyspnoea, mucositis, nausea, pain, fever and headache.
Mild or moderate infusion-related reactions may occur (≥ 1/10) comprising symptoms such as fever, chills, nausea, vomiting, headache, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first cetuximab infusion [45]. They can be managed by

slowing the infusion rate of cetuximab and by the continued use of pre- medications for subsequent doses in addition to the mandatory use for the first infusion.
Severe infusion-related reactions may occur (≥ 1/100, < 1/10), in rare cases with fatal outcome. They usually develop during or within 1 hour of the initial cetuximab infusion and may include symptoms such as rapid onset of airway obstruction (bronchospasm, stridor, hoarseness, difficulty in speaking), urticaria, hypotension, or loss of consciousness; in rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed. Severe infusion reactions (grade 3 or 4) require immediate interruption of the cetuximab infusion and permanent discontinuation from further treatment [45].
A large multinational study of cetuximab plus irinotecan in irinotecan-resistant metastatic colorectal cancer (MABEL) investigated in a post-hoc analysis whether the type of prophylactic pre-medication had an impact on the incidence of infusion-related reactions including allergic/hypersensitivity reactions. The incidence of infusion-related reactions was lower in patients who received anti-histamines and corticosteroids as prophylactic medication (9.6%, n=700) compared to patients who received anti-histamines but not corticosteroids (25.6%, n=422). A similar trend was seen in the analysis of the grade 3/4 infusion-related reactions (1% vs. 4.7%). These data suggest that the addition of corticosteroids to antihistamines as prophylactic pre-medication seems to reduce the incidence of infusion-related reactions such as allergic/-hypersensitivity reactions [47].
Progressively decreasing serum magnesium levels have been observed leading to severe hypomagnesaemia in some patients. Hypomagnesaemia is reversible following discontinuation of cetuximab. Depending on severity, other electrolyte disturbances, mainly hypocalcaemia or hypokalaemia, have also been observed. Determination of serum electrolyte levels is recommended prior to and periodically during cetuximab treatment. Electrolyte repletion is recommended, as appropriate.

For supplementary information see also the EU Summary of Product Characteristics (4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

2.3.2.4 Clinically relevant adverse events related to cetuximab

Skin reactions are the most common AEs associated with cetuximab. They usually present as an acneform rash, acne-like rash or, less frequently, as nail disorders. Acneform rash/Acne-like rash usually occurs in the first 3 weeks of treatment on the face, upper chest and back, but occasionally extends to the extremities. It occurs as multiple follicular or pustular lesions characterized histologically as lymphocytic perifolliculitis or suppurative superficial folliculitis. It tends to resolve without sequelae over time following cessation of therapy. In patients who have received cetuximab in doses lower than 100 mg/m^2, the acne-like rash has been reported infrequently and has been restricted to grades 1 and 2. The etiology of the acne-like rash is believed to be the result of cetuximab interfering with the role of EGFR in the homeostasis of epidermis, hair follicle and sebaceous glands as well as in the regulation of cutaneous inflammation. Clinical trials in patients with CRC have shown that the occurrence of acne-like skin reactions were correlated with better efficacy outcomes (response, and time to progressive disease and survival).

Nail disorders: Another typical but less frequent reported AE is nail disorder which presents as pain, tenderness and fissuring of the distal finger tufts to different degrees. The patients developed paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers. The most commonly affected digits are the great toes and thumbs. From investigator reports, it is known that nail disorders may persist for up to 3 months after discontinuation of cetuximab. Dermatological advice should be sought.

Allergic/hypersensitivity reactions: Grade 3 or 4 hypersensitivity reactions (including allergic and anaphylactic reactions) characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension, have been observed in 2.5% patients treated with cetuximab. Approximately 80% of all allergic/hypersensitivity

reactions occurred during the first infusion of cetuximab and were observed during or within 1 hour of the completion of the infusion.

Prior to the first administration of cetuximab, patients must be premedicated with an antihistamine as well as with a glucocorticoid. This premedication is also recommended prior to all subsequent infusions of cetuximab as there were patients who experienced their first severe allergic/hypersensitivity reaction during later infusions. In studies with cetuximab to date, patients who experienced severe reactions received standard treatment, and all with the exception of three patients recovered without sequelae and were withdrawn from the studies concerned. Three reports exist which are associated with death.

The occurrence of allergic/hypersensitivity reactions does not appear to be related to single-drug therapy or combination therapy, underlying disease, or previous exposure to murine monoclonal antibodies. Mild to moderate allergic/hypersensitivity reactions can generally be managed by slowing the infusion rate of cetuximab

2.4 Rationale for the 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 the combination of cetuximab with standard chemotherapy or radiotherapy has mainly be investigated in clinical trials focusing on colorectal and/or head and neck cancer.
The results obtained from theses studies were 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 are encouraging showing that cetuximab can 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 present study is 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 can be increased by addition of an EGFR-targeted therapy.

2.5 Risk-benefit assessment

The clinical data available to date suggest that cetuximab in combination with a standard radiochemotherapy should be well tolerated and aggravations of 5-FU-related or radiation-related toxicities are not expected. However, in one study in head and neck cancer with high-dose radiation and cisplatin combined with cetuximab severe toxicities were observed [29]. 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 has recently closed recruitment without reporting of safety issues. As determined in our Phase I study (LEOPARD Phase I) a dose of 1000 mg/m^2 of continuous infusional 5-FU is 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 enhancement 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 is regarded as justifiable and there is no indication that patients are exposed to an increased risk associated with study participation.

If therapy-related toxicities occur during the study, dose modifications of cetuximab and 5-FU will be performed as outlined in section 5.4 of this protocol.

2.6 Contributing Scientific Investigations

2.6.1 Determination of TKR-Receptors and their Soluble Ligands

For esophageal cancer, major steps of carcinogenesis are still unknown. However, as tumor cellular blockade of different angiogenic and anti-apoptotic pathways are well known to promote carcinogenesis, expression and regulation of the EGF and other kinase dependent receptor pathways and their soluble ligands are of major interest in translational research. Thus, the targeted blockade of their pathways may be very effective to induce tumor regressions and a better clinical outcome than traditional chemotherapeutic regimens.

Thus, it is the aim of the translational study, to prospectively analyse the expression of EGF and other kinase dependent receptor pathways and their soluble ligands during Cetuximab therapy in these cancer patients. Their expression profiles will be correlated with clinical outcome, responses and survival times.

For this purpose, the serum samples, paraffin-embedded tissues, and when available fresh frozen specimens, of included patients will be characterized via ELISA, immunohistochemistry and PCR, respectively (if patient agrees to participate in translational study).

In addition, a prospective follow-up of serum levels of targeted ligands (ELISA) is planned before and during Cetuximab therapy to correlate the kinase dependent receptor pathways with initial tumor staging and response (according to Hector program, Weinheim).

2.6.2 Functional Magnetic Resonance Tomography (DC-MRT)

The functional magnetic resonance tomography (DC-MRT) can quantify blood flow, arterial permeability and the percentage of extracellular volume in tumor tissue. Clinically, the DC-MRT is of special interest to analyze the efficacy of new biological substances, which block angiogenesis or lymphangiogenesis.
One important precondition for these techniques is the development of special MRT-sequences and a program, with which the data can be processed and tissue specific parameters can be quantified. These have been established at the Department of Radiology or Dept. of Nuclear Medicine in conjunction with the Department of Physics of the Max Planck Institute in Mainz, Germany. Currently Mainz University works with the program Medlab. Pharmacokinetics can also be automatically documented. At present, the Department of Radiology of Mainz University runs three phase I to II multicenter studies with these techniques, looking at new biological substances, such as LBH589 in hematological disorders or PTK787 in lung cancer. Responsible for the project in the protocol will be K. Oberholzer, MD, Radiology Department. Therefore, the DC-MRT will be performed in an explorative manner before and during Cetuximab-therapy to analyze the influence of therapy to the tumor microcirculation with its blood flow and arterial permeability

3 Study objectives

3.1 Primary objective

Assessment of the 2-year overall survival (OS)

3.2 Secondary objectives

The secondary objectives of this study are 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 4.0)
- Overall response rate (RECIST Version 1.1)

In addition the following parameters will be assessed irrespective of a specific time point:

- OS
- PFS
- MFS

4 Study design

4.1 Overall study design and plan

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

Up to approximately 15 German centers will participate in the trial (up to 134 patients). However, the randomization to one of the two treatment groups will be stopped at December 31, 2016, at the latest, which is 2.5 years later than originally planned.

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

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
- Comorbidity:
  Pulmonary function
  Other
- Tumor location
  Upper third of the esophagus
  Relation to other organs/structures
- Other reasons (please define in CRF)

Patients will be randomized into two treatment arms (Arm A and B) and according to this treated plus or minus cetuximab.

Patients in Arm A will receive 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 course 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 course 3 and 4, i.e. on days 71-74 and 99-102. The time period between course 2 and 3 is prolonged to 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 8-11, 36-39, 71-74 and 99-102.

- Radiotherapy: 59.4 Gy (33 fractions of 1.8 Gy) will 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 will be administered to the loco-regional lymph nodes (mediastinum). If resectability has been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy will be stopped at 45 Gy and patient will undergo surgery.

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

Patients in Arm B will be 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 course 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 course 3 and 4, i.e. on days 64-67 and 92-95. The time period between course 2 and 3 is prolonged to 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) will 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 will be administered to the loco-regional lymph nodes (mediastinum). If resectability has been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy will be stopped at 45 Gy and patient will undergo surgery.

At the end of study treatment or at the time of premature withdrawal for any reason the patient will undergo an end of treatment evaluation.

The assessments to be performed in this study are summarized in the study schedule.

4.2 Selection of the study population

4.2.1 Study population and justification of choice of gender

Patients with locally advanced unresectable esophageal cancer are eligible for this study if all of the following criteria are fulfilled and the patients have provided written informed consent. There is no preferred enrolment of men or women within this study. However, pregnant or breast-feeding women are excluded from participation.

4.2.2 Inclusion criteria

For inclusion in the study, **all** of the following criteria must be met:

- 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 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 (please define in CRF).

- KPS ≥ 70
- Women of child-bearing potential must 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, hemoglobin $\geq$ 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 Cockroft-Gault equation)
- No known allergy against chimeric antibodies.
- Effective contraception for both male and female patients if the risk of conception exists

4.2.3 Exclusion criteria

Patients are not eligible for this study, if they meet **one or more** of the following 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

4.2.4 Removal of patients from the study or study treatment

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

The patient must 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 is clinically relevant and affects the patient's safety
- Occurrence of AEs, if discontinuation is 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 is a medical reason for withdrawal, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values.

If a patient has failed to attend scheduled assessments in the study, the investigator must 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 be performed, if possible. In any case, the CRF section entitled "End of Treatment" must be completed.

4.2.5 Study discontinuation

The whole study may be discontinued at the discretion of the coordinating investigator (LKP) in the event of any of the following:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs.

Safety data from the study will be reviewed by the DSMB on a regular and ongoing basis to ensure that the continuation of the study is appropriate as described in Section 10.

4.2.6 Definition of the end of treatment

Treatment of the individual patient continues until the end of treatment evaluation (i.e. 14 weeks) or until one of the criteria listed under 4.2.4 is fulfilled.

4.2.7 Plan for treatment after the end of study

Following the end of treatment evaluation or end of treatment for any other cause, patients will be treated and followed according to the guidelines of the German Cancer Society.

4.2.8 Definition of the end of study

The study terminates after the last patient has completed the 2-year Follow-up phase.

5 Treatments

5.1 Treatments administered

5.1.1 Cetuximab

5.1.1.1 Recommended materials, compatibility, storage requirements and stability

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 are recommended for use.

Cetuximab must be stored under refrigeration at +2ºC to +8ºC. It may not be exposed to direct sunlight or heat. **DO NOT FREEZE CETUXIMAB.**

Cetuximab is stable, and is compatible with infusion systems made from any combination of the recommended infusion system components when administered at room temperature (up to 25°C). Preparations of cetuximab in the recommended infusion containers are chemically and physically stable for up to 48 hours at controlled room temperatures up to 25 °C. The product contains no antimicrobial agent and should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. In-use storage at 2-8 °C should not exceed 24 hours, unless preparation has taken place under controlled and validated aseptic conditions. Discard any unused portion of the vial.

5.1.1.2 Instructions for use and handling

Do not mix cetuximab solution with any intravenously administered medicinal product other than a sterile 0.9 % NaCl solution. Use a separate infusion line for cetuximab infusion. For dose reduction due to adverse events, see the *section 5.4.1*. **If the patient is to receive chemotherapy on the same day, wait at least one hour after completing the cetuximab infusion.**

Preparation and Administration of the Infusion

Cetuximab solution contains no antimicrobial preservative or bacteriostatic agent. This means care must be taken to ensure aseptic handling when preparing the infusion.

There are two options:

Syringe Pump:

- Calculate the required amount of cetuximab per patient and administration (e.g., 250 mg/m² for a 2 m² patient = 500 mg cetuximab). Calculate the required amount in

volume cetuximab solution at 5 mg/mL (e.g., 500 mg cetuximab = 100 mL cetuximab 5 mg/mL)

- Draw up the volume calculated above from one or several cetuximab 5 mg/mL vials, using one or several appropriate sterile syringes attached to a suitable needle.
- Remove the needle, affix the infusion line to the first filled syringe, and prime it with cetuximab.
- Put the first filled syringe into the syringe pump and set the rate. Repeat for remaining syringes.
- Monitor the infusion rate. The calculated infusion rate must not exceed the maximum infusion rate of 10 mg/min, i.e. 120 mL/h of the ready-to-use solution.
- Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

Infusion Pump or Gravity Drip:

- Calculate the required amount of cetuximab per patient and administration (e.g., 250 mg/m² for a 2 m² patient = 500 mg cetuximab). Calculate the required amount in volume cetuximab solution at 5 mg/mL (e.g., 500 mg cetuximab = 100 mL cetuximab 5 mg/mL)
- Take an infusion bag of adequate size (e.g., 250 mL) of 0.9% NaCl solution for infusion (isotonic saline for infusion).
- Draw up the volume calculated above from the NaCl bag, using an appropriate sterile syringe attached to a suitable needle. Discard the drawn up NaCl solution.
- Draw up the volume calculated above from one or several cetuximab 5 mg/mL vials, using one or several appropriate sterile syringes attached to a suitable needle.
- Fill the calculated volume of cetuximab into the NaCl infusion bag.
- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Monitor the infusion rate. The calculated infusion rate must not exceed the maximum infusion rate of 10 mg/min.
- Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

A one-hour observation period is recommended after the cetuximab infusion.

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

The maximum infusion rate must not exceed 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).

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

Prior to the first infusion, patients must receive premedication with an antihistamine and glucocorticoid. This premedication is recommended prior to all subsequent infusions. Check the vital signs pre-, mid-, post- and one hour post-infusion.

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

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

5.1.2 5-Fluoruracil (5-FU)

The mechanism of action of 5-FU is based on its use as a “false” nucleotide in DNA synthesis. Like uracil, 5-FU is converted into its deoxymonophosphate within the cell. F-deoxy-UMP competitively inhibits the enzyme thymidilate synthetase and therefore stops DNA synthesis. Therefore, 5-FU shows maximal cytotoxic activity in the S-phase of the cell cycle.

5-FU is one of the oldest and most commonly used cytotoxic agents in the treatment of cancer. Main adverse reactions observed are myelosuppression, nausea and vomiting, mucositis and diarrhea. Following continuous infusion, hand-foot syndrome is commonly observed.

Commercially available 5-FU will be used. Investigators should refer to the respective Summary of Product Characteristics (SmPC) for complete prescription information such as dosage and administration, safety issues (warning, precautions), adverse reactions, dose modifications and omissions and storage information. Investigators should also follow institutional procedures for the administration of 5-FU.

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

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

5.1.3 Cisplatin

The cytotoxicity of cisplatin might be due to its ability to crosslink different DNA stands. Thus DNA replication is inhibited. Nevertheless, the mechanism of how platinum-caused DNA defects can lead to cell death is not yet known in detail.

Cisplatin is one of the most effectiv and most frequently applied substances in the treatment of metastasized and advanced gastric cancers. It is the basis of different combination regimes like ECF (epirubicin, cisplatin, 5-FU), FUP (5-FU, cisplatin), MCF (mitomycin, cisplatin, 5-FU), EAP (Etoposid, Doxorubicin, Cisplatin) FLEP (5-FU, folinic acid, etoposid, cisplatin) or FLP (5-FU, folinic acid, cisplatin).

In this trial commercially available cisplatin will be used. Investigators should refer to the respective Summary of Product Characteristics (SmPC) for complete prescription information such as dosage and administration, safety issues (warning, precautions), adverse reactions, dose modifications and omissions and storage information. Investigators should also follow institutional procedures for the administration of cisplatin.

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

All subjects must receive adequate anti-emetic therapy prior to the administration of cisplatin. It is recommended that a 5HT3 antagonist (e.g. Granisetron) and dexamethasone 8mg i.v. are administered prior to each cycle of treatment.

5.2 Methods of assigning patients to treatment

5.2.1 Randomization

Randomization (assigning patients to treatment arms A and B) will be performed centrally by the

GSO Gesellschaft für Studienmanagement
und Onkologie mbH
Harvestehuder Weg 21
20148 Hamburg
Tel.: 040 44 19 54 - 60
Fax: 040 44 19 54 - 78

The notification will be carried out via Fax with a standardized randomization-form.

To achieve uniform distribution within both treatment arms the patients will be 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 will be assigned a unique 6-digit identification number during randomization.. The first 2 digits of this number indicate the center number. The last 4 digits are 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.

5.2.2 Blinding

Not applicable

5.2.3 Procedure for emergency code-breaks

Not applicable

5.3 Special precautions

5.3.1 Cetuximab administration

Allergic/Hypersensitivity reactions

Allergic/Hypersensitivity reactions may occur during or following the administration of cetuximab. Subjects must therefore be pretreated with an appropriate antihistamine and a glucocorticoid before the first infusion. Pretreatment with an antihistamine and a glucocorticoid is recommended before subsequent infusions. As a routine precaution, subjects enrolled into this study should be observed closely for any potential AEs and a physician able to give emergency medical treatment must be present from the start of cetuximab infusion until at least 1 hour after the end of the infusion. The subject should be observed in an area with resuscitation equipment and other agents available (epinephrine, prednisolone equivalents etc). Should an allergic/hypersensitivity or infusion reaction to cetuximab occur, then the subject must be treated according to the best available medical practices. For adjustment of cetuximab treatment, see section 5.4.1. Grade 3 or 4 allergic/hypersensitivity reactions require immediate interruption of the cetuximab infusion, appropriate medical measures and permanent discontinuation of treatment. Subjects should be carefully monitored until the complete resolution of all signs and symptoms.

Skin reactions

The most common AE associated with cetuximab administration are skin reactions, particularly acne-like rash. If a subject experiences a grade 3 skin reaction, cetuximab therapy must be interrupted for up to 2 consecutive weeks. Treatment may only be resumed, if the reaction has resolved to grade 2. For recommended adjustments in dose regimen, see section 5.4.1. If grade 3 skin reactions occur a fourth time or do not resolve to grade ≤ 2 during treatment interruption, permanent discontinuation of cetuximab treatment is required.

Interstitial pneumonitis

Severe interstitial pneumonitis has been described in subjects treated with the EGFR-pathway targeting therapy gefitinib. To date, no increased risk of interstitial pneumonitis has been identified with cetuximab. Nevertheless, all subjects must have adequate chest imaging prior to commencing cetuximab therapy in the study, as a safety precaution in order to document the baseline pulmonary condition. If there are respiratory symptoms at study entry, lung function tests and further diagnostic procedures must also be undertaken in order to diagnose pre-existing pulmonary fibrosis or interstitial pneumonitis. Furthermore, subjects will be regularly questioned about pulmonary symptoms during the study. Should pulmonary symptoms appear or worsen during or after cetuximab treatment, a detailed description is required and investigators should use their discretion in ordering such diagnostic procedures as are necessary to elicit an accurate diagnosis.

Electrolyte disturbances

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia is reversible following discontinuation of cetuximab. In addition, hypokalaemia may develop as a consequence of diarrhoea. Hypocalcaemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcaemia may be increased. Determination of serum electrolyte levels is recommended prior to and periodically during cetuximab treatment. Electrolyte repletion is recommended, as appropriate.

Neutropenia and related infectious complications

Patients who receive cetuximab in combination with platinum-based chemotherapy are at an increased risk for the occurrence of severe neutropenia, which may lead to subsequent infectious complications such as febrile neutropenia, pneumonia or sepsis. Careful monitoring is recommended in such patients, in particular in those who experience skin lesions, mucositis or diarrhoea that may facilitate the occurrence of infections.

Cardiovascular disorders

An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed in the treatment of non-small cell lung cancer, squamous cell carcinoma of the head and neck and colorectal carcinoma. In some studies (non-small cell lung cancer) association with age ≥ 65 years has been observed. When prescribing cetuximab, the cardiovascular status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account.

5.3.2 Chemotherapy administration

5-Fluorouracil and cisplatin are commercially available antineoplastic agents. Investigators should use the approved package inserts of these drugs for complete prescribing information, including any special precautions.

5.4 Selection, timing and modification of dose for each patient

5.4.1 Cetuximab

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

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

Initial dose:

The total **initial dose** (first infusion) is **400 mg/m² (80 mL/m² ready-to-use solution)** and is 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 be pre-treated with an antihistamine as well as a glucocorticoid. Observe the patient during infusion and for one hour afterwards. Check the vital signs pre-, mid-, post- and one hour post-infusion. Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

Further infusions:

The **weekly dose** (all further infusions) is **250 mg/m² (= 50 mL/m² ready-to-use solution)** and is administered over a period of 60 minutes (maximum infusion rate of 10 mg/min, corresponding to 2 mL/min ready-to-use solution). It is recommended that the patient is pre-treated with an antihistamine as well as a glucocorticoid prior to each infusion. Observe the patient during infusion and for one hour afterwards. Check the vital signs pre-, mid-, post- and one hour post-infusion. Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

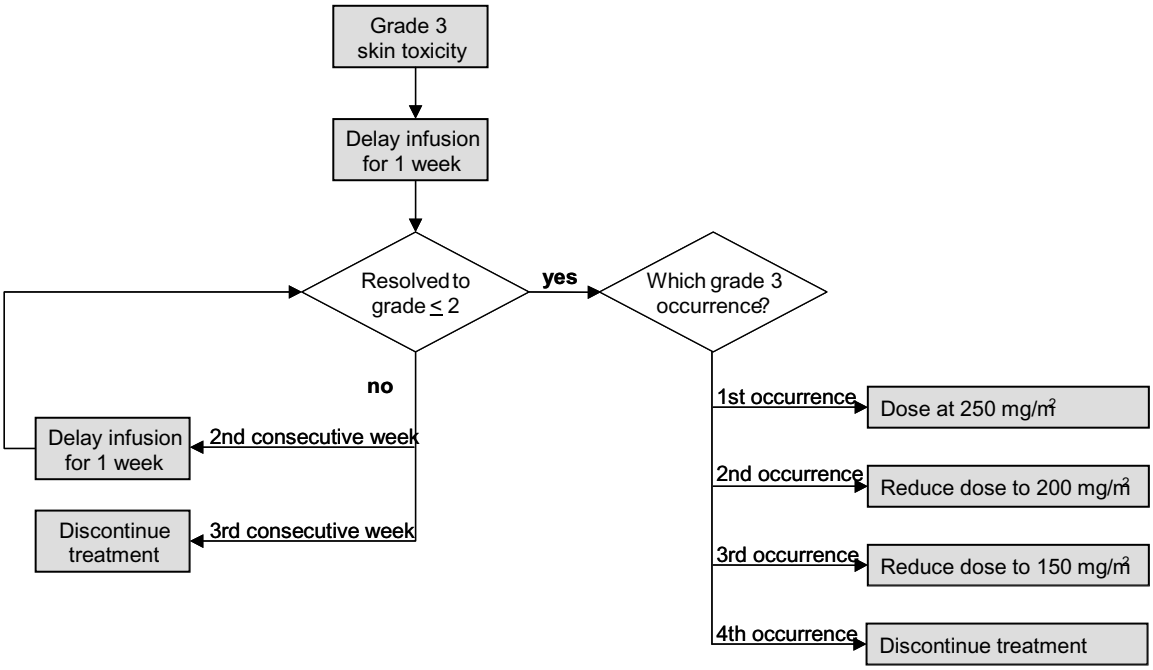
5.4.1.1 Skin toxicities

If a subject experiences a grade 3 skin toxicity (as defined in the US National Cancer Institute's - Common Toxicity Criteria [NCI-CTC], Version 4.0), cetuximab therapy may be 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 be considered. Patients with grade ≥ 3 reactions should be referred to the dermatologist for advice and management. If pruritus occurs an oral antihistamine is advised. In case of dry skin the use of emollient creams is beneficial. Fissures may occur in dry skin and topical dressings are helpful. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may resume. With the second and third occurrences of grade 3 skin toxicity, cetuximab therapy may 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 are permanent. Subjects should discontinue cetuximab if more than two consecutive infusions are withheld or a fourth occurrence of a grade 3 skin toxicity occurs despite appropriate dose reduction (see figure 1).

However, if in the opinion of the investigator the discontinuation of cetuximab is considered necessary, the subject should be withdrawn immediately.

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

Figure 1: Treatment adjustment in the event of grade 3 skin toxicity considered to be related to cetuximab.



5.4.1.2 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 may be applicable.

Table 2 Treatment adjustment in the event of cetuximab caused allergic / hypersensitivity reaction.

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, broncho- dilators, 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 has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped and the subject should be removed from the study. If a subject experiences a Grade 3 or 4-allergic/hypersensitivity reactions at any time, cetuximab should be discontinued.

5.4.1.3 Other reasons for cetuximab discontinuation

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

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

5.4.2 5-Fluorouracil

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

5.4.2.1 Dose modifications and treatment alterations for 5-FU

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

Once a 5-FU dose modification has occurred, the dosage may not be re-escalated for this patient. If therapy is delayed for longer than 2 weeks, the patient will be withdrawn from the study.

If on the day of planned 5-FU infusion one of the following toxicities occurs, a dose modification according to the following scheme will 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 occurs, a dose modification of 5-FU at the next planned infusion will be performed according to the following scheme:

Table 4: Dose modification for 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	≥ Grad 3 (≥ stools/day or incontinence)	5-FU 75% of original dose
Nausea/vomiting	≥ Grad 3	5-FU 75% of original dose

5.4.3 Cisplatin

5.4.3.1 Dose modifications and treatment alterations for cisplatin

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

Creatinine value	Dose modification
≤ 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 have to be fulfilled prior to every chemotherapy course:

- Neutrophils ≥ 1,5 x 10^9/L
- Thrombocytes ≥ 100 x 10^9/L
- Diarrhea NCI-CTC Version 4.0 Grade < 2

If these parameters are not appropriately at the scheduled time point of the new course, cisplatin administration has to be discontinued until the criteria above will be fulfilled.

If cisplatin cannot be administered for less than two weeks, the therapy will be continued with the initial dosing.

If cisplatin cannot be administered for more than two weeks the administered dose will be 75% of the original value.

If at any time during the radiochemotherapy one of the following toxicities occurs, a dose modification of cisplatin at the next planned infusion will 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
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

5.5 Radiotherapy

The radiotherapy will be administered over 6.5 - 7 weeks, in 33 fractions of 1.8 Gy up to total dose of 59.4 Gy. 50,4 Gy will be administered to the loco-regional lymph nodes. If resectability has been achieved after 4-4.5 weeks (36-41.4 Gy), radiotherapy will be stopped at 45 Gy and patient will undergo surgery.

5.5.1 Technique and dosage of radiotherapy

Radiotherapy starts 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) will be delivered in daily fractions of 1.8 Gy for 6.5 - 7 consecutive weeks (5 fractions/week). Irradiation will be performed using high energetic photons, preferably a linear accelerator with photon energies of at least 6 MV. The 95% isodose should cover the target volume.

Isocentric 3- or 4- field techniques with individual absorbers will be used. To adequately perform planning a treatment simulator and computerized 3-D-treatment planning must be used. The CT-slices should be 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 should be performed.

5.5.1 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 will be symptomatic. Generally, these acute adverse reactions abate within two to four weeks following completion of radiotherapy. In severe cases, the treatment may be interrupted for up to one week, if deemed necessary be the responsible radio-oncologist. If radiotherapy has to be stopped due to adverse reactions, the LKP has to be informed. Rare severe events are e.g.: skin reactions, pneumonitis, arrhythmia.

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

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 withbleedingnot induced by minor trauma or abrasion or perforation	Stop radiotherapy

5.6 Prior and concomitant therapy

All concomitant medication or medication administered within the 4 weeks preceding study start and during the study must be recorded in the CRF. The generic name of the medication must be specified along with the duration of the treatment.

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

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

Additional concurrent chemotherapy of radiation therapy may not 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 may be given to assist in the management of pain, infection, and other complications of the malignancy. Patients must be premedicated with an antihistamine and a glucocortiocoid prior to receiving the initial dose of cetuximab. Premedication with an antihistamine and a glucocorticoid is recommended prior to further subsequent weekly doses.

5.7 Other study conditions

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

5.8 Treatment compliance

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

The date and the exact amount of cetuximab given at each infusion will be documented in the CRF.
As a routine precaution, patients enrolled in this study will 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 has to be interrupted during infusion, the clinical staff should make an estimate of the percentage of dose received by the patient and document it in the CRF. Any reason for non-compliance should also be documented. Insufficient compliance is 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 will be considered in mutual agreement between the investigator and the Investigator-Sponsor.

6 Assessment of safety

6.1 Adverse events

6.1.1 Definition of adverse event, adverse drug reaction and serious adverse event

6.1.1.1 Adverse events (or adverse experience) (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Due to regulatory requirements, events occurring during pre- and post-treatment periods should also be designated as AEs. Therefore, safety surveillance - reporting of (S)AEs - commences at the time when the subject is enrolled into the study (date of signature of the informed consent) until the End of Study Visit has been performed. Therefore events occurring in the period between the signed informed consent and beginning of the study drug administration are to be designated as AEs. This procedure complies with requirements by some authorities.

6.1.1.2 Adverse drug reaction (ADR):

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out.

6.1.1.3 Serious adverse event or reaction/experience (SAE):

A serious AE (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

  NOTE: The term ”life-threatening” in the definition of ”serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignant tumors when they are histologically different from the primary tumor.

6.1.1.4 Other events to be treated as SAEs

Exposure to drug during pregnancy/lactation.

In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. The Investigator-Sponsor must be notified without delay and the subject followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. The “Serious Adverse Event Form” (SAE report form) should be used, even though pregnancy is not considered a SAE. No “serious criterion box” should be checked. The SAE report form is solely used to ensure expedited reporting.

6.1.1.5 Events not to be treated as SAEs

Progression of disease is not to be regarded as a SAE.

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form:

- Elective hospitalization and surgery for treatment of disease
- Elective hospitalization to simplify treatment or study procedures

6.1.2 Methods of recording and assessing adverse events

All AEs must be documented in the appropriate section of the CRF. For SAEs, a SAE report form (initial or follow up) must be completed in addition.

The following aspects must be recorded for each event in the CRF:

- A description of the AE in medical terms, not as reported by the subject;
- The date of onset (start date)
- The date of recovery (stop date)
- The grade as assessed by the investigator according to the definitions in NCI-CTC, Version 4.0.

  Grade 1 = mild

  Grade 2 = moderate

  Grade 3 = severe

  Grade 4 = life-threatening or disabling

  Grade 5 = death related to AE
- The causal relationship to cetuximab or chemotherapy as assessed by the investigator; the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study drug or study procedures are to be used:

  Not Related = There is not a temporal relationship to study drug administration (too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

  Not Likely = There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE,

  Possible = There is a reasonable causal relationship between the study drug and the AE. Dechallenge information (information referring to withdrawal of drug) is lacking or unclear.

  Probable = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge (withdrawal of study drug). Rechallenge is not required.

  Certain/Definite = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge and recurs with rechallenge, when clinically feasible.
- Action taken on cetuximab (none, medication discontinued, dose reduction, medication delayed, reduction of infusion rate).
- Other action (none, concomitant medication given, new or prolonged hospitalization, procedural surgery, chemotherapy delayed, chemotherapy discontinued, chemotherapy dose reduction).
- The outcome according to the following definitions:

  Recovered with sequelae.

  Recovered without sequelae.

  Ongoing, no therapy.

  Ongoing, therapy.

  Died.

  Change in toxicity grade/severity.

- Seriousness: yes or no
- In case of SAEs it must be indicated whether the SAE is the leading event, i.e. the primary medical reason for SAE reporting.

If in any one subject the same AE occurs on several occasions, then the AE in question must be documented and assessed anew each time.

6.1.3 Procedure for reporting serious adverse events

In the event of the occurrence of any clinical AE or abnormal laboratory test value that is serious or medically important during the course of the study or the post-treatment period, irrespective of the treatment received by the subject, the investigator is obliged to immediately inform the Investigator-Sponsor.

The immediate report by the investigator to the Investigator-Sponsor shall be followed by detailed, written reports using the SAE report form (for an “initial” SAE or for “follow-up” information on a previous SAE). The immediate and follow up reports shall identify subjects by unique code numbers assigned to the latter.

For names, addresses, telephone and fax numbers, see SAE report form.

The Investigator-Sponsor shall ensure that all reporting requirements according to the respective national law are followed. “Expectedness” to be assessed with regard to the valid IB for cetuximab. “Expectedness” with respect to a comparator or a concomitant anti-cancer treatment, if applicable, is to be assessed according to either the respective IB or versus the Product Information. A CIOMS-1 format shall be used for submitting expedited reports to the competent authorities, the ethics committee and to all investigators involved in this study according to all appropriate national and international laws. Where necessary, the CIOMS-1 form shall be accompanied by the relevant pages of the case report form.

Cetuximab **SUSARs** represent Serious Adverse Events related to cetuximab (=Adverse Reactions), considered “unexpected” with regard to the valid IB for cetuximab.

With respect to cetuximab, the Investigator-Sponsor shall only copy Merck in any cetuximab individual case safety report, which has been submitted expeditedly to the competent authorities. The report to Merck shall be sent via Fax only at the same time of reporting to the competent authorities.

The Investigator-Sponsor shall ensure that for a reported death of a subject, the investigator shall supply the Investigator-Sponsor and the Ethics Committee with any additional information as requested.

6.1.4 Monitoring of subjects with adverse events

Any AE that occurs in the course of a clinical study must be monitored and followed up until the End of Study Visit. Ongoing adverse events related to study treatment will be followed for 6 weeks (skin toxicities until outcome is known) after end of treatment. In addition SAEs must be reported via a SAE report form (see section 6.1.1.3 Procedure for reporting serious adverse events).

It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.

6.1.5 Overdose and intoxication with the study drug

There is no experience with single doses of cetuximab higher than 500 mg/m² body surface area in human clinical trials. In the event of a drug overdose occurring in the course of the present study, this must be reported as a SAE.

6.2 Laboratory assessments

All clinical laboratory evaluations will be performed at the local laboratory of the investigational site complying with GCP and local requirements.

A safety laboratory examination consisting of hematology must be performed at baseline, weekly during radio-immunochemotherapy and at the end of treatment evaluation. Clinical chemistry must be performed at baseline, on day 1 of every course (every 4 weeks) of the radio-immunochemotherapy, and at the end of treatment evaluation.

Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity according to local regulation) within 7 days prior to the start of the study medication.

Safety laboratory parameters

- Hematology (5 ml)

  Leucocytes, neutrophils, platelets, erythrocytes, hemoglobin
- Clinical chemistry (10 ml)

  Sodium, potassium, calcium, magnesium, creatinine, bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, γ-GT
- Pregnancy test (if applicable)

  Male or female patients must be practicing a medically accepted contraception.

6.3 Vital signs and physical examination

A physical examination including weight and height will be performed at screening.

Resting blood pressure (systolic/diastolic, supine, after 5 minutes rest) and heart rate (after 5 minutes rest) will be measured at screening, weekly during radio-immunochemotherapy and at the end of treatment.

7 Schedule of assessments

The table below summarizes the assessments to be made during (pre)-screening and during the study. Descriptions of the methodology to be used are given in the following sections.

Table 8: Overview of assessments during screening and during the study.

Screening and During Study	Includes
Informed Consent	• Written informed consent for participation in the study

Medical History	• Demographic data • Tumor diagnosis • Check of inclusion and exclusion criteria • Previous relevant diseases other than esophageal cancer • Concomitant medications within 4 weeks preceding study start
Vital signs	• Resting heart rate • Resting blood pressure (systolic/diastolic) • Height / weight • Body surface area
Performance status	• Karnofsky performance status
Safety lab	• Hematology • Clinical chemistry • Pregnancy test (where applicable)
Cardiac evaluation	• ECG and measurement of ejection fraction (LVEF)
Lung function test	• FEV_1
Clinical staging and imaging	• Endoscopy • Endoscopic ultrasound (optional) • CT • DC-MRT (in selected centers)

7.1 Screening examinations

After the patient has signed the informed consent, all eligibility criteria will be checked. Patients may only be enrolled, if all inclusion criteria and none of the exclusion criteria are met.

If frozen tissues or immunohistochemical blocks from previous biopsies are available at the local study site or the regional Pathology Department, they should be transported to Mainz for further analysis.

7.1.1 Examinations within 4 weeks prior to treatment start

- Written informed consent for participation in the study
- Medical History
- Clinical staging (endoscopy incl. biopsy)
- Endoscopic ultrasound

- Tumor Assessment CT/MRI chest and abdomen
- ECG and LVEF
- FEV_1
- Evaluation by a surgeon with respect to resectability
- Tissue immunohistochemistry

7.1.2 Examinations within 7 days prior to treatment start

- Height, weight, vital signs
- Karnofsky-Performance Status
- Hematology (leucocytes, neutrophils, platelets, erythrocytes, hemoglobin)
- Clinical chemistry (sodium, potassium, calcium, magnesium, creatinine, bilirubin, , SGOT, SGPT, LDH, alkaline phosphatase, γ-GT)
- Pregnancy test in women of child-bearing potential
- Serum sample (10 ml) and whole blood sample (10 ml) for EGFR and ligands determination (if patient agrees to participate in translational study)

7.2 Evaluations during radio-immunochemotherapy

7.2.1 Weekly examinations

- Vital signs
- Weight
- Hematology (leucocytes, neutrophils, platelets, erythrocytes, hemoglobin)
- Clinical signs and symptoms, toxicity according to the NCI-CTC version 4.0
- DC-MRT: at day 7 (+/-2) or day 14 (+/-2) of the first cycle (in selected centers)

7.2.2 Examinations every 4 weeks

- Karnofsky-Performance Status
- Biochemistry (sodium, potassium, calcium, magnesium, creatinine, bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, γ-GT)

7.2.3 Examinations after 4 weeks of treatment

- Endoscopy (incl. biopsy, if patient agrees to participate in translational study)
- Endoscopic ultrasound (optional)
- Tumor assessment (CT/MRI chest and abdomen)
- serum sample (10 ml) for EGFR and ligands determination (if patient agrees to participate in translational study)
- Tissue immunochemistry (if patient agrees to participate in translational study; immunohistochemical blocks should be transported to Mainz for further analysis)
- Re-evaluation by a surgeon with respect to resectability*

**If resectability has been achieved, radiochemotherapy +/- cetuximab is stopped after 45 Gy, and the patient is referred to surgery. If resectability has not been achieved, radiochemotherapy +/- cetuximab is continued as indicated above.*

7.3 End of Treatment Evaluations

After completion of the radio-immunochemotherapy or at the time of premature withdrawal for any reason the following assessments will be performed:

- Vital signs
- Karnofsky performance status
- Hematology (leucocytes, neutrophils, platelets, erythrocytes, hemoglobin)
- Clinical chemistry (sodium, potassium, calcium, magnesium, creatinine, bilirubin, , SGOT, SGPT, LDH, alkaline Phosphatase, γ-GT)
- Assessment of clinical signs or symptoms, toxicity according to NCI-CTC version 4.0
- Endoscopy (incl. biopsy, if patient agrees to participate in translational study)
- Endoscopic ultrasound (optional)
- Tumor Assessment (CT/MRI chest and abdomen)

serum sample (10 ml) for EGFR and ligands determination (if patient agrees to participate in translational study)

7.4 Evaluations during the Follow up phase

Follow-up assessments will terminate 2 years after the last patient has completed end of treatment (incl. biopsy, if patient agrees to participate in translational study).

- Evaluation of toxicity
- Treatment outcome
- Endoscopic ultrasound (optional)

Tumor Assessment (CT/MRI chest and abdomen)

7.5 Evaluation of Efficacy

7.5.1 Tumor assessment

Assessment of tumor response will be evaluated using the international criteria proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee (New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), Eisenhauer EA et al., Eur J Cancer 2009, see Appendix 4 for further reference).

Only subjects with measurable disease may 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 must be performed at baseline (within 28 days before start of treatment) for eligibility and also to establish a baseline tumor assessment.
The same method of assessment and the same technique should be used to characterize the reported lesion at baseline and during the following tumor assessments. A switch from CT- to MRI-scan is considered the only acceptable change in modality and should not preclude response assessment if, in the judgment of the radiologist, there is no significant difference in the assessment by CT- and MRI-scan.
CT- and MRI-scan are the best currently available and most reproducible methods of measuring index lesions selected for response assessment. CT- or MRI-scans of the chest and abdomen anatomies are required at baseline. Thereafter, at each imaging time point, a chest CT- or MRI-scan and abdomen CT-or MRI scan are required. CT- or MRI-scans of the chest and abdomen are required at the Final Tumor Assessment visit.
The CT- or MRI-scans should be performed with spiral technique using a 5 mm or less contiguous reconstruction algorithm. Non-spiral CT is also allowed with a recommended reconstruction algorithm or slice thickness of 10 mm or less. Intravenous and oral contrast should be administered if it is not contraindicated. At baseline, tumor lesions will be

categorised measurable if the minimum size is 10 mm (if CT scans are performed at 5 mm slice thickness or less). If CT scans at slice thickness greater than 5 mm are used, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.
The lesion will be assessed with imaging with the same method as at baseline and at the end of treatment to monitor progression of disease. Furthermore, at the end of treatment visit, the investigator will exclude symptomatic deterioration suggestive of progression of disease (e.g. a decrease in Karnofsky performance status, metastases). If progression of disease is suspected for any reason during the treatment phase, radiological confirmation is necessary and a new scan must be performed unless a scan taken no more than 14 days earlier is available.

Resectability / Response Criteria per Time Point:

Resectability of the primary tumor and the lymph nodes will be assessed by a surgeon after 4-4.5 weeks of treatment (see 7.2.3).

Overall response will be 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, and will be assessed at week 5 and at the end of treatment.

Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of best overall response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Table 9: RECISIT 1.1 Evaluation of best overall response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PR	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.5.2 Residual tumor classification (R-classification) in patients undergoing surgery

The R-classification will be performed by the pathologist using the resected tumor. The pathologist will determine, if residual tumor is present at the resection lines. The definitive R-classification considers clinical and pathological information and includes the following categories:

R0 no residual tumor
R1 microscopic residual tumor
R2a macroscopic residual tumor, microscopically not confirmed
R2b macroscopic residual tumor, microscopically confirmed

8 Statistical Considerations

Having fixed the safe dose in our former phase I study (LEOPARD Phase I), 134 patients should be treated at a dose of 1000 mg/m^2 FU and 20 mg/m^2 cisplatin to evaluate the 2-year overall survival of the immuno-radiochemotherapy. However, the last patient will be randomized on December 31, 2016 at the atest, which is 2.5 years later than originally planned.

8.1 Analysis set descriptions

Safety Analysis Set
The safety population includes all patients who received at least one dose of trial medication and for whom at least one post-baseline safety measurement is available.

Full Analysis Set
The Full Analysis Set includes all patients who received at least one dose of trial medication and for whom at least one post-baseline efficacy measurement is available.

Per Protocol Set
This population includes 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. Detailed criteria will be defined before analysis.

All safety analyses will be performed on the Safety Analysis Set. For efficacy analysis of the trial, the primary analyses will be based on the per-protocol set. Additional analyses will be performed on the Full Analysis Set for sensitivity purposes.

8.2 Target variables

8.2.1 Primary variables

For quantification of efficacy the primary objective is the 2-year overall survival.

8.2.2 Secondary variables

- The 1-year overall survival
- The 1-year and 2- year progression-free survival
- The 1-year and 2-year loco-regional control
- The 1-year and 2-year metastases-free survival
- The overall response rate3 (RECIST Version 1.1)
- Toxicity (NCI-CTC 4.0)
- Quality of Life (EORTC QLQ-C30 and QLQ-OES18)

In addition the following parameters will be assessed irrespective of a specific time point:

- OS
- PFS
- MFS

8.3 Statistical analysis

8.3.1 Statistical Methode

Treatment outcome:

Loco-regional control is defined as absence of loco-regional progression based on findings of endoscopy, endoscopic ultrasound, and computed tomography.
OS, PFS, MFS and LC are calculated for both treatment groups and for several potential prognostic factors with the Kaplan-Meier method and measured from the day of randomization .
Such potential prognostic factors are: age (≤60 vs. >60 years), Karnofsky performance status (100%-80% vs. 70%), tumor location (upper third vs. middle third vs. lower third), tumor length (<7 cm vs. ≥7 cm, according to endoscopy), 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 hemoglobin before radiotherapy (<12 vs. 12-14 vs. > 14 g/dl).
Differences between the Kaplan-Meier curves are evaluated with the log-rank test. Results are considered significant if $P < 0.05$. Potential prognostic factors found to be significant in the univariate analysis, are evaluated in a multivariate analysis performed with the Cox proportional hazard model.

Stratification at randomization according to :
Histology (SCC vs. adeno)
KPS (100%-80% vs. 70%)
Stage (T1-3 N0-1 vs. T4 and/or N2 and/or M1a)

Toxicity:

Both treatment groups are compared for toxicity using the Chi-square test.

8.3.2 Present therapeutic situation

The most effective radiochemotherapy regimens, containing 5-FU and cisplatin, achieve a overall survival (OS) rate of 36% to 40% after two years [49, 50, 52]. Thus, a 40% OS rate at 2 years is assumed as the baseline efficacy level for the present trial.

8.3.3 Rationale for the application of a randomized phase II design

The present trial is designed as a randomized phase II study which aims at estimating the therapeutic efficacy of the experimental targeted regimen including the EGFR antibody in relation to the standard combination. The OS rate after 2 years is chosen as primary efficacy endpoint.

The estimation of the efficacy rate of the experimental cetuximab regimen is to be based on an explorative pilot study, since immediate embarking on a large scale comparative efficacy trial would not be acceptable from the point of view of resources. Moreover, this would induce ethical objections, as it does 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 [48]. The key idea of randomizing already in the phase II of the 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 randomized 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 randomized 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 randomized, if the results of the experimental group(s) are considered to be promising.

8.3.4 Design and assumptions

- Explorative randomized phase II study with 2 parallel groups.
- Primary endpoint: Overall survival rate after 2 years. Survival time will be calculated from time of randomization until death for any reason, or until last date known to be alive, whichever occurs first. In patients without death, the last date known to be alive will 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 is 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.

- In order to detect potential differences with respect to the investigated study endpoints between female and male gender, subgroup analyses will be performed for both female and male patients. Furthermore, the potential prognostic impact of gender will be analyzed in a univariate and a multivariate manner. Because an adequate statistical power cannot be expected in each of the two subgroups, the statistical evaluation analyses with respect to gender related differences will be presented in a descriptive manner.

8.4 Sample size calculation

This phase II study is an explorative randomized study with 2 parallel groups. Using a standard single-stage phase II design by FLEMING (1981), n = 62 patients evaluable for efficacy have to be recruited. As a similar number of patients is to be recruited to the standard arm, a total number of 124 patients is required. The standard treatment control group serves 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 potentially drop outs 67 patients per arm will be recruited.

The OS rate after 2 years is chosen as primary efficacy endpoint. The estimation of the efficacy rate of 40% of the reference group is based on the findings of several studies [49-54]. Therefore, the respective experimental therapy arm would be rated as insufficiently active, if the observed OS rate at 2 years is 40 % or lower.

On the other hand, the experimental therapy would be considered to be a very 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.

Probability to accept the experimental therapy as promising (> 45% OS rate) with respect to efficacy, in spite of a true OS rate of ≤ 40%: 5% (type I error).

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

However, the last patient will be randomized on December 31, 2016 at the latest, which is 2.5 years later than originally planned. Based on number of patients randomized until end of July and who received study treatment (n=66) it is expected that the total number of patients in the Full Analysis Set (FAS) will be between 72 and 78 patients, while the number of patients in the Per Protocol Population is expected to be between 66 and 72 patients.

The final conclusion of the phase II trial will depend on the definite 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.

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

Based on the expected number of patients randomized until end of 2016, the following difference (hazard ratios) can be detected between the two treatment arms with 80% power and 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 10: 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

8.5 Data Management

To ensure that the database accurately reflects the data reported on the CRF, a double data entry procedure (data entered by different staff members in two different data files) will be used. In addition to an electronic comparison of these two data files, mainly electronic validation of the data will take place (e.g. check of ranges, consistency and plausibility). Additionally the CRFs will be reviewed by qualified personnel for completeness, consistency and plausibility. Unclear data will be clarified using data correction forms. The procedures of data entry, comparison and correction will be tracked and appropriately documented. All data management procedures and systems will be described in detail in the Data Validation Plan which will be approved by the sponsor.

9 Immuno(histo)chemistry and blood samples (applicable if patient agrees to participate in translational study)

Serum samples, paraffin-embedded tissues, and when available fresh frozen specimens (if applicable) of included patients will be characterized via ELISA, immunohistochemistry and PCR, respectively. In addition, a prospective follow-up of serum levels of targeted ligands (ELISA) is planned before and during Cetuximab therapy to correlate the receptor pathways with initial tumor staging and clinical response.

The tissues were collected during diagnosis and follow up (operations, biopsies) of the patient. They are stored frozen in the study centers and will be transported to Mainz. Serum samples will be collected at screening, after 4 weeks of treatment and at the end of treatment. A full blood sample will be collected at screening for SNP-analysis. All samples will be transported to Mainz for further analysis.

Tissues and serum samples will be analysed by: Klinische Immunologie, Frau Annett Müller, Universitätsklinik Mainz, I. Medizinische Klinik und Poliklinik, Gebäude 206, U2, Langenbeckstraße 1, 55101 Mainz

9.1 DC-MRT

The DC-MRT will be performed in an explorative manner before the beginning of the first cycle, and 7 (+/-2) days or 14 (+/-2) days after start of the first cycle to analyze the efficacy of Cetuximab to influence the tumor microcirculation with its blood flow and arterial permeability.

One important precondition for using MRT is the development of special imaging sequences and programs, with which the data can be processed and tissue specific parameters can be quantified. This has been established at the Department of Radiology and Nuclear Medicine in conjunction with the Department of Physics of the Max Planck Institute in Mainz, Germany. Currently Mainz University works with the program Medlab. Pharmacokinetics can also be automatically documented. Responsible for the project in the protocol will be Dr. K. Oberholzer, MD, Radiology Department. Regarding MRT scanning programs, all study centers are invited to participate.

10 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be implemented that independently supervises the trial with respect to any potential safety issues. The DSMB will function in accordance with the principles of the following documents: EMEA guideline on data monitoring committees (EMEA/CHMP/EWP/5872/03 Corr); ICH Note for guidance E3 (structure and content of clinical study reports), ICH Note for guidance E6 (Good Clinical Practice) and ICH Note for Guidance E9 (Statistical Principles for Clinical Trials).
The DSMB will be an independent board consisting of a group of 2 physicians with experience in oncology. A physician is not allowed to participate in this clinical trial while serving on the DSMB. The DSMB will be supported by an independent statistician, if necessary.
The DSMB will formally review safety data when 20 patients and again when 67 patients (50% of the entire cohort) are randomized have completed 4 weeks of treatment. The DSMB will focus on safety and survival data only. An interim analysis with respect to efficacy/futility is planned after recruitment stop at December 31, 2016. In addition, the DSMB will be provided with regular reports every 3 months summarizing the same safety information used for the formal review.

The key safety parameters to be monitored will be

- Overall incidence of patients with any CTCAE-grade III/IV adverse event
- Incidence of Serious Adverse Events (SAEs)

A separate DSMB charter will be set up which defines the roles and responsibilities of the DSMB, delineates qualifications of the membership, describes the purpose and timing of meetings, provides the procedures for ensuring confidentiality and proper communication, and outlines the content of the reports. In addition, the statistical guidance for evaluating safety and their associated stopping rules will be presented. These rules are meant as guidance rather than as mandatory decision rule. In case of unexpected results, the DSMB has the discretion to deviate appropriately form this guidance.
In case of significant excess toxicity associated with the experimental arm, the DSMB may decide together with the sponsor to stop the trial early due to safety concerns.

11 Ethical and regulatory aspects

11.1 Responsibilities of the Investigator

The investigator shall be responsible for ensuring that the clinical study is performed in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (World Medical Association Declaration of Helsinki) as well as with the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Humans Use (ICH) Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) approved July 17, 1996 and applicable regulatory requirements. These documents state that the informed consent of the patients is an essential precondition for participation in the clinical study.

11.2 Patient information

An unconditional prerequisite for a subject participating in the study is his/her written informed consent. Adequate information must therefore be given to the subject by the investigator before informed consent is obtained. A person designated by the investigator may give the information, if permitted by local regulations. A subject information sheet in the local language and prepared in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) will be provided for the purpose of obtaining informed consent. In addition to this written information, the investigator or his designate will inform the subject verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

The subject information sheet will be revised whenever important new information becomes available that may be relevant to the consent of subjects.

11.3 Patient consent

11.3.1 Informed Consent procedures

The consent of the patient to participate in the clinical study has to be given in writing before any study-related activities are carried out. It must be signed and personally dated by the subject and by the investigator/person designated by the investigator to conduct the informed consent discussion.

Provision of consent will be confirmed in the CRF by the investigator. The signed and dated declaration of informed consent will remain at the investigator’s site and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the subject prior to participation.

11.3.2 Witnessed informed consent

If the subject or legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject‘s right to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witnesses. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

11.4 Patient insurance

Insurance coverage shall be provided for at Allianz Versicherungs-AG, 10900 Berlin, Germany, policy number AS-9100160845 as stipulated by law, for all patients enrolled in the study from the time of patients‘ inclusion into the study (date of given second consent or screening visit).

This insurance covers any damage to health arising from participation in the study up to maximum sum required by law.

In order not to violate the insurance cover, the patient must immediately notify the insurance company in case of any damage to health arising from participation in the clinical study.

A copy of the complete insurance terms and conditions will be made available to the patient.

11.5 Ethics Committee or Institutional Review Board

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, investigator‘s brochure) to the relevant EC for their favorable opinion.

The study will only commence following provision of a written favorable opinion, documenting the date of the meeting, constitution of the committee and voting members present at the meeting as well as clearly identifying the trial, protocol version, and consent documents reviewed.

Any amendments to the protocol will be submitted to the EC and they will be informed about SAEs in accordance with national and/or local requirements.

11.6 Notification to authorities

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, investigator‘s brochure) to the regulatory authority for their favorable opinion. According to the German Drug Law, the study may only commence after approval by the regulatory authority. This approval is granted, if no objections have been issued by the regulatory authority within 30 days after submission of the documents.

To comply with § 67 of the German Drug Law, the study and the investigators will also be notified to the local authorities.

11.7 Sponsorship

This is an investigator sponsored trial. The study will be sponsored by the University Hospital Schleswig-Holstein, Campus Luebeck, Germany.

12 Study management

12.1 Case Report Form handling

The main objective is to obtain those data required by the study protocol in a complete, accurate, legible and timely fashion. The data in the CRF should be consistent with the relevant source documents.

The data recorded in the course of this study must be documented in the CRF and/or the form ARF, and must be forwarded to the data management. They shall then be processed, evaluated, and stored anonymously in accordance with the data-protection regulations.

The investigator must ensure that the CRFs forwarded to the data management and any other associated documents contain no mention of any patient names.

The CRFs must be filled in completely and legibly (with either black or blue ballpoint pen, acceptable for use on official documents). Any amendments and corrections necessary must be undertaken and countersigned by the investigator, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids (e.g. Tipp-Ex®). The investigator must state his/her reasons for the correction of important data.

In the case of missing data/remarks, the entry spaces provided for in the case report form should be cancelled out so as to avoid unnecessary follow-up inquiries.

The CRFs are regulatory documents and must be suitable for submission to authorities.

12.2 Source data and subject files

The investigator has to keep a written or electronic subject file for every subject participating in the clinical study. In this subject file, the available demographic and medical information of a subject has to be documented, in particular the following: name, date of birth, sex, height, weight, subject history, concomitant diseases and concomitant drug (including changes during the study), statement of entry into the study, study identification, subject number, the date of informed consents, all study visit dates, predefined performed examinations and clinical findings, observed AEs (if applicable), and reason for withdrawal from the study if applicable. It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file.

It must be possible to identify each subject by using this patient file.

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. All these documents have to bear at least subject identification and the printing date printed by the recording device to indicate to which subject and to which study procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator.

Computerized subject files will be printed whenever source data verification is performed by the monitor. Printouts must be signed and dated by the investigator, countersigned by the monitor and kept in a safe place.

Data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data) are considered to be source data.

12.3 Investigator Site File and archiving

The investigator will be provided with an ISF at the start of the study. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study.

It is the responsibility of the investigator to ensure that the patient-identification sheets are stored for at least 15 years beyond the end of the clinical study. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the Investigator-Sponsor.

12.4 Monitoring, Quality Assurance and inspection by authorities

This study is to be conducted in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) dated July 17, 1996. The appointed clinical monitor will arrange regular visits to the study center(s) on a regular basis to check progress with the study and to collect completed CRFs.

During monitoring visits the monitors will:

• 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 are 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 will include verification of data entered in the CRFs against original patient records. This verification will be performed by direct access to the original patient records and the monitoring organization guarantees that patient confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification. Data generated at the pre-screening visit are verified against source data only in case the patient enters the study.

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

In the course of the clinical study, the CRFs shall be forwarded to the data management organization 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 shall be subject to an Clinical Quality Assurance. Audits can be conducted to assure the validity of the study data.

12.5 Changes to the study protocol

Changes to, or formal clarifications of, the study protocol must be documented in writing.

Major changes to the protocol will be described in a “Protocol Amendment“. It will be submitted to the relevant ECs and to authorities where required. Approval/favorable opinion from the relevant ECs will be required prior to implementation of the amendment.

Any Amendment affecting the subject requires the subject’s informed consent prior to implementation.

Changes of administrative or technical nature will be recorded in a document entitled “Administrative Change to Study Protocol“. It will be sent for information to the relevant ECs or to authorities, if so required.

Amendment and Administrative Changes will be signed by all signatories of the protocol. All investigators will acknowledge the receipt and confirm by their signature on the Amendment or Administrative Change Signature Sheet that they will adhere to the Amendment/Administrative Change. This sheet will be issued in duplicate and after signing one will be filed in the Investigator Study File and one in the Study Master File.

12.6 Study report and publication policy

After the clinical cut-off date of the study, an integrated clinical and statistical study report shall be written by the Investigator-Sponsor in consultation with the coordinating investigator. The first publication will be a full publication of all data of all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by investigators or their representatives will require pre-submission review by the Investigator-Sponsor.

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Appendix 1

Protocol Signature Pages

Approval of the Protocol

Study protocol No.	LEOPARD -II
EudraCT No.	2010-023427-18
Title	Definitive radiochemotherapy with 5-FU / cisplatin plus/minus cetuximab in locally advanced unresectable esophageal cancer: a phase II study.
Version	final 3.0 2016.10.06

I confirm that the protocol and the appendices include all necessary information for the proper conduct of the study and are in compliance with Good Clinical Practice and applicable regulatory requirements.

Sponsor/Coordinating Investigator Prof. Dr. Dirk Rades	Date

Investigator Signature Page

Study protocol No. LEOPARD -II

EudraCT No. 2010-023427-18

Title Definitive radiochemotherapy with 5-FU / cisplatin plus/minus cetuximab in locally advanced unresectable esophageal cancer: a phase II study.

Version final 3.0 2016.10.06

I agree to conduct the study in accordance with the protocol described in this document and in compliance with Good Clinical Practice and applicable regulatory requirements.

Center Number
Investigator's name
Institution
Address

Signature Investigator Date

Appendix 2

Patient Information Sheet and Consent Form

Appendix 3

Karnofsky Performance Status Scale

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 4

RECIST criteria Version 1.1


C:\Dokumente und Einstellungen\pilz\Eige

Appendix 5

Treatment of acneiform skin reactions related to cetuximab

(English version as requested by clinicaltrials.gov; for presentation at clinicaltrials.gov only)

Proposed modifications to the NCI–CTCAE v4.03 grading and grade-specific management strategies for patients developing radiation dermatitis during treatment with cetuximab plus radiotherapy.

[Bernier J et al., Ann Oncol. 2011 Oct;22(10):2191-200. doi: 10.1093/annonc/mdr139]

	Grade of dermatitis associated with radiation-based therapy			
	Grade 1	**Grade 2**[a]	**Grade 3**[a]	**Grade 4**[a]
Definition: NCI–CTCAE, v4.03 dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Definition: Proposed modification of NCI–CTCAE, v4.03	Faint erythema or dry desquamation	Moderate to brisk erythema and/or dry desquamation; patchy moist desquamation, or non-hemorrhagic crusts mostly confined to skin folds and creases	Moist desquamation or hemorrhagic crusts; non-hemorrhagic crusts other than in skin folds and mostly confined to skin folds and creases; bleeding induced by minor trauma or abrasion; superinfection requiring oral antibiotics	Life-threatening consequences; extensive confluent hemorrhagic crusts or ulceration (>50% of involved field); extensive spontaneous bleeding from involved site (>40% of the involved site); skin necrosis or ulceration of full-thickness dermis or any size ulcer with extensive destruction, tissue necrosis or damage to muscle, bone or

	Grade of dermatitis associated with radiation-based therapy			
	Grade 1	**Grade 2**[a]	**Grade 3**[a]	**Grade 4**[a]
				supporting structures with or without full-thickness skin loss[b]; skin graft indicated; ulceration associated with extensive superinfection with i.v. antibiotics indicated
General management approaches	Reinforce general management approaches[c]	Reinforce general management approaches[c]	Reinforce general management approaches[c]	Reinforce general management approaches[c]
Grade-specific management approaches	• Weekly follow-up is adequate, unless rapid progression is noted	• Consider twice-weekly assessments to monitor for rapid change *A. Dry desquamation without crusts:* • Consider glucocorticosteroid cream or ointment for a limited period (1–2 weeks) • Topical antiseptics and antibiotics at any sign of superinfection • Consider the use of topical antiseptics and antibiotics for the prevention of more severe reactions *B. Moist desquamation in skin folds:* • Topical antiseptic • Consider adding daily topical glucocorticosteroid lotion to reduce inflammation for a limited period (1–2 weeks) • Topical antibiotics	• Evaluate the need for daily assessment • Closely monitor for signs of local or systemic infection • For grade 3 reactions occurring at <50 Gy, consider brief interruption in treatment *A. Confluent moist desquamation without crusts:* • Topical antiseptic• Consider adding daily topical glucocorticosteroid lotion to reduce inflammation for a limited period (1–2 weeks) • Topical antibiotics active against *S. aureus* at any sign of superinfection • If superinfection becomes more severe, consider the use of i.v. antibiotics if unresponsive to oral antibiotics	• Consider interrupting treatment with both radiotherapy and cetuximab. Cetuximab should be interrupted until the skin reaction has resolved to at least grade 2 • In the case of severe superinfection, consider the use of i.v. antibiotics if unresponsive to oral antibiotics • Hospitalize the patient

Grade of dermatitis associated with radiation-based therapy			
Grade 1	**Grade 2[a]**	**Grade 3[a]**	**Grade 4[a]**
	active against *Staphylococcus aureus* at any sign of superinfection. Consider systemic antibiotics if superinfection becomes more severe • Topical eosin or soft zinc preparations in the skin folds. A thin layer of a soft zinc preparation may be used in skin folds, but should be removed before treatment with radiotherapy to avoid radiation dosimetric problems. Topical eosin in skin folds or on erosive lesions may also be a useful treatment approach. *C. Dry desquamation with isolated non-hemorrhagic crusts:* • Topical antiseptic • Consider adding daily topical glucocorticosteroid lotion to reduce inflammation for a limited period (1–2 weeks) • Topical antibiotics active against *S. aureus* at any sign of superinfection. Consider systemic antibiotics if superinfection becomes more severe • Topical eosin or soft zinc preparations in the skin folds. A thin layer of a soft zinc preparation may be used in skin folds but should be removed	• Topical eosin or soft zinc preparations in the skin folds. A thin layer of a soft zinc preparation may be used in skin folds, but should be removed before treatment with radiotherapy to avoid radiation dosimetric problems. Topical eosin in skin folds or on erosive lesions may also be a useful treatment approach *B. Confluent moist desquamation with crusts:* • Topical antiseptic • If superinfection becomes more severe, consider the use of i.v. antibiotics if unresponsive to oral antibiotics • Consider debridement using hydrogels. Skin trauma should be avoided to prevent superinfection • If hydrocolloid dressings are used, the thickness of the dressing should be taken into account for the radiotherapy dosimetry. Hydrofiber dressings can be used after completion of radiotherapy	

	Grade of dermatitis associated with radiation-based therapy			
	Grade 1	**Grade 2**[a]	**Grade 3**[a]	**Grade 4**[a]
		before treatment with radiotherapy to avoid radiation dosimetric problems • Hydrogels can be used to keep crusts flexible • Consider debridement using hydrogels. Skin trauma should be avoided to prevent superinfection		
Management team	Radiation oncologist, medical oncologist, nurse, dermatologist[d]	Radiation oncologist, medical oncologist, nurse, dermatologist[d]	Radiation oncologist, medical oncologist, nurse, dermatologist[d]	Involve a wound-healing specialist in addition to the radiation oncologist, medical oncologist, nurse, dermatologist[d]

[a] Possibility of local superinfection as indicated by the clinical appearance (moist desquamation and crusts, with yellowing) and by microbiological assessment (from swabs of the area and blood tests); suspected systemic superinfection is indicated by the presence of at least two of the following four variables of systemic inflammatory response syndrome; fever with a core temperature >38°C or <36°C, heart rate >90 beats per min, respiratory rate >20 breaths per min, leukocytosis (>12 × 10^9/l) or leukopenia (<4 × 10^9/l).

[b] Skin necrosis of full-thickness dermis is rarely seen with the recommended doses of cetuximab plus radiotherapy and this type of diagnosis should be based only on a biopsy of tissue from the involved site.

[c] See 'General Measures' section in the text.

[d] Early involvement of a dermatologist may facilitate effective management.

Appendix 6

Management options for radiation dermatitis and co-existing acneiform skin reactions related to Cetuximab

Appendix 7

NCI Common Toxicity Criteria Version 4.0

Appendix 8

Summary of Product Characteristics Cetuximab

Appendix 9

Summary of Product Characteristics 5-FU (Example)

Appendix 10

Summary of Product Characteristics Cisplatin