

## Clinical Trial Protocol

<b>Clinical Trial Protocol Number</b>	EMR062202-060
<b>Title</b>	A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil alone for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck
<b>Phase</b>	III
<b>IND Number</b>	Not applicable
<b>EudraCT Number</b>	Not applicable
<b>Coordinating Investigators</b>	PPD [Redacted] PPD [Redacted]
<b>Sponsor</b>	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
<b>Clinical Trial Protocol Version</b>	26 February 2018 / Final 3.0
<b>Replaces Version</b>	20 April 2016 / Final 2.0
	- [Redacted] -

This document is the property of Merck KGaA, Darmstadt, Germany, or one of its subsidiaries. It is intended for restricted use only and may not – in full or part – be passed on, reproduced, published or used without express permission of Merck KGaA, Darmstadt, Germany, or its subsidiaries. Copyright © 2018 by Merck KGaA, Darmstadt, Germany, or its affiliate. All rights reserved.

## Protocol Table of Contents

Protocol Table of Contents .....	2
Table of In-Text Tables .....	7
Table of In-Text Figures .....	7
List of Abbreviations .....	8
1 Synopsis .....	11
2 Sponsor, Investigators and Trial Administrative Structure .....	20
3 Background Information .....	21
3.1 Cetuximab .....	21
3.2 Epidermal Growth Factor Receptor in Cancer .....	21
3.3 Epidermal Growth Factor Receptor Inhibition and the Cell Cycle .....	22
3.4 Nonclinical Studies of Cetuximab .....	22
3.4.1 Nonclinical Absorption, Distribution, Metabolism, and Excretion .....	22
3.4.2 Nonclinical Toxicology .....	23
3.4.3 Nonclinical Efficacy Pharmacology and Safety Pharmacology .....	23
3.5 Dose Selection Criteria and Clinical Pharmacokinetics of Cetuximab .....	24
3.6 Immunogenicity .....	24
3.7 Clinical Development of Cetuximab .....	24
3.7.1 Clinical Pharmacology .....	24
3.7.2 Cetuximab plus Chemotherapy in the Treatment of Recurrent and/or Metastatic SCCHN .....	25
3.7.3 Reasonably Anticipated Serious Adverse Events .....	26
3.7.4 Related Adverse Events .....	26
3.8 Trial Rationale .....	28
3.9 Risk-Benefit Assessment .....	28
4 Trial Objectives .....	29
4.1 Primary objective .....	29
4.2 Secondary objectives .....	29
5 Investigational Plan .....	29
5.1 Overall Trial Design and Plan .....	29

---

---

5.2	Discussion of Trial Design .....	32
5.3	Selection of Trial Population .....	33
5.3.1	Inclusion Criteria .....	33
5.3.2	Exclusion Criteria .....	34
5.4	Criteria for Subject Withdrawal.....	35
5.4.1	Withdrawal from Trial Therapy.....	35
5.4.2	Withdrawal from the Trial .....	37
5.5	Premature Termination of the Trial .....	37
5.6	Definition of End of Trial .....	37
6	Investigational Medicinal Product and Other Drugs Used in the Trial.....	38
6.1	Description of Investigational Medicinal Product.....	38
6.2	Dosage and Administration .....	38
6.2.1	Selection and Timing of Cetuximab .....	38
6.2.2	Dose Reductions and Treatment Alterations for Cetuximab .....	40
6.3	Assignment to Treatment Arms.....	44
6.4	Noninvestigational Medicinal Products to be Used.....	44
6.4.1	Chemotherapy.....	44
6.4.2	Other Drugs .....	51
6.5	Concomitant Medications and Therapies .....	52
6.5.1	Permitted Medicines .....	52
6.5.2	Prohibited Medicines .....	53
6.5.3	Other Trial Considerations .....	53
6.5.4	Special Precautions.....	54
6.6	Packaging and Labeling of the Investigational Medicinal Product .....	54
6.7	Preparation, Handling and Storage of the Investigational Medicinal Product.....	54
6.8	Investigational Medicinal Product Accountability .....	55
6.9	Assessment of Investigational Medicinal Product Compliance .....	56
6.10	Blinding .....	56
6.11	Emergency Unblinding.....	56

---

---

6.12	Treatment of Overdose .....	56
6.13	Medical Care of Subjects after End of Trial .....	57
7	Trial Procedures and Assessments .....	57
7.1	Schedule of Assessments .....	57
7.1.1	Screening Visit .....	57
7.1.2	Weekly Cetuximab Administration Visit .....	58
7.1.3	Start of Each Cycle Visit (Day 1 of Each 21-Day Cycle) .....	59
7.1.4	6-Weekly Evaluation Visit .....	59
7.1.5	End of Efficacy Assessment Visit .....	60
7.1.6	Safety Follow-Up Visit .....	60
7.1.7	Survival Follow-Up .....	60
7.2	Demographic and Other Baseline Characteristics .....	61
7.2.1	Demographic Data .....	61
7.2.2	Diagnosis of Tumor .....	61
7.2.3	Medical History .....	61
7.2.4	Viral Serology .....	61
7.2.5	Pregnancy Testing and Contraception .....	61
7.2.6	Echocardiogram .....	62
7.2.7	Creatinine Clearance .....	62
7.2.8	Other Baseline Assessments .....	62
7.3	Efficacy Assessment .....	62
7.3.1	Documentation of Tumor Assessments .....	62
7.3.2	Criteria for Tumor Response Evaluation .....	63
7.4	Assessment of Safety .....	63
7.4.1	Adverse Events .....	64
7.4.2	Pregnancy and In Utero Drug Exposure .....	69
7.4.3	Clinical Laboratory Assessments .....	69
7.4.4	Vital Signs, Physical Examinations, and Other Assessments .....	70
7.5	Pharmacokinetics .....	71
7.6	Biomarkers/Pharmacogenetics .....	71

---

---

7.7	Other Assessments.....	71
8	Statistics.....	72
8.1	Sample Size.....	72
8.2	Randomization.....	72
8.3	Endpoints.....	73
8.3.1	Primary Endpoint.....	73
8.3.2	Secondary Endpoints.....	73
8.3.3	Safety Endpoints.....	73
8.4	Analysis Sets.....	74
8.5	Description of Statistical Analyses.....	75
8.5.1	General Considerations.....	75
8.5.2	Analysis of Primary Endpoint.....	76
8.5.3	Analysis of Secondary Endpoints.....	77
8.5.4	Analysis of Safety.....	78
8.6	Interim and Additional Planned Analyses.....	79
9	Ethical and Regulatory Aspects.....	79
9.1	Responsibilities of the Investigator.....	79
9.2	Subject Information and Informed Consent.....	79
9.3	Subject Identification and Privacy.....	80
9.4	Emergency Medical Support and Subject Card.....	80
9.5	Clinical Trial Insurance and Compensation to Subjects.....	81
9.6	Independent Ethics Committee or Institutional Review Board.....	81
9.7	Health Authorities.....	81
10	Trial Management.....	82
10.1	Case Report Form Handling.....	82
10.2	Source Data and Subject Files.....	82
10.3	Investigator Site File and Archiving.....	83
10.4	Monitoring, Quality Assurance and Inspection by Health Authorities.....	83
10.5	Changes to the Clinical Trial Protocol.....	84
10.6	Clinical Trial Report and Publication Policy.....	84

---

10.6.1	Clinical Trial Report.....	84
10.6.2	Publication.....	84
11	References Cited in the Text.....	85
12	Appendices.....	89
Appendix I	Response Evaluation Criteria in Solid Tumors Version 1.1.....	89
Appendix II	Signature Pages and Responsible Persons for the Trial.....	99
	Signature Page – Protocol Lead.....	99
	Signature Page – Coordinating Investigator.....	100
	Signature Page – Principal Investigator.....	102
Appendix III	Protocol Amendment 1.0 and List of Changes.....	104
Appendix IV	Protocol Amendment 1.0_Changes on Schedule of Assessment Table 1.1.....	111
Appendix V	Protocol Amendment 1.0_Changes on Figure 5.1.....	114
Appendix VI	Protocol Amendment 2.0 and List of Changes.....	115

**Table of In-Text Tables**

Table 1.1	Schedule of Assessments.....	17
Table 3.1	Adverse Events that Have Been Found to Have an Association with Cetuximab.....	26
Table 6.1	Dose and Administration Procedure for Cetuximab.....	39
Table 6.2	Recommended Prophylaxis for Skin Toxicities .....	40
Table 6.3	Treatment Adjustment for Symptoms of Cetuximab Infusion-related Reactions.....	43
Table 6.4	Chemotherapy Regimen Every 21 Days in Arm A and B.....	45
Table 6.5	Dose Reductions for Chemotherapy .....	48
Table 6.6	Chemotherapy Dose Reduction and Treatment for Febrile Neutropenia.....	50
Table 6.7	Criteria for Dose Reductions Based on Hematologic Results on the Schedule Day of Treatment .....	50
Table 6.8	Criteria for Dose Reductions Based on Nonhematologic Toxicities on the Scheduled Day of Treatment .....	51
Table 7.1	Standard Safety Laboratory Parameters .....	69
Table 8.1	Expected Outcome of the Trial Given Different True Hazard Ratios .....	72

**Table of In-Text Figures**

Figure 5.1	Schematic of the Trial Design .....	30
Figure 6.1	Treatment Adjustment in the Event of Grade 3 Skin Reactions Considered to be Related to Cetuximab .....	41

## List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
C <sub>max</sub>	Peak concentration
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EOEA	End of efficacy assessment
5-FU	5-fluorouracil
FDG-PET	Fludeoxyglucose Positron Emission Tomography
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent to Treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Affairs
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response

RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normality

**1 Synopsis**

<b>Clinical Trial Protocol Number</b>	EMR062202-060
<b>Trial title</b>	A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil alone for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck
<b>Trial Phase</b>	III
<b>IND Number</b>	Not applicable
<b>FDA covered trial</b>	No
<b>EudraCT number</b>	Not applicable
<b>Coordinating Investigators</b>	PPD [REDACTED]
<b>Sponsor</b>	Merck KGaA, Darmstadt, Germany
<b>Trial centers/country</b>	Approximately 30 trial centers in mainland China
<b>Planned trial period (first subject in-last subject out)</b>	The third quarter of 2015-The fourth quarter of 2018
<b>Trial Registry</b>	This trial was registered on clinicaltrials.gov as well as chinadrugtrials.org.cn
<p><b>Objectives:</b></p> <p><u>Primary objective:</u> The primary objective of this trial is to evaluate whether progression-free survival (PFS) time, as assessed by an Independent Review Committee (IRC), in subjects receiving cetuximab in combination with cisplatin plus 5-fluorouracil (5-FU) is longer than that in subjects receiving cisplatin plus 5-FU alone in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN).</p> <p><u>Secondary objectives:</u> The secondary objectives are to compare the 2 treatment arms in the following:</p> <ul style="list-style-type: none"> <li>• PFS time, as assessed by the Investigator</li> <li>• Overall survival (OS) time</li> </ul>	

- Best overall response (BOR) rate
- Disease control rate (DCR)
- Duration of response
- Safety

**Methodology:**

This is an open-label, randomized, parallel-group trial. At the end of a 28-day screening period, all eligible subjects will be randomly assigned into treatment Arm A or B in a 2:1 ratio. Subjects in Arm A will receive a maximum of 6 cycles of chemotherapy (cisplatin plus 5-FU) and cetuximab weekly in the absence of progressive disease (PD), as assessed by the Investigator, and unacceptable toxicity. After 6 cycles of treatment, subjects who derive clinical benefit will continue treatment with cetuximab as monotherapy until either PD or unacceptable toxicity. Subjects in Arm B will receive the same chemotherapy regimen as Arm A alone for a maximum of 6 cycles in the absence of PD and unacceptable toxicity.

Tumor assessment will be performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The baseline tumor assessment is to be performed during the screening period within 28 days before the start of trial treatment. Computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement is recommended for tumor assessment. Subsequent tumor response evaluations will be assessed every 6 weeks ( $\pm 3$  days) starting from the first dose of trial treatment until occurrence of PD regardless of any cycle delay. If treatment is discontinued for reasons other than PD, subjects will continue to have tumor assessments until either PD, the start of a new antitumor treatment, death, the termination of the trial, or loss of follow up, whichever comes first. If symptoms are suggestive of PD, subjects will be evaluated by imaging studies thereafter for documentation and confirmation of the tumor responses.

All subjects in Arm A and B will be followed up continuously for safety evaluations according to schedule of assessments in Table 1.1 starting from date of first signature of informed consent. A Safety Follow-up visit will be performed 30 days ( $\pm 3$  days) after the last dose of trial treatment or immediately before starting any new antitumor treatment. During the treatment period, additional safety evaluations will be on a weekly basis (Arm A only) for physical examination, vital signs, documentation of adverse events and concomitant medications, and also at the start of each cycle (for both arms) Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG), hematology, biochemistry and urinalysis. Survival data will be collected every 3 months after the end of efficacy assessment (EOEA) visit until either death, loss of follow up, or the termination of the trial, whichever comes first.

The trial will be terminated when the last subject has discontinued the trial treatment or OS cut-off, whichever is later. After OS cut-off and before the trial termination, only SAEs during treatment and at the EOEA visit will be reported, following the usual reporting procedure.

Information collected in the EOEAs will be limited to data on date of trial treatment completion, date of last treatment, subject status at end of trial, reason for discontinuation, disease progression (yes/no). From alive, but trial-treatment-discontinued subjects, no tumor response data, anti-cancer treatment and survival information will be collected.

**Planned number of subjects:** 240 subjects.

**Primary endpoint:** The primary endpoint is PFS time, as assessed by an IRC.

**Secondary endpoints:** The secondary endpoints include PFS time, as assessed by the Investigator, OS time, BOR rate, DCR, duration of response, and safety.

**Pharmacokinetics:** Not applicable.

**Other assessments:** Not applicable.

**Diagnosis and key inclusion and exclusion criteria:**

Trial population: Subjects who have recurrent and/or metastatic SCCHN excluding nasopharyngeal carcinoma and who have not received chemotherapy for recurrent and/or metastatic SCCHN.

Key inclusion criteria:

- $\geq 18$  years of age.
- Histologically and/or cytologically confirmed diagnosis of SCCHN.
- Recurrent and/or metastatic SCCHN, not suitable for local-regional treatment. Subjects with recurrent disease only (no metastases) must have received prior radiotherapy (as adjuvant treatment after surgery or as treatment for locally advanced SCCHN) as part of “loco-regional treatment”, and the radiotherapy must have been completed more than 6 months before screening imaging.
- Presence of at least 1 measurable lesion according to RECIST version 1.1.
- Signed written informed consent before any trial-related activities are carried out.
- ECOG performance status of 0 or 1.

Key exclusion criteria:

- Prior systemic chemotherapy, except if given as part of multimodal treatment, for locally advanced SCCHN that was completed more than 6 months before randomization.
- Major surgery or irradiation within 4 weeks before randomization.
- Previous treatment with monoclonal antibody or signal transduction inhibitors targeting epidermal growth factor receptor.
- Nasopharyngeal carcinoma.
- Known central nervous system metastasis and/or leptomeningeal disease.
- Medical or psychological condition that would not permit the subject to complete the trial or sign informed consent.
- Legal incapacity or limited legal capacity.

**Investigational Medicinal Product: dose/mode of administration/ dosing schedule:**

Cetuximab, supplied in ready-to-use 20 mL vials containing 5 mg/mL solution, will be administered on a weekly basis to subjects in Arm A. The initial dose will be 400 mg/m<sup>2</sup> as an intravenous infusion up to a maximum speed of 5 mg/minute. The subsequent weekly dose will be 250 mg/m<sup>2</sup> as an intravenous infusion up to a maximum speed of 10 mg/minute.

**Reference therapy: dose/mode of administration/dosing schedule:**

Subjects in both arms will receive a maximum of 6 cycles of chemotherapy of 75 mg/m<sup>2</sup> cisplatin as intravenous infusion (refer to China package insert) on Day 1 of each 21-day treatment cycle, and then 750 mg/m<sup>2</sup>/day of 5-FU as a continuous intravenous infusion over 24 hours ± 6 hours a day from Day 1 to Day 5 of each 21-day treatment cycle.

In the case of cisplatin-related nonhematologic toxicity, cisplatin may be replaced by carboplatin at a dose of target area under the serum concentration time curve of 5 in subsequent cycles. The decision needs to be made in discussion with the Medical Monitor on a case-by-case basis. Carboplatin will be administered using an intravenous infusion of 15 minutes or longer, and in accordance with the China package insert on Day 1 of each 21-day treatment cycle.

**Planned treatment duration per subject:**

The treatment duration per subject may vary. Subjects will be treated with a maximum of 6 cycles of chemotherapy and/or cetuximab weekly in the absence of PD, as assessed by the Investigator, and unacceptable toxicity. Subjects (in Arm A) who demonstrate at least a tumor response of stable disease (RECIST version 1.1) after 6 cycles of trial treatment will continue monotherapy with cetuximab until either PD or occurrence of unacceptable toxicity. Subjects who stop treatment before reaching PD will continue to have tumor assessments (CT or MRI) every 6 weeks until either PD, the start of a new antitumor treatment, death, or termination of the trial, or loss of follow up, whichever comes first. Upon occurrence of PD, all trial treatments should be discontinued.

**Statistical methods:**

Sample Size Calculation: CCI



Randomization: Randomization will be performed centrally using an interactive web response system (IWRS). A central stratified permuted block randomization procedure will be used to balance between treatment arms. The stratification factors are ECOG performance status (0 versus 1) and the primary tumor site (oral cavity versus hypopharynx versus others).

Statistical Analyses:

The hazard ratio between the treatment arms in PFS time (based on imaging as assessed by IRC) will be estimated by Cox's proportional hazards model stratified by randomization strata to assess the stratified hazard ratio. The 95% confidence interval (CI) will also be provided to characterize the variability of the point estimate. In discussion with Chinese Health Authority, this bridging trial would be regarded as positive from regulatory point of view if the point estimation for stratified hazard ratio less than or equal to 0.77. All secondary analyses of the primary variable will be performed to support the results of the primary confirmatory analysis and regarded as purely exploratory.

The time-to-event endpoints will follow standard methodology by employing Kaplan-Meier estimates, Cox's proportional hazard model to estimate stratified hazard ratios and corresponding 95% CI.

The counts and percentages will be summarized for dichotomous data.

The main statistical analysis of data is event driven and is expected to be approximately 22 months after trial initiation (i.e., after the 144 PFS events with respect to the primary endpoint have occurred). The final analysis of OS (OS cut-off date should be at least 180 deaths [e.g., 75% of randomized subjects] have been reported, or up to 12 months after the last subject is randomized, whichever is earlier), will be presented in a clinical trial report addendum. Safety data collected after the OS cut-off will be reported through patient profile. No additional statistical analyses will be conducted.

**Table 1.1 Schedule of Assessments**

Trial Period	Screening		Cycle 1			Cycles 2-6			> 6 cycles <sup>1</sup>			6-weekly evaluation <sup>2</sup>	EOEA <sup>3</sup>	Safety Follow-Up <sup>4</sup>	Survival Follow-Up <sup>5</sup>
	-28 to -1		1	8	15	1	8	15	1	8	15				
Day												± 3 days			
Informed consent	X														
Randomization <sup>6</sup>		X													
Primary tumor diagnosis	X														
Demographics, height	X														
Medical history	X														
Physical examination/weight	X		X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs <sup>7</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG	X		X			X						X	X	X	
ECG <sup>8, 11</sup>	X		X <sup>19</sup>			X						X	X	X	
Hematology <sup>9, 11</sup>	X		X <sup>19</sup>			X						X	X	X	
Biochemistry <sup>9, 11</sup>	X		X <sup>19</sup>			X						X	X	X	
Urinalysis <sup>10, 11</sup>	X		X <sup>19</sup>			X						X	X	X	
Calculated creatinine clearance <sup>12</sup>	X														
24 hours creatinine clearance <sup>12</sup>	X														
Serum pregnancy test (if applicable <sup>13</sup> )	X														
HBV, HCV, HIV tests <sup>14</sup>	X														
Known HPV status <sup>15</sup> , tobacco, and alcohol consumption status collection	X														

Trial Period	Screening	Cycle 1			Cycles 2-6			> 6 cycles <sup>1</sup>			6-weekly evaluation <sup>2</sup>	EOEA <sup>3</sup>	Safety Follow-Up <sup>4</sup>	Survival Follow-Up <sup>5</sup>
		1	8	15	1	8	15	1	8	15				
Day	-28 to -1											30 days after treatment discontinuation	3-monthly	
± 3 days														
Echocardiogram	X													
Inclusion/Exclusion criteria	X													
Tumor assessment <sup>6</sup>	X	Will be done every 6 weeks (± 3 days)										X		
Cetuximab administration <sup>17</sup>		X	X	X	X	X	X	X	X	X				
Cisplatin <sup>18</sup> and 5-FU		X			X									
Survival and antitumor therapies													X	
Adverse events assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	

5-FU: 5-fluorouracil, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CT: computed tomography, ECG: electrocardiogram, ECOG: Eastern Cooperative Oncology Group, EOEA: end of efficacy assessment, GGT: gamma-glutamyl transferase, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HPV: human papilloma virus, MRI: magnetic resonance imaging, PD: progressive disease, RECIST: Response Evaluation Criteria in Solid Tumors.

1. Arm A only: until PD or unacceptable toxicity.
2. All subjects in Arm A and B will be followed up continuously for safety evaluations according to schedule of assessments in this table starting from date of first signature of informed consent. The evaluations which are completed within 7 days at 6-weekly evaluation visit for physical examination/weight; vital sign; ECG; hematology; biochemistry, and urinalysis can be accepted, and these evaluations at 6-weekly evaluation visit will be optional.
3. EOEA visit will be performed on the day of the last efficacy assessment, whether or not at the end of a cycle. The day of the last efficacy assessment is defined as the day on which it is determined that the subject will no longer be followed up for efficacy.
4. Safety Follow-up visit will be performed 30 days (± 3 days) after the last dose of trial treatment or immediately before starting any new antitumor treatment.
5. Survival follow-up (telephone contact) will be performed every 3 months after the EOEA visit until death or the termination of the trial, whichever comes first.
6. If the Investigator is willing to administer prophylactic tetracycline to reduce the incidence of Grade 3 skin reactions related to cetuximab, randomization and the initiation of prophylactic tetracycline should be performed on Day -1 (1 day before the initiation of cetuximab treatment).
7. Heart rate and blood pressure will be measured in a supine position after 5 minutes at rest. For those in Arm A, vital signs must be continuously monitored before, during, and up to 1 hour after each cetuximab infusion.
8. All 12-lead ECGs will be performed after the subject has rested for 5 minutes.
9. The results of all safety laboratory parameters must be available within 3 days before start of next chemotherapy cycle. Required hematologic parameters include hemoglobin, red blood cell count, white blood cell count and differential count, and platelet count. Required biochemistry parameters include

creatinine, AST, ALT, GGT, total bilirubin (including direct bilirubin if total bilirubin abnormal), total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, glucose, blood urea, and uric acid. Blood samples will be collected after fasting for at least 8 hours.

10. Urinalysis dipstick will be followed by microscopic examination if results are abnormal.

11. If 6 weekly evaluation visits and EOGA visit take place after safety follow up visit, the ECG, hematology, biochemistry, urinalysis tests can be optional.

12. If calculated creatinine clearance is <60 mL/min, 24 hour creatinine clearance might be requested by the Investigator for confirmation.

13. Only for female subjects of childbearing potential, including those who have had a tubal ligation. Performed within 7 days before the first dose of the trial treatment. Regular urine pregnancy tests are also recommended during the trial for female subjects of childbearing potential.

14. Viral serology will be performed only if clinically indicated.

15. This information to be collected is only for those who have known HPV status of their tumor at screening.

16. Tumor assessment will be performed according to RECIST version 1.1. The baseline tumor assessment is to be performed during the screening period within 28 days before the start of trial treatment. The CT or MRI with contrast enhancement is recommended for tumor assessment. Subsequent tumor response evaluations will be assessed every 6 weeks starting from the first dose of trial treatment until occurrence of PD regardless of any cycle delay. If treatment is discontinued for reasons other than PD, subjects will continue to have tumor assessments until either PD, the start of a new antitumor treatment, death, the termination of the trial, or loss of follow up, whichever comes first. If symptoms are suggestive of PD, subjects will be evaluated by imaging studies thereafter for documentation and confirmation of the tumor responses. Imaging must include CT or MRI of the neck (base skull to clavicles), chest, and abdomen. A CT or MRI of the brain and a bone scan or positron emission tomography should be considered for subjects who have possible central nervous system metastasis and possible bone metastasis, respectively. Tumor assessment should include a complete assessment of all target and nontarget lesions.

17. Arm A only: until PD or unacceptable toxicity.

18. Arm A and B for a maximum of 6 cycles in the absence of PD or unacceptable toxicity. If cisplatin results in a nonhematologic toxicity, cisplatin may be replaced by carboplatin in subsequent cycles.

19. Only if screening/last assessments were performed more than 7 days before Cycle 1, Day 1.

---

19/131

## 2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial with cetuximab will be sponsored by Merck KGaA, Darmstadt, Germany.

This trial will be conducted at approximately 30 centers with inpatient setting in mainland China.

The Coordinating Investigators **PPD** [REDACTED], represent all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigators will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigators as well as a list of Sponsor responsible persons are in [Appendix II](#).

The trial appears in the following clinical trial registry: clinicaltrials.gov and chinadrugtrials.org.cn (preregister number: CDEL20140112).

An Independent Review Committee (IRC) will conduct a blinded review of the images and predefined clinical data of all subjects according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, based on a separate charter outlining details of the review process.

An Independent Data Monitoring Committee (IDMC) will perform periodic reviews to evaluate the safety of the subjects in this trial. The details and periodicity of the safety monitoring process will be specified in a dedicated charter.

The Sponsor will supply the cetuximab medication. Cetuximab will be produced under Good Manufacturing Practice (GMP) conditions by the Sponsor, and will be finally released by the Department of Clinical Trial Supplies of the Sponsor.

Trial monitoring, data management and statistical analysis of this trial will be performed by the Sponsor or a designated contract research organization.

The Department of Drug Safety of the Sponsor or their designated representatives will supervise drug safety and the timely reporting of adverse events (AEs) and serious AEs (SAEs) to all concerned parties in accordance with applicable guideline, laws, and regulations.

Quality assurance will be supervised by the Quality Assurance Department of the Sponsor.

Details of structures and associated procedures will be defined in a separate Manual of Operation, which will be prepared under the supervision of the Clinical Trial Leader.

### 3 Background Information

#### 3.1 Cetuximab

As an antibody to epidermal growth factor receptor (EGFR), as of 2015, Erbitux<sup>®</sup> (cetuximab) was granted marketing authorizations in 100 countries for colorectal cancer and 98 countries for squamous cell carcinoma of head and neck (SCCHN). The indications included metastatic colorectal cancer in combination with irinotecan and/or as monotherapy, and SCCHN in combination with radiotherapy (locally advanced SCCHN), in combination with platinum-based chemotherapy, and/or as monotherapy (in subjects with recurrent or metastatic disease). Cetuximab is a chimerized antibody of the immunoglobulin G1 subclass, which was originally derived from a mouse myeloma cell-line (1). It was constructed by cloning the heavy and light chains of a murine monoclonal antibody directed against the EGFR (M225) and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization process resulted in an antibody with binding affinity to EGFR approximately one log higher than endogenous ligands, such as epidermal growth factor (EGF) and transforming growth factor alpha (2, 3).

Cetuximab blocks the binding of EGF and other ligands to the EGFR and prevents EGFR dimerization (4), thereby inhibiting ligand induced activation of this receptor tyrosine kinase. This results in the inhibition of cell growth, induction of apoptosis, and decreased production of matrix metalloproteinase and vascular endothelial growth factor (2).

Cetuximab also stimulates EGFR internalization (5) and eventual degradation (6), by removing the receptor from the cell surface and thereby preventing interaction with its ligand. In addition, cetuximab can mediate antibody-dependent cell-mediated cytotoxicity (7), a process dependent on both the affinity of cetuximab for the extracellular domain of EGFR and the level of cellular EGFR expression (8).

#### 3.2 Epidermal Growth Factor Receptor in Cancer

The EGFR is a commonly expressed transmembrane glycoprotein of the tyrosine kinase growth factor receptor family. The EGFR gene, which is expressed in many normal human tissues, has been found to be a proto-oncogene; its activation results in the high expression of EGFR in many human tumor types. As a transmembrane glycoprotein, the extracellular domain of the EGFR is a ligand-binding site for transforming growth factor alpha and EGF. Upon ligand binding, the intracellular domain of EGFR is activated, thereby triggering cellular mechanisms that regulate cell growth (9). The EGFR signal transduction network plays an important role in multiple tumorigenic processes, including cell cycle progression, angiogenesis, and metastasis, as well as protection from apoptosis (10).

The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicles. In addition, high EGFR expression and/or gene copy number is common in a range of human tumors, including head and neck (11), colorectal (12), pancreatic, renal and non-small

---

cell lung cancers (13), and is often associated with poor prognosis (11, 14). The EGFR is richly expressed by a wide variety of solid tumors, including SCCHN, in which nearly all lesions demonstrate EGFR expression on immunohistochemistry analysis (15). High levels of expression appear to be directly correlated with aggressive tumor growth and reduced survival (16, 17, 18). The EGFR is also known to mediate the resistance of cancer cells to radiation in a manner proportional to the degree of receptor expression (19). The prognostic significance of high levels of expression has emphasized the importance of EGFR as an anticancer drug target (20, 21, 22, 23).

### **3.3 Epidermal Growth Factor Receptor Inhibition and the Cell Cycle**

The effects of EGFR blockade on cell cycle progression have been investigated in several human cell types, including DiFi colon adenocarcinoma cells, non-transformed breast epithelial MCF10A cells, A431 squamous epithelial cancer cells, and DU145 prostatic cancer cells (24). These studies suggest that blocking EGFR with monoclonal antibodies such as cetuximab leads to cell cycle arrest in G1, which is accompanied by a decrease in cyclin-dependent kinase 2 activity, and an increase in the expression of cyclin-dependent kinase inhibitor p27KIP1 (25). In addition to inducing G1-phase arrest, EGFR blockade has also been shown to lead to cell death via apoptosis in DiFi colon adenocarcinoma cells (24, 26).

### **3.4 Nonclinical Studies of Cetuximab**

#### **3.4.1 Nonclinical Absorption, Distribution, Metabolism, and Excretion**

The pharmacokinetics (PK) and toxicokinetics of cetuximab were studied in single-dose and repeat-dose toxicity studies in rats and cynomolgus monkeys. In single-dose and 4-week toxicology studies in rats, serum concentration of cetuximab was increased along with an increase of dose. No significant accumulation was observed over 8 doses administered twice weekly during the 4-week trial. In cynomolgus monkeys, mean peak serum levels across treatment groups were dose dependent without significant gender differences. In the 39-week toxicology trial, steady-state levels of cetuximab were reached in Trial Week 4. The dose and the apparent half-life (between 50 and 94 hours) showed a linear PK relationship within the dose range from 7.5 mg/kg to 38 mg/kg weekly (low dose and mid-dose levels). At the high dose (120 mg/kg initially followed by 75 mg/kg weekly), elimination was becoming saturated by showing a greater area under the concentration-time curve (AUC), a longer half-life, and a slower clearance. No significant gender differences and no accumulation of cetuximab were observed in this trial. In the development toxicity trial in pregnant female cynomolgus monkeys, toxicokinetic parameters were similar to those found in the 39-week trial with the same doses (12/7.5, 38/24, and 120/75 mg/kg).

### 3.4.2 Nonclinical Toxicology

Rodent data are not relevant for assessment of mechanism-based toxicity because cetuximab does not react with rodent (mice and rats) EGFR.

In a 39-week toxicology trial in cynomolgus monkeys, infusions of 0, 7.5, 24, and 75 mg/kg were administered weekly via intravenous infusion over 1 hour following a 1-time 2-hour infusion of 0, 12, 38, and 120 mg/kg, respectively on Day 1. The peak concentration ( $C_{max}$ ) and AUC from the time of dosing to the last measurable concentration achieved with the high dose under steady-state conditions were approximately 21- and 17-fold, respectively, as the values found in humans at the recommended dose. In the high-dose group, treatment was terminated after 36 weeks in 2 males and 3 females reported as secondary bacterial infection and intercurrent deaths. The animals in the high-dose group displayed reduced food consumption, weight loss or reduced weight gain, apathy, prostration, and general morbidity. Epithelial effects on the skin and the oral, oesophageal, and nasal mucosa were the major toxicologically relevant lesions.

Skin reactions were dose-related. Epidermal lesions of the skin, including hyperparakeratosis, acanthosis, and acantholysis with clefts, pustules, and vesicle formation were observed by histopathological tests. The low- and intermediate-dose levels were considered to be tolerated. Cetuximab showed good local tolerability after single IV, paravenous, intramuscular, and subcutaneous administrations in rabbits (Merck KGaA Studies T15386 [2002], T15509 [2003], and T15510 [2003]). Single intra-arterial administration of cetuximab led to a reddening of the ear, which was regarded as a transient sign of intolerance. Cetuximab showed no indications of genotoxic potential under in vitro and in vivo conditions (Merck KGaA Studies T15386 [2002] and T15361 [2002]).

### 3.4.3 Nonclinical Efficacy Pharmacology and Safety Pharmacology

In vitro assays and in vivo animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express EGFR. No antitumor effects of cetuximab were observed in human tumour xenografts lacking EGFR expression. In animal studies, the addition of cetuximab to cisplatin and oxaliplatin resulted in an increase in antitumor effects compared to chemotherapy alone.

Cardiovascular and respiratory endpoints relevant for a safety pharmacological assessment were evaluated within the 39-week repeat-dose primate toxicity trial (070-087) without resulting in any treatment-related changes in electrocardiogram (ECG) data, heart rate, arterial blood pressure, or respiratory rate. Clinical observations within this trial revealed no findings indicative of central nervous system effects related to cetuximab. An additional trial (0070/100) assessed safety pharmacologically relevant hemodynamic and respiratory parameters in anesthetized male cynomolgus monkeys without yielding noticeable changes of the cardiovascular and respiratory system attributable to cetuximab treatment.

### 3.5 Dose Selection Criteria and Clinical Pharmacokinetics of Cetuximab

An initial dose of 400 mg/m<sup>2</sup> followed by repetitive weekly doses of 250 mg/m<sup>2</sup> is the dosing regimen included in the approved label. Detailed information on the PK of cetuximab in humans can be found in the Investigator's brochure.

### 3.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic responses to cetuximab were assessed using either a double-antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to high drug levels in the circulation, antibody determination may be impaired by enabling measurement of anti-drug antibodies in the presence of excess drug. Anti-cetuximab antibodies have been detected in 4.9% (49 of 1001) of evaluable subjects. In subjects with positive anti-cetuximab antibody, the median time to onset was 44 days (range: 8 to 281 days). Although the number of sero-positive subjects is limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumor activity of the molecule.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab with the incidence of antibodies to other products may be misleading.

### 3.7 Clinical Development of Cetuximab

A large clinical development program has investigated cetuximab in various cancer indications including SCCHN, colorectal cancer, non-small cell lung cancer, breast cancer, pancreatic cancer, renal carcinomas, and gastric cancer. In these studies, cetuximab was given at a fixed dose regimen, either in combination with radiotherapy or chemotherapy or as a single agent. The completed and ongoing Phase I, II and III clinical studies that have been performed with cetuximab are discussed in more detail in the Investigator's brochure.

#### 3.7.1 Clinical Pharmacology

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear PK. The AUC increased in a greater than dose-proportional manner as the dose increased from 20 to 400 mg/m<sup>2</sup>. Cetuximab clearance decreased from 0.08 to 0.02 L/h/m<sup>2</sup> as the dose increased from 20 to 200 mg/m<sup>2</sup>, and at doses > 200 mg/m<sup>2</sup>, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2 to 3 L/m<sup>2</sup>. Following a 2-hour infusion of 400 mg/m<sup>2</sup> of cetuximab, C<sub>max</sub> was 199 µg/mL (range: 70 to 380 µg/mL) and the mean elimination half-life was

---

97 hours (range: 41 to 213 hours). A 1-hour infusion of 250 mg/m<sup>2</sup> produced a mean C<sub>max</sub> of 168 µg/mL (range: 69 to 404 µg/mL).

Following the recommended dose regimen (400 mg/m<sup>2</sup> initial dose 250 mg/m<sup>2</sup> weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life was 112 hours (range: 63 to 230 hours).

### **3.7.2 Cetuximab plus Chemotherapy in the Treatment of Recurrent and/or Metastatic SCCHN**

A large development program, including phase I-II studies, has also investigated the efficacy and safety of cetuximab alone or in combination with platinum-based chemotherapy in human subjects with recurrent and/or metastatic SCCHN who failed platinum-based regimens given for recurrent or metastatic disease (27, 28, 29). In studies investigating the combination of cetuximab with platinum-based chemotherapy, the overall response rate was 11 to 13% and the disease control rate (DCR) was 51% in these chemorefractory subjects. In a trial where cetuximab alone was investigated in the same refractory setting (EMR 62 202-016 trial) (29), the overall response rate was 12% and the DCR was 45.5%.

The use of cetuximab plus platinum-based chemotherapy as first-line treatment of subjects with recurrent and/or metastatic SCCHN has been investigated in a number of studies. The largest trial, the EXTREME trial (EMR 62 202-002) confirmed the benefit of adding cetuximab to platinum-based chemotherapy in the first-line treatment of recurrent and/or metastatic SCCHN subjects. A total of 442 subjects were randomized to a regimen of cisplatin or carboplatin and 5-fluorouracil (5-FU) with or without cetuximab. The addition of cetuximab to platinum-based chemotherapy significantly improved overall survival (OS) time versus chemotherapy alone (median 10.1 versus 7.4 months; hazard ratio: 0.80; p= 0.04). Progression-free survival (PFS) time was significantly improved in the combination arm (5.6 months) compared with chemotherapy alone (3.3 months; 46% risk reduction, p < 0.001). Furthermore, there was an absolute difference of 16% in response rate in the combination arm compared with chemotherapy alone (objective response rate 36% versus 20%, p < 0.001). The addition of cetuximab only slightly modified the characteristic AE profile of platinum-based chemotherapy and did not have a negative impact on quality of life (30).

A further phase III trial performed by the Eastern Cooperative Oncology Group (ECOG) compared cisplatin plus cetuximab versus cisplatin plus placebo in 117 subjects (E5397) (31). All efficacy time parameters favored the cetuximab-containing arm, although the treatment differences did not reach statistical significance (OS time: 9.2 versus 8.0 months, PFS time: 4.2 versus 2.7 months), and the overall response rate was superior (26% versus 10%, p= 0.03). Notably, the safety profile of cisplatin was not affected by concomitant administration of cetuximab.

A phase I/II trial (EMR 62-202-008) (32) also showed that cetuximab does not alter the known safety profile of the chemotherapeutic combination and vice versa. Efficacy data were promising in the cisplatin group with an overall response rate of 33.3%, a DCR of 67%, and a median OS

---

time of 10.6 months, and in the carboplatin group, with an overall response rate of 38.5%, a DCR of 80.8%, and a median OS time of 8.5 months. An overall 36% response rate was observed with a regimen of cetuximab plus cisplatin or carboplatin and 5-FU.

### 3.7.3 Reasonably Anticipated Serious Adverse Events

In the solid tumor population, the occurrence of acute cardiovascular events, acute cerebrovascular events, deep vein thrombosis, and symptoms or signs of (progression of) underlying malignancy are reasonably anticipated due to age, comorbid conditions or the disease state, and concomitant medications. However, if adverse signs and symptoms occur in association with disease (tumor) progression, such as dyspnea, tumor pain, bleeding etc., then these should be recorded as AEs or reported as SAEs (see [Section 7.4.1.1](#)).

### 3.7.4 Related Adverse Events

Safety data are summarized in the Investigator's Brochure in tabular format for all Phase I trials, by indication for Phase II trials, and by indication for Phase III trials.

Cetuximab was investigated in 4 randomized controlled trials in more than 3000 subjects with metastatic colorectal cancer: cetuximab in combination with irinotecan plus 5-FU in trial EMR 62202-013, cetuximab in combination with irinotecan in trial CA225006, cetuximab in combination with oxaliplatin plus infusional 5-FU/folinic acid in trial EMR 62202-047, and cetuximab as a single agent and best supportive care in trial CA225025. In addition, cetuximab was investigated in combination with radiotherapy in subjects with locally advanced SCCHN in trial EMR 62202-006 and in combination with platinum-based chemotherapy in recurrent and/or metastatic SCCHN in trial EMR 62202-002.

Safety data of these 6 trials with more than 2,100 cetuximab-treated subjects are available. The known side effects of cetuximab are listed in [Table 3.1](#).

**Table 3.1 Adverse Events that Have Been Found to Have an Association with Cetuximab**

Nervous system disorders	Headache (common) Aseptic meningitis (frequency not known)
Eye disorders	Conjunctivitis (common) Blepharitis, keratitis (uncommon)
Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism (uncommon) Interstitial lung disease (rare)
Gastrointestinal disorders	Diarrhea, nausea, vomiting (common)
Skin and subcutaneous tissue disorders	Skin reactions (very common) Stevens-Johnson syndrome/toxic epidermal necrolysis (very rare) Superinfections of skin lesions (frequency not known)

Metabolism and nutrition disorders	Hypomagnesaemia (very common) Dehydration, hypocalcaemia, anorexia which may lead to weight decrease (common)
Vascular disorders	Deep vein thrombosis (uncommon)
General disorders and administration site conditions	Mild or moderate infusion-related reactions comprising symptoms such as fever, chills, dizziness, or dyspnoea (very common) Mucositis, in some cases severe. Mucositis may lead to epistaxis (very common) Severe infusion-related reactions, in rare cases with fatal outcome (common) Fatigue (common)
Hepatobiliary disorders	Increase in liver enzyme levels (aspartate amino transferase, alanine aminotransferase, and alkaline phosphatase) (very common)

Note: The expected frequencies in brackets are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), frequency not known (cannot be estimated from the available data).

**Skin reactions:** Skin reactions may develop in more than 80% of subjects and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g., paronychia). Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. The majority of skin reactions develop within the first 3 weeks of treatment. They generally resolve without sequelae over time following cessation of treatment, if the recommended adjustments in dose regimen are followed. According to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, Grade 2 skin reactions are characterized by rash affecting up to 50% of body surface area (BSA), while Grade 3 reactions affect equal or more than 50% of BSA. Skin lesions induced by cetuximab may predispose subjects to superinfections (e.g., with *Staphylococcus aureus*), which may lead to subsequent complications, e.g., cellulitis, erysipelas or potentially fatal outcomes such as staphylococcal scalded skin syndrome or sepsis.

**Infusion-related reactions:** Mild or moderate infusion-related reactions are very common and comprise symptoms such as fever, chills, dizziness, or dyspnea that occur in a close temporal relationship, mainly to the first cetuximab infusion. Severe infusion-related reactions may occur commonly, but the outcome is rarely fatal. They usually develop during or within 1 hour of the initial cetuximab infusion, but may occur after several hours or with subsequent infusions. Although the underlying mechanism has not been identified, some of these reactions may be anaphylactoid/anaphylactic in nature and may include symptoms such as bronchospasm, urticaria, decrease or increase in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

**Combination with 5-FU:** When cetuximab was used in combination with intermittent infusional 5-FU, the frequencies of cardiac ischemia including myocardial infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysesthesia) were increased compared to infusional 5-FU alone.

**Combination with platinum-based chemotherapy:** If cetuximab is used in combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia, and sepsis compared to platinum-based chemotherapy alone.

### 3.8 Trial Rationale

The use of cetuximab plus platinum-based chemotherapy as first-line treatment of subjects with recurrent and/or metastatic SCCHN has been investigated in a number of studies. The largest trial, the EXTREME trial (EMR 62202-002) confirmed the benefit of adding cetuximab to platinum-based chemotherapy in the target population. A total of 442 subjects were randomized to a regimen of cisplatin or carboplatin and 5-FU with or without cetuximab. The addition of cetuximab to platinum-based chemotherapy significantly improved OS time versus chemotherapy alone (median 10.1 versus 7.4 months; hazard ratio: 0.80;  $p=0.04$ ). Progression-free survival time was significantly improved in the combination arm (5.6 months) compared with chemotherapy alone (3.3 months; 46% risk reduction,  $p<0.001$ ). Furthermore, there was a significant increase in response rate in the combination arm compared with chemotherapy alone (objective response rate 36% versus 20%, odds ratio [95% confidence interval (CI)], 2.326 [1.504, 3.600],  $p<0.001$ ). The addition of cetuximab only slightly modified the characteristic AE profile of platinum-based chemotherapy and did not have a negative impact on quality of life (30).



This trial aims to assess efficacy and safety of cetuximab when given in combination with chemotherapy compared with chemotherapy alone in Chinese subjects with recurrent and/or metastatic SCCHN as the first-line treatment, in response to the Chinese Health Authority requirements regarding trial design and sample size for local registration proposes.

### 3.9 Risk-Benefit Assessment

The efficacy and safety of cisplatin plus 5-FU has already been widely demonstrated.

The preclinical, clinical-pharmacological, and current clinical data on cetuximab suggest a favorable benefit/risk of cetuximab in combination with platinum-based chemotherapy and that the treatment is effective in subjects with recurrent and/or metastatic SCCHN.

In Asia, the treatment guidelines follow the National Comprehensive Cancer Network guidelines. The proposed trial will use a dosage regimen of 75 mg/m<sup>2</sup> cisplatin on Day 1 and 750 mg/m<sup>2</sup>/day 5-FU from Day 1 to Day 5 of each 3-week treatment cycle to allow for the different chemotherapy tolerability profiles that are seen in Asian subjects. Cetuximab will be given according to the dosage regimen approved for use in the European Union and the United States.

The benefit/ risk has been carefully considered in the preparation of this trial protocol. Based on the preclinical and clinical data available to date, the conduct of the trial is considered justifiable using the dose(s) and dosage regimen(s) of the Investigational Medicinal Product (IMP) as specified in this protocol. During the trial conduct the benefit/risk of the IMP will be assessed on an ongoing basis by an IDMC.

The trial will be conducted in compliance with the clinical trial protocol, GCP and the applicable regulatory requirement(s).

## **4 Trial Objectives**

### **4.1 Primary objective**

The primary objective of this trial is to evaluate whether PFS time, as assessed by an IRC, in subjects receiving cetuximab in combination with cisplatin plus 5-FU is longer than that in subjects receiving cisplatin plus 5-FU alone in the first-line treatment of recurrent and/or metastatic SCCHN.

### **4.2 Secondary objectives**

The secondary objectives are to compare the 2 treatment arms regarding the following:

- PFS time, as assessed by the Investigator.
- OS time.
- Best overall response (BOR) rate.
- DCR.
- Duration of response.
- Safety.

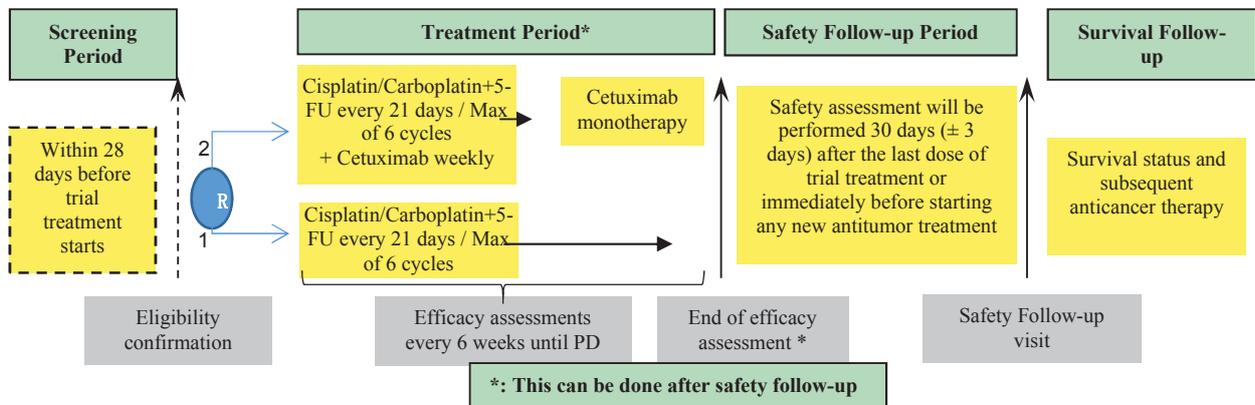
## **5 Investigational Plan**

### **5.1 Overall Trial Design and Plan**

This multicenter, open-label, randomized, parallel-group, phase III trial will randomize approximately 240 subjects with recurrent and/or metastatic SCCHN and involve approximately 30 trial centers in China. The overall trial design is illustrated in [Figure 5.1](#).

---

Figure 5.1 Schematic of the Trial Design



5-FU: 5-fluorouracil, PD: progressive disease.

All eligible subjects will be randomized to 1 of 2 treatment arms in a 2:1 ratio:

- Arm A (cetuximab plus chemotherapy): Combination of cetuximab and cisplatin plus 5-FU. Subjects who are without progressive disease (PD) after 6 cycles of treatment will continue monotherapy with cetuximab until occurrence of PD or unacceptable toxicity.
- Arm B (chemotherapy alone): Cisplatin plus 5-FU only.

Randomization will be performed centrally using an interactive web response system (IWRS). Randomization will be stratified according to ECOG performance status (0 versus 1) and the primary tumor site (oral cavity versus hypopharynx versus others) (see Section 6.3).

**Definition of treatment cycle:** The ideal cycle in each arm is 21 days long and is determined by the chemotherapy as follows:

- Arm A: 1 treatment cycle consists of dosing with chemotherapy plus cetuximab on Day 1, and doses of cetuximab on Days 8 and 15, with follow-up through to Day 21 of the cycle.
- Arm B: 1 treatment cycle consists of dosing with chemotherapy starting from Day 1 of each cycle.

The regimen of cetuximab for subjects in Arm A is shown in Table 6.1. Subjects in Arm A and B will receive the same chemotherapy regimen every 21 days, which is based on cisplatin plus 5-FU and is shown in Table 6.4.

**Duration of treatment for subjects in Arm A:** Subjects with absence of PD, as assessed by the Investigator, and unacceptable toxicity will receive a maximum of 6 cycles of chemotherapy (cisplatin plus 5-FU) and cetuximab weekly. Subjects who have not experienced PD after end of chemotherapy will continue treatment with cetuximab until either PD, as assessed by the

Investigator, or occurrence of an unacceptable toxicity. Subjects with an unacceptable toxicity due to one of the trial drugs will receive other trial drug(s) without unacceptable toxicity until either PD or completion of 6 cycles of chemotherapy. If treatment with cetuximab is delayed because of a related toxicity, the 21-day rhythm of chemotherapy is retained. A maximum of 2 consecutive cetuximab infusions can be withheld (no more than 21+3 days without cetuximab infusions) due to unacceptable toxicity, otherwise the subject must stop cetuximab. If treatment is delayed because of toxic effects of the chemotherapy, the 7-day rhythm of cetuximab infusions is retained. Chemotherapy can be delayed for a maximum of 21+3 days; after this, the subject must stop the chemotherapy treatment. The subject may continue on cetuximab monotherapy (if still benefiting).

**Duration of treatment for subjects in Arm B:** Subjects with absence of PD, as assessed by the Investigator, and unacceptable toxicity will receive a maximum of 6 cycles of chemotherapy. Subjects with an unacceptable toxicity due to one of the trial drugs will receive other trial drug(s) without unacceptable toxicity until either PD, as assessed by the Investigator, or completion of 6 cycles of chemotherapy. Chemotherapy can be delayed for a maximum of 21+3 days; after this, the subject must stop the chemotherapy treatment.

**Tumor assessment:** Tumor assessment will be performed according to RECIST version 1.1. The baseline tumor assessment is to be performed during the screening period within 28 days before the start of trial treatment. Computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement is recommended for tumor assessment. Subsequent tumor response evaluations will be assessed every 6 weeks ( $\pm 3$  days) starting from the randomization day until occurrence of PD regardless of any cycle delay. If treatment is discontinued for reasons other than PD, subjects will continue to have tumor assessments until either PD, the start of a new antitumor treatment, death, the termination of the trial, or loss of follow up, whichever comes first. If symptoms are suggestive of PD, subjects will be evaluated by imaging studies thereafter for documentation and confirmation of the tumor responses. The details of documentation of tumor assessment is described in [Section 7.3.1](#).

**Safety follow-up period:** All subjects in Arm A and B will be followed up continuously for safety evaluations according to schedule of assessments in [Table 1.1](#) starting from date of first signature of informed consent. A Safety Follow-up visit will be performed 30 days ( $\pm 3$  days) after the last dose of trial treatment or immediately before starting any new antitumor treatment. During the treatment period, additional safety evaluations will be on a weekly basis (Arm A only) for physical examination, vital signs, documentation of AEs and concomitant medications, and also at the start of each cycle (for both arms) for ECOG performance status, ECG, hematology, biochemistry and urinalysis. Survival data and any information on new antitumor treatments will be collected every 3 months after the EOE visit until either death, loss of follow up, or the termination of the trial, whichever comes first.

**Primary and secondary endpoints:** The primary endpoint of this trial is PFS time, as assessed by an IRC. Secondary endpoints include PFS time, as assessed by the Investigator, OS time, BOR rate, DCR, duration of response, and safety (see [Section 8](#)).

---

**Duration of the whole trial:** The anticipated duration of the recruitment period is from the fourth quarter of 2015 to the fourth quarter of 2017. The trial will be terminated when the last subject discontinued to the trial or OS cut-off, whichever is later. The OS cut-off date should be at least 180 deaths (e.g., 75% of randomized subjects) have been reported, or up to 12 months after the last subject is randomized, whichever is earlier. The last subject's last visit is anticipated in November 2018. The actual duration of recruitment period will be based on the trial set-up process.

The medical care of subjects after the termination of this trial is described in [Section 6.13](#).

## 5.2 Discussion of Trial Design

This clinical trial is being proposed in response to the Chinese Health Authority which requested that a randomized controlled trial be performed for local registration proposes.

The use of cetuximab plus platinum-based chemotherapy as first-line treatment of subjects with recurrent and/or metastatic SCCHN has been investigated in a number of trials. The treatment duration, control group, and treatment allocation designed for this trial are similar to those in the largest trial, the EXTREME trial (EMR 62 202-002), which confirmed the benefit of adding cetuximab to platinum-based chemotherapy in the first-line treatment of subjects with recurrent and/or metastatic SCCHN. The dose of cisplatin and 5-FU applied in this trial has been modified according to local clinical practice (cisplatin dose intensity decreased by 25% and 5-FU dose intensity decreased by 6.25% compared with that in the EXTREME trial) (33). CCI

[REDACTED] If cisplatin results in a nonhematologic toxicity (see [Section 6.4.1.2.2](#)), cisplatin may be replaced by carboplatin in subsequent cycles. The dose of carboplatin in this trial is the same as that in the EXTREME trial, which is accepted by Chinese Investigators (33).

The primary endpoint in this trial is PFS time, as assessed by an IRC. While OS time is still considered the 'gold standard' of clinical efficacy, PFS time has been recommended in SCCHN trials as a primary endpoint. A recently published trial analyzed aggregate data from all published phase III clinical trials (ECOG, EXTREME, and SPECTRUM) using EGFR monoclonal antibodies as first-line treatment in recurrent and/or metastatic SCCHN, to investigate PFS time as a surrogate endpoint to OS time. The limited data indicated a linear relationship between PFS time and OS time with a constant difference between them of 5 months. This data suggested that PFS time to be a useful surrogate endpoint for OS time in this indication (33).

In addition, especially in China, OS time data may be confounded by a cross-over and/or second- and third-line treatments, while the treatment effect on PFS time is not confounded by these factors.

The PFS as primary endpoint has been well recognized and accepted as a surrogate endpoint by the Chinese Health Authority. Therefore, PFS is considered as an acceptable primary endpoint for this trial.

The endpoint of PFS time will be assessed by an IRC to mitigate any Investigator bias in determining PFS time in this open-label trial. Progression-free survival, as assessed by the Investigator, will be one of the secondary endpoints.

### 5.3 Selection of Trial Population

Subjects who have recurrent and/or metastatic SCCHN excluding nasopharyngeal carcinoma and who have not received chemotherapy for recurrent and/or metastatic SCCHN.

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Before performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in [Section 9.2](#).

#### 5.3.1 Inclusion Criteria

For inclusion in the trial, subjects should fulfill all of the following inclusion criteria:

1.  $\geq 18$  years of age.
2. Histologically and/or cytologically confirmed diagnosis of SCCHN.
3. Recurrent and/or metastatic SCCHN, not suitable for local-regional treatment. Subjects with recurrent disease only (no metastases) must have received prior radiotherapy (as adjuvant treatment after surgery or as treatment for locally advanced SCCHN) as part of "loco-regional treatment", and the radiotherapy and the radiotherapy must have been completed more than 6 months before screening imaging.
4. Presence of at least 1 measurable lesion according to RECIST version 1.1.
5. Signed written informed consent before any trial-related activities are carried out.
6. ECOG performance status of 0 or 1.
7. Neutrophils  $\geq 1.5 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and hemoglobin  $\geq 90$  g/L.
8. Total bilirubin  $\leq 2 \times$  upper limit of normality (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 3 \times$  ULN (if liver metastasis exists, ALT and AST  $\leq 5 \times$  ULN).
9. Serum corrected calcium, potassium and magnesium corrected within normal range (electrolyte correction is permitted during screening).
10. Creatinine clearance  $\geq 60$  mL/minute (24 hours creatinine clearance might be requested by the Investigator for confirmation, if calculated creatinine clearance is  $< 60$  mL/min).

11. Effective contraception if procreative potential exists (applicable for both male and female subjects) until at least 3 months after the last dose of trial treatment.

### 5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following criteria:

1. Prior systemic chemotherapy, except if given as part of multimodal treatment for locally advanced SCCHN that was completed more than 6 months before randomization.
2. Major surgery or irradiation within 4 weeks before randomization.
3. Previous treatment with monoclonal antibody or signal transduction inhibitors targeting EGFR.
4. Nasopharyngeal carcinoma.
5. Known allergic reaction against any of the components of the trial treatment.
6. Active infection including active tuberculosis, known and declared human immunodeficiency virus (HIV) infection, or active hepatitis B/C virus (HBV/HCV) infection resulting in an impaired liver function or cirrhosis (see [Section 7.2.4](#)).
7. History of organ allograft, autologous/allogeneic stem cell transplantation, and renal replacement therapy.
8. Asymptomatic severe hypertension or hypertensive crisis defined as systolic blood pressure  $\geq 180$  mmHg and/or diastolic blood pressure  $\geq 110$  mmHg under resting conditions.
9. Impaired cardiac function, evidenced by any of the following conditions:
  - Left ventricular ejection fraction  $< 45\%$
  - Serious arrhythmia
  - Unstable angina pectoris
  - Congestive heart failure New York Heart Association class III or IV
  - Myocardial infarction within the 12 months before randomization
  - Pericardial effusion.
10. Known central nervous system metastasis and/or leptomeningeal disease. Subjects with neurological symptoms should undergo a CT/MRI of the brain to exclude brain metastasis.
11. Known uncontrolled diabetes mellitus, pulmonary fibrosis, interstitial lung diseases, acute pulmonary diseases, or liver failure.
12. Peripheral neuropathy or hearing loss  $\geq$  Grade 2.
13. Subjects not recovered from any acute effects of prior surgery, chemotherapy, or radiation therapy, that is, to  $\leq$  Grade 1 (CTCAE, version 4.03). Chronic late toxicities resulting from

prior radiation and/or surgery (pharyngeal/laryngeal toxicity, i.e., xerostomia, speech, swallowing abnormalities etc.) are permitted if nutritional status is stable.

14. Known alcohol and/or drug abuse.
15. Medical or psychological condition that would not permit the subject to complete the trial or sign informed consent.
16. Past or current history of neoplasm other than SCCHN, except for curatively treated nonmelanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years.
17. Any investigational medication within 30 days before randomization.
18. Female subjects who are pregnant (absence to be confirmed by serum  $\beta$ -human chorionic gonadotropin [HCG] test) or breast feeding, or males and females of reproductive potential not willing or not able to employ a highly effective method of birth control/contraception to prevent pregnancy from 2 weeks before receiving trial treatment until 3 months after receiving the last dose of trial treatment. A highly effective method of contraception is defined as having a low failure rate (< 1% per year) when used consistently and correctly.
19. Concurrent treatment with a prohibited medication (see [Section 6.5.2](#)).
20. Subjects with any concurrent medical condition or disease that will potentially compromise the conduct of the trial at the discretion of the Investigator.
21. Legal incapacity or limited legal capacity.

Subjects must fulfill all eligibility criteria to be enrolled in this trial. No exemption from any inclusion and exclusion criteria will be allowed. If any deviation from eligibility is retrospectively detected for an already enrolled subject, the Investigator and Sponsor must decide immediately whether it is safe to treat this subject further within the trial (see [Section 5.4.2](#)).

## **5.4 Criteria for Subject Withdrawal**

### **5.4.1 Withdrawal from Trial Therapy**

A subject must be withdrawn from all trial treatment (cetuximab and chemotherapy) in the event of any of the following but should stay in the trial:

- Occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety and discontinuation is considered necessary by the Investigator and/or Sponsor.
- Occurrence of AEs and discontinuation of trial treatment is desired or considered necessary by the Investigator and/or the subject.
- Occurrence of pregnancy during trial treatment.
- Occurrence of PD according to RECIST version 1.1.

- Intake of prohibited medications, as defined in [Section 6.5.2](#), if deemed necessary by the Investigator and/or Sponsor.
- Non-compliance.

CCI [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

In case of premature withdrawal from the trial treatment for reasons other than PD, the subjects will be asked to attend scheduled visits until an assessment of PD as planned.

## 5.4.2 Withdrawal from the Trial

Upon death or loss of follow-up, subjects may be considered as having completed the trial. Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial.

A subject must be withdrawn if any of the following occur during the trial:

- Withdrawal of consent.
- Participation in another clinical trial (In this case, collection of survival data should continue).

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible, and record the reasons in appropriate sections of the electronic case report form (eCRF).

## 5.5 Premature Termination of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, such as:
  - Evidence of inefficacy of the IMP,
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP.
- Withdrawal of IMP from the market for safety.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The clinical trial may also be terminated or suspended upon request of Health Authorities.

## 5.6 Definition of End of Trial

The trial will be terminated when the last subject has discontinued the trial treatment or OS cut-off, whichever is later.

The OS cut-off will occur when the following conditions are met:

---

- Follow-up after the randomization of the last subject is at least 12 months, OR
- At least 180 deaths have been reported in this trial.

## **6 Investigational Medicinal Product and Other Drugs Used in the Trial**

In this trial, trial treatment consists of cetuximab and cisplatin plus 5-FU. Cetuximab is considered as the IMP and cisplatin plus 5-FU as the background first-line standard chemotherapy for recurrent and/or metastatic SCCHN. If cisplatin results in a nonhematologic toxicity (see [Section 6.4.1.2.2](#)), cisplatin may be replaced by carboplatin in subsequent cycles.

Cisplatin, carboplatin, and 5-FU are commercially available cytotoxic agents for the treatment of various cancers, including SCCHN. The chemotherapeutic drugs for this trial will be supplied by the local pharmacy/the third party vendor at each trial center. The Sponsor will provide financial compensation for the cost of chemotherapeutic drugs depending on the procedures of each participating center.

### **6.1 Description of Investigational Medicinal Product**

Cetuximab will be made available in ready-to-use 20 mL vials containing 5 mg/mL solution.

Cetuximab (Erbix<sup>®</sup>) 5 mg/mL is manufactured by the Sponsor, packed, labeled and distributed for clinical trial supply by a suitable service provider, and finally released by the Sponsor under GMP conditions.

Cetuximab 5 mg/mL gained approval from the European Medicines Agency in March 2007 and a licence for first-line SCCHN in the European Union in November 2008. This formulation of cetuximab does not require filtration before administration. Cetuximab is formulated as 5 mg protein/mL in glycine/sodium chloride/tween/citrate buffer solution at pH 5.5 ± 0.2, and is aseptically filled in sterile glass vials.

Batch numbers will be provided in the certificates of release. From the documentation of cetuximab, it will be possible to retrace the composition and pharmaceutical quality according to current GMP guidelines. The Sponsor will provide cetuximab free of charge for all eligible subjects.

### **6.2 Dosage and Administration**

#### **6.2.1 Selection and Timing of Cetuximab**

Subjects in Arm A only, will receive cetuximab in combination with cisplatin or carboplatin plus 5-FU chemotherapy. Cetuximab will be given every 7 days as outlined in [Table 6.1](#).

**Table 6.1 Dose and Administration Procedure for Cetuximab**

	Dosage	Infusion rate	Flush of line with saline solution (0.9%) at the end of infusion	Prophylactic pretreatment with an appropriate antihistamine and corticosteroid
First infusion	400 mg/m <sup>2</sup>	maximum 5 mg/minute	Yes	Mandatory
Subsequent infusions	250 mg/m <sup>2</sup>	maximum 10 mg/minute	Yes	Recommend

The cetuximab dose will be based on the subject’s BSA and has to be recalculated and the dose adjusted accordingly before each cetuximab infusion. The BSA should be calculated according to the Mosteller formula:  $BSA (m^2) = \sqrt{([height (cm) \times weight (kg)] / 3600)}$ . The calculation will be based on the weight measured at each relevant visit and the height as measured and recorded at the screening visit.

The maximum infusion rate must NOT exceed 5 mg/minute for first infusion and must NOT exceed 10 mg/minute at subsequent infusions.

Cetuximab will always be administered before cisplatin or carboplatin on Day 1 of a cycle. Cetuximab infusions should be performed, if possible, on the same day of each week with no more than 3 days deviation.

Pretreatment with an appropriate antihistamine and a corticosteroid are mandatory at least 1 hour before the first cetuximab administration and these premedications are recommended before all subsequent infusions of cetuximab (see Section 6.4.2).

Before, during, and up to 1 hour after each cetuximab infusion, subjects must have their vital signs continuously monitored to detect any AEs (specifically, allergic/hypersensitivity reactions). A physician should be available during each cetuximab administration, i.e., until the complete infusion has been given and for 1 hour after the end of the infusion. Exact documentation of actual dose, date, start time, and end time of each cetuximab infusion is mandatory.

Cetuximab must not be mixed with any other substance and therefore requires a separate infusion line. If another intravenous infusion is required at the same time as the cetuximab infusion (e.g., for hydration), a second line must be used.

All subjects randomized to Arm A will receive cetuximab until radiographically documented PD, as assessed by the Investigator, or unacceptable toxicity occurs, or consent is withdrawn. If chemotherapy is delayed, administration of cetuximab every 7 days is continued. If chemotherapy is discontinued for any reason, treatment with cetuximab monotherapy every 7 days is continued.

## 6.2.2 Dose Reductions and Treatment Alterations for Cetuximab

### 6.2.2.1 Skin Reactions

Prophylactic use of oral tetracyclines is highly recommended for subjects in Arm A for reducing the incidence of Grade 3 skin reactions (34). Unless there are contraindications based on subject and/or health care provider factors, prophylactic systemic treatment with minocycline 100 mg daily or doxycycline 100 mg twice daily is recommended for 6-8 weeks for subjects randomized to Arm A, starting 1 day before the administration of the first dose of cetuximab (34, 35). The recommended prophylaxis for skin toxicities are described in Table 6.2.

**Table 6.2 Recommended Prophylaxis for Skin Toxicities**

Treatment	Dose	Start	Stop	Alternatives
<b>Systemic therapy<sup>1</sup></b>				
Minocycline Or Doxycycline	1 × 100 mg/day  2 × 100 mg/day	Day -1	6-8 weeks <sup>2</sup>	In case of intolerance: <ul style="list-style-type: none"> <li>• First generation cephalosporins</li> <li>• Amoxicillin</li> <li>• Erythromycin</li> <li>• Limecycline</li> </ul>
<b>Topical therapy</b>				
Low potency steroid creams such as: <ul style="list-style-type: none"> <li>• Alclometasone 0.05%</li> <li>• Desonide 0.05%</li> <li>• Fluocinolone 0.01%</li> </ul>	2 × daily on face and chest	Day -1	6-8 weeks	
Emollient (creams or ointments)	3 × daily to the hands, and after hand washing  2 × daily on the rest of the body	Day -1	Continue	

- 1 If infection is suspected (yellow crusts, purulent discharge, painful skin / nares), obtain culture and change to oral antibiotic based on sensitivities.
- 2 May be continued beyond 6-8 weeks at the Investigator's discretion in the event of CTCAE Grade 2 rash.

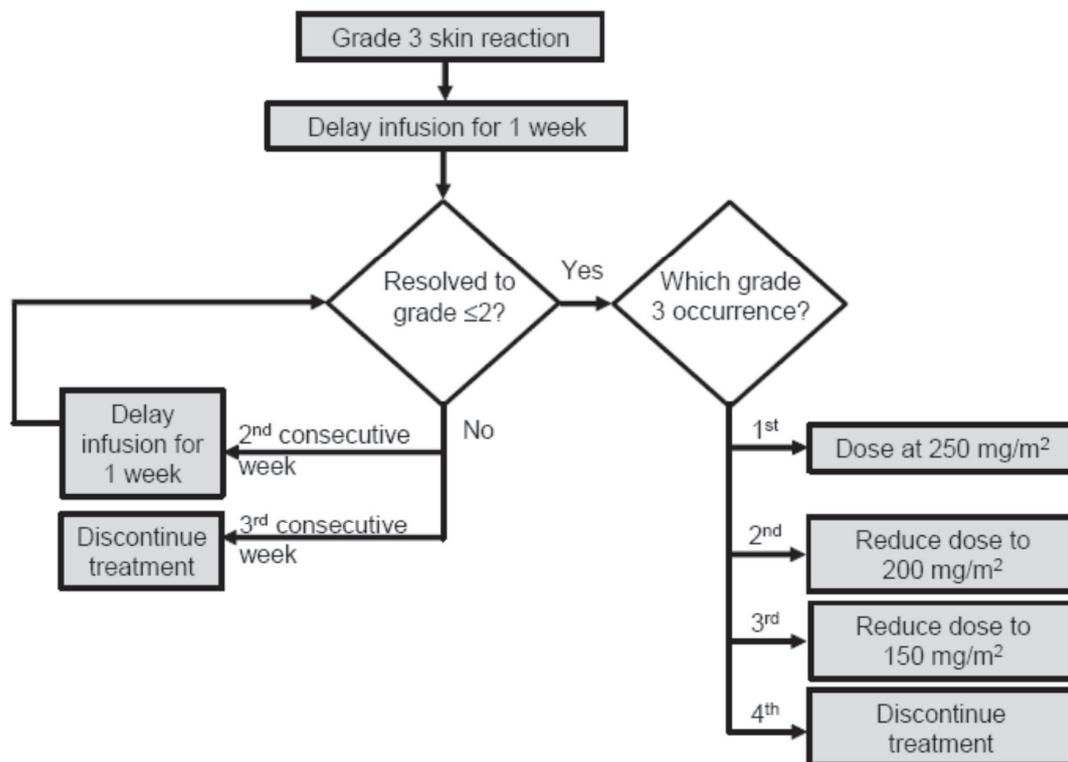
For a Grade 1 or 2 acne-like rash (as defined in the CTCAE version 4.03), treatment with topical antibiotics (e.g., benzoylperoxide, erythromycin) or systemic antibiotics (e.g., oral tetracyclines) should be considered. Subjects with at least Grade 3 reactions should be referred to a dermatologist for advice and management if needed. If pruritus occurs, an oral antihistamine is advised. In the case of dry skin, the use of emollient creams is beneficial. Fissures may occur in dry skin and topical dressings are helpful.

If a subject experiences a Grade 3 skin reaction (as defined in the CTCAE version 4.03), cetuximab treatment may be delayed for up to 14 days (omission of 1 or 2 scheduled administrations) without changing the dose level (see Figure 6.1). If skin reactions resolve to Grade 2 or less by the following treatment period, treatment may be resumed.

If Grade 3 skin reactions occur for a second and third time, cetuximab treatment may again be delayed for up to 14 days with dose reductions to 200 mg/m<sup>2</sup> and then 150 mg/m<sup>2</sup>. Cetuximab dose reductions are permanent. Subjects must discontinue cetuximab if more than 2 consecutive infusions are withheld or Grade 3 skin reactions occur for a fourth time despite the appropriate dose reduction (see Figure 6.1). Any Grade 4 toxicity (including skin reactions) considered related to cetuximab is to result in discontinuation of cetuximab treatment permanently.

If, in the opinion of the Investigator, the discontinuation of cetuximab is considered necessary, the subject should be withdrawn from cetuximab treatment immediately, but should be further treated with chemotherapy and remain in the trial for scheduled visits.

**Figure 6.1 Treatment Adjustment in the Event of Grade 3 Skin Reactions Considered to be Related to Cetuximab**



### 6.2.2.2 Infusion-related Reactions

Mild or moderate infusion-related reactions are very common. Symptoms include fever, chills, dizziness or dyspnea occurring in a close temporal relationship mainly to the first cetuximab infusion.

Severe infusion-related reactions may occur, in some cases with a fatal outcome. Some of these reactions may be anaphylactoid/anaphylactic in nature or represent a cytokine release syndrome. This syndrome typically occurs within 1 hour after infusion and is less commonly associated with bronchospasm and urticaria, but may also occur for up to several hours after infusion or with subsequent infusions. Cytokine release syndrome is normally most severe in relation to the first infusion.

Symptoms of severe infusion-related reaction may include bronchospasm, urticaria, hypertension or hypotension, loss of consciousness, or shock. In rare cases angina pectoris, myocardial infarction, or cardiac arrest have been observed.

Anaphylactic reactions may occur as early as within a few minutes of the first infusion, e.g., due to preformed Immunoglobulin E antibodies cross-reacting with cetuximab. These reactions are commonly associated with bronchospasm and urticaria. They can occur despite the use of premedication.

These symptoms usually occur during the first infusion and up to 1 hour after the end of infusion, but may happen several hours after or with subsequent infusions. It is recommended to warn subjects of the possibility of such a late onset and to instruct them to contact their physician if symptoms of an infusion-related reaction occur. Special attention is recommended for subjects with reduced performance status and pre-existing cardiopulmonary disease.

The Investigator must treat all symptoms of infusion-related reactions with the best available medical measures. Based on previous experience with cetuximab infusion-related reactions, the treatment guidelines given in [Table 6.3](#), graded according to the CTCAE version 4.03 should be followed:

**Table 6.3 Treatment Adjustment for Symptoms of Cetuximab Infusion-related Reactions**

CTCAE Grade <sup>1</sup>	Treatment adjustment for cetuximab
<b>Grade 1 mild</b> Transient flushing or rash; drug fever < 38°C;	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 240 minutes.
<b>Grade 2 moderate</b> Rash: flushing; urticaria; dyspnea; drug fever ≥38°C	Stop cetuximab infusion and immediately administer treatment for symptoms.  Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
<b>Grade 3 or Grade 4 severe or life-threatening</b> Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension Grade 4 Anaphylaxis;	Stop the cetuximab infusion immediately and disconnect infusion tubing from the subject.  Treat symptoms vigorously. Subjects have to be withdrawn immediately from treatment and must not receive any further cetuximab treatment.

1 Graded according to Common Terminology Criteria for Adverse Events, version 4.03.

### Resumption of cetuximab treatment following infusion-related reactions

Once the cetuximab infusion rate has been decreased after an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction on the slower infusion rate, the infusion should be stopped and the subject should be withdrawn from cetuximab treatment permanently. If a subject experiences a Grade 3 or 4 infusion-related reaction (excluding fever) at any time, she/he must discontinue cetuximab immediately, but should be further treated with chemotherapy and remain in the trial for scheduled visits.

### 6.2.2.3 Other Reasons

If a subject develops an intercurrent illness (e.g., infection) that, in the opinion of the Investigator and/or Sponsor, mandates interruption of treatment, this intercurrent illness must resolve within a time frame such that no more than 2 consecutive cetuximab infusions are withheld. In the event of delayed cetuximab treatment, there will be no new 400 mg/m<sup>2</sup> initial dose at treatment restart, and all subsequent treatments will be continued at the assigned dose level or the last dose before interruption if the dose had been reduced.

If cetuximab must be withheld for a longer period of time, cetuximab treatment will be permanently discontinued; in special cases, the Investigator may request that the subject is allowed to continue to receive cetuximab after consulting the Sponsor.

Cetuximab treatment will not be delayed for a chemotherapy-related toxicity. Therefore, if there is a delay for chemotherapy, the subject will continue to receive weekly infusions of cetuximab. If chemotherapy is completely terminated for a related toxicity, cetuximab may be continued as monotherapy up to until either PD, as assessed by the Investigator, unacceptable toxicity, or withdrawal of consent. No other antitumor treatment should be given to subjects until radiographically documented PD. Subjects will continue to receive scheduled evaluation visits until PD, as assessed by the Investigator.

### 6.3 Assignment to Treatment Arms

All subjects will be assigned a subject number by the Investigator at the screening visit. Subjects who enter the trial will retain this number throughout the trial.

Randomization will occur on Day 1, the same day the trial treatment is initiated, but before the first dose of trial treatment. For subjects randomized to Arm A, prophylactic administration of a tetracycline is recommended, starting 1 day before the administration of the first dose of cetuximab. In this case, trial treatment will be initiated 1 day after randomization which will be performed on Day -1. Once an eligible subject has signed the informed consent form (ICF), the center will use an IWRS and receive instructions regarding treatment assignment. Allocation to the 2 treatment arms will be in a ratio of 2:1.

Randomization will be stratified according to ECOG (0 versus 1) and the primary tumor site (oral cavity versus hypopharynx versus others) to balance these factors across the treatment arms and thus improve comparability of the results.

The randomization list will be generated by the designated contract research organization under the responsibility of the Sponsor's trial statistician. Specific details will be provided in a separate Manual of Operations.

### 6.4 Noninvestigational Medicinal Products to be Used

#### 6.4.1 Chemotherapy

All subjects will receive chemotherapy for up to 6 cycles. As a rule, each cycle will last 21 days. In the absence of PD and unacceptable toxicity, subjects will receive 6 cycles of chemotherapy. The start of each cycle of chemotherapy will be defined by the start of cisplatin infusion (or carboplatin infusion, if cisplatin have been switched to carboplatin). Chemotherapy should be administered, if possible, on the same day of each cycle with no more than 3 days deviation.

Details of chemotherapy regimens are given in [Table 6.4](#).

**Table 6.4 Chemotherapy Regimen Every 21 Days in Arm A and B**

Order of administration	Drug	Dose
First	Cisplatin infusion (refer to China package insert) on Day 1	75 mg/m <sup>2</sup>
In the case of cisplatin intolerability <sup>1</sup>	Carboplatin infusion time of 15 minutes or longer, and in accordance with the China package insert on Day 1	AUC 5
Then	5-Fluorouracil Day 1 to Day 5	750 mg/m <sup>2</sup> /day continuous infusion

Abbreviation: AUC, area under serum concentration time curve.

<sup>1</sup> If cisplatin results in a nonhematologic toxicity (see Section 6.4.1.2.2), cisplatin may be replaced by carboplatin in subsequent cycles.

### 6.4.1.1 Selection and Timing of Chemotherapy

#### 6.4.1.1.1 Cisplatin

Cisplatin (75 mg/m<sup>2</sup>) will be administered as intravenous infusion (refer to China package insert) on Day 1 of each 21-day treatment cycle.

For any BSA value more than 2.0 m<sup>2</sup>, the cisplatin dosage must be restricted to the dose appropriate for a BSA of 2.0 m<sup>2</sup>. Adequate hydration and maintenance of sufficient urinary output is mandatory. Centers should follow their related local practice and the approved local package insert or the following hydration scheme:

- Before cisplatin: 2 liters of any fluid taken orally on the day before chemotherapy AND 1 liters orally plus a minimum of 500 mL of intravenous fluid given on the morning of cisplatin treatment. The 500 mL of intravenous fluid may be part of the antiemesis infusion.
- After cisplatin: Immediately after cisplatin, an intravenous infusion of 200 to 250 mL/hour of 5% dextrose in half normal saline, 5% dextrose in normal saline, or normal saline and 30 mEq KCl/L will be given for 4 to 6 hours.

Total hydration fluid volume, including enteral and parenteral, should be at least 3500 mL on the day of cisplatin administration.

There must be at least 1 hour between the end of the cetuximab infusion and the start of the cisplatin infusion. Intravenous prehydration can be performed concomitant to cetuximab administration but a separate line must be used.

Antiemetic prophylaxis is mandatory to prevent acute and delayed nausea and vomiting due to the high emetogenicity of cisplatin. It is highly recommended that the guidelines of the Multinational Association of Supportive Care in Cancer and the American Society of Clinical Oncology are followed, i.e., inclusion of dexamethasone, a 5-hydroxytryptamine-3 antagonist and a neurokinin-1 antagonist.

All infusions and medications given for hydration, urinary output maintenance and antiemesis must be documented in the eCRF. Investigators should refer to the approved cisplatin package insert for additional information such as safety issues, adverse reactions, and storage information.

Exact documentation of the actual doses, dates, and start and end times of infusions is mandatory.

#### **6.4.1.1.2 Carboplatin**

If cisplatin results in a nonhematologic toxicity (see [Section 6.4.1.2.2](#)), carboplatin at a dose of target AUC=5 may be used as the replacement of cisplatin in subsequent cycles. The decision needs to be made in discussion with the Medical Monitor on a case-by-case basis.

Carboplatin will be administered using an intravenous infusion of 15 minutes or longer (refer to China package insert) on Day 1 of each 21-day treatment cycle. The dose of carboplatin will be calculated considering the subject's renal function as described by the glomerular filtration rate using the Calvert formula or the Chatelut formula, given that the target AUC is 5.

For those subjects in Arm A, there must be at least 1 hour between the end of the cetuximab infusion and the start of the carboplatin infusion.

Exact documentation of the actual doses, dates, and start and end times of infusions is mandatory.

#### **6.4.1.1.3 5-Fluorouracil**

Investigators should treat subjects with commercially available forms of 5-FU, and must refer to the approved 5-FU prescribing information on dosage and administration, safety issues (warnings, precautions), adverse reactions, dose reductions and omissions. Investigators should also follow their related local practice for the administration of 5-FU.

5-Fluorouracil will be administered as a dose of 750 mg/m<sup>2</sup>/day as a continuous intravenous infusion over 24 hours a day from Day 1 to Day 5 ( $\pm$  6 hours of the overall duration) of each 21-day treatment cycle. Administration of 5-FU is to start upon completion of cisplatin/carboplatin administration and may be performed via the same infusion line.

For those subjects in Arm A, there must be at least 1 hour between the end of the cetuximab infusion and the start of the 5-FU infusion.

Exact documentation of the actual doses, dates, and start and end times of infusions is mandatory.

---

#### 6.4.1.1.4 Criteria for Starting the Next Cycle of Chemotherapy

Before starting the next cycle of chemotherapy, the following criteria must be fulfilled:

- Absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/L$ .
- Platelet count is  $\geq 100 \times 10^9/L$ .
- Nonhematologic chemotherapy-related toxicities have resolved to  $\leq$  Grade 1 or baseline (excluding weight loss, skin reactions, paronychia, fatigue, ototoxicity or neurotoxicity which must have resolved to  $\leq$  Grade 2).

If these criteria are not met, the start of the next cycle must be delayed to allow for recovery. If a delay of more than 21 days is necessary as a result of an unresolved toxicity, one or both of the chemotherapeutic drugs should be discontinued.

If the start of the next cycle must be delayed due to either a cisplatin/carboplatin-, or 5-FU-related toxicity, the start of the other compound should also be postponed. However, if either cisplatin/carboplatin or 5-FU dosing must be permanently discontinued, dosing should be continued with the remaining compound according to the schedule.

The BSA must be recalculated and the cisplatin and 5-FU doses adapted accordingly before each subsequent cycle (for formula see [Section 6.4.1.1.1](#)). A delay in the next cycle of up to 3 calendar days from the calculated Day 1 of that cycle for administrative reasons such as a weekend is at the discretion of the treating Investigator.

For those in Arm A, in case of cetuximab-related toxicity, chemotherapy will not be delayed and the planned schedule for administration should be maintained. If cetuximab treatment is terminated for a cetuximab-related toxicity, chemotherapy will be continued. If chemotherapy is completely terminated for a related toxicity, cetuximab may be continued as monotherapy until either PD, as assessed by the Investigator, an unacceptable toxicity or withdrawal of consent.

#### 6.4.1.2 Dose Reductions of Chemotherapy

Every effort will be made to administer the full doses of cisplatin/carboplatin and 5-FU.

Dose reductions are always based on the dose of the previous cycle. Only 2 dose reductions for cisplatin and 5-FU and 1 dose reduction for carboplatin are permitted. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be withdrawn from chemotherapy (see [Table 6.5](#)).

**Table 6.5 Dose Reductions for Chemotherapy**

	Dose reduction levels	Dosage <sup>1</sup>
Cisplatin	0	75mg/m <sup>2</sup>
	-1 (decreased by 20%)	60mg/m <sup>2</sup>
	-2 (decreased by 20% from -1 level)	48mg/m <sup>2</sup>
Carboplatin <sup>2</sup>	0	AUC 5
	-1 (decreased by 20%)	AUC 4
5-Fluorouracil	0	750mg/m <sup>2</sup>
	-1 (decreased by 20%)	600mg/m <sup>2</sup>
	-2 (decreased by 20% from -1 level)	480mg/m <sup>2</sup>

Abbreviation: AUC, area under serum concentration time curve.

- 1 The doses which have been reduced for toxicity must not be re-escalated.
- 2 Carboplatin can be considered, if the subject experiences a nonhematologic toxicity. The starting dose of carboplatin would be the first dose level of AUC 5 at the Investigator's discretion.

Dose adjustments are to be made according to the body system showing the greatest degree of toxicity experienced during the previous cycle. Toxicities will be graded using the CTCAE version 4.03.

All implemented dose reductions are permanent. The doses must be modified according to the lowest hematology values and the highest degree of nonhematologic toxicities observed at the scheduled date of chemotherapy. If a subject develops several different toxic effects and there are conflicting recommendations, the dose modification will be based on the AE on the scheduled day of treatment.

Dose reduction and delays and related management will be documented in the subject's medical record and in the related section in the eCRF.

If a subject has a Grade 3 or 4 toxicity after 2 dose reductions, or if a treatment delay is longer than 3 consecutive weeks, then the discontinuation of chemotherapy treatment has to be considered.

For those in Arm A, chemotherapy will not be delayed for cetuximab-related toxicities.

**Major toxicities observed with cisplatin:** nephrotoxicity; ototoxicity; myelodepression with leukopenia, thrombocytopenia and anemia; infectious complications; nausea and vomiting; and peripheral neuropathies.

Renal function will be assessed on a regular basis as specified in the protocol (see [Table 1.1](#)). Cisplatin should be used with caution in subjects with pre-existing peripheral neuropathy. Cisplatin is contraindicated in subjects with a pre-existing hearing deficit. Audiometric testing and periodic neurological examination at baseline and during treatment are recommended to monitor the effects of cisplatin on hearing and neurological function.

**Major toxicities observed with carboplatin:** myelodepression with thrombopenia, leucopenia, neutropenia and/or anemia; infectious complications; nausea and vomiting; ototoxicity; and peripheral neuropathies.

**Major toxicities observed with 5-FU:**

- Cardiac toxicity: The typical signs of cardiac toxicity related to 5-FU are ischemic pain occurring a few hours after a bolus or after the start of a continuous infusion, together with characteristic ECG changes. Silent ECG alterations may also occur. Myocardial infarction has been reported. Thus, treatment with 5-FU must be stopped in subjects who develop such symptoms or have any other cardiac events of unclear origin during or after treatment with 5-FU.
- Hand-Foot syndrome: Subjects treated with 5-FU may develop hand-foot syndrome, characterized by redness and swelling of the palms and soles of the feet. Mild hand-foot syndrome is painless, but in 10 to 15% of cases it can be painful and is usually associated with blisters, ulcerations, cracks, and desquamation. Pyridoxine (vitamin B6) at 100-150 mg per day may be helpful.
- Diarrhea and mucositis: Subjects treated with 5-FU may develop mucositis, or more commonly diarrhea. In case of diarrhea, symptomatic treatment with loperamide is recommended.

#### 6.4.1.2.1 Chemotherapy Hematologic Toxicities

##### Febrile Neutropenia

Febrile neutropenia is defined as follows:

- Grade 2 fever (temperature  $\geq 38.1^{\circ}\text{C}$ ) concomitant with Grade 4 neutropenia ( $\text{ANC} < 500/\text{mm}^3$ ) requiring intravenous antibiotics and/or hospitalization.

Fever should be graded using the CTCAE version 4.03 grading system. The reported temperature should be the axillary temperature.

In cases of febrile neutropenia, the following approach is recommended:

- Hospital admission except where outpatient care may be suitable.
- Pre-antibiotic evaluation (e.g., antibiogram).
- White blood cell count with differential and blood culture should be performed.
- Dose reductions and commencement of an antibiotic treatment as outlined in [Table 6.6](#).

**In case of febrile neutropenia, blood counts must be done every 2 days until recovery to  $\text{ANC} \geq 500/\text{mm}^3$  or temperature  $< 38.1^{\circ}\text{C}$ .**

**Table 6.6 Chemotherapy Dose Reduction and Treatment for Febrile Neutropenia**

Adverse Event	Treatment
Febrile neutropenia Documented infection	<p>1) The first episode of febrile neutropenia or documented infection will result in antibiotic treatment and reduction by 20% of both the cisplatin and 5-FU doses while maintaining the duration of 5-FU infusion of 5 days (or dose reduction of carboplatin to AUC 4 if applicable)</p> <p>2) If there is a second episode despite dose reduction, the subject must receive prophylactic antibiotics (quinolone) during the subsequent cycles and a second dose reduction by 20% of both cisplatin and 5-FU during the subsequent cycles</p> <p>3) If there is a third episode, the subject will be withdrawn</p>

### Criteria for Dose Reductions Based on Hematologic Results

If a subject's blood sample on the scheduled day of treatment shows abnormal hematology results, chemotherapy dose may need to be reduced. If any of the hematologic criteria presented in Table 6.7 are met, a dose reduction of chemotherapy is required.

**Table 6.7 Criteria for Dose Reductions Based on Hematologic Results on the Schedule Day of Treatment**

Neutropenia	Grade 3 (500-999/mm <sup>3</sup> )	Chemotherapy treatment delay until $\leq$ Grade 1 ( $\geq$ 1500/mm <sup>3</sup> )
	Grade 4	Chemotherapy treatment delay until no more than Grade 1; dose reduction of all further doses of cisplatin or carboplatin <b>and</b> 5-FU by 20%
Thrombopenia	Grade 1	Chemotherapy treatment delay until thrombocytes > 100000/mm <sup>3</sup>
	At least Grade 2	Chemotherapy treatment delay until thrombocytes > 100000/mm <sup>3</sup> ; dose reduction of all further doses of cisplatin or carboplatin <b>and</b> 5-FU by 20%

### 6.4.1.2.2 Nonhematologic Toxicities

If a subject has a Grade 3 or 4 toxicity, as defined in Table 6.8, after 2 dose reductions, or if a treatment delay is longer than 3 consecutive weeks, then the discontinuation of chemotherapy treatment has to be considered.

**Table 6.8**                      **Criteria for Dose Reductions Based on Nonhematologic Toxicities on the Scheduled Day of Treatment**

Toxicity	Grade <sup>1</sup>	Action to be taken
Mucositis	Grade 1	Delay chemotherapy treatment until Grade 0
	> Grade 1	Delay chemotherapy treatment until Grade 0; dose reduction of all further doses of 5-FU only by 20%
Diarrhea	Grade 1	Delay chemotherapy treatment until Grade 0
	> Grade 1	Delay chemotherapy treatment until Grade 0; dose reduction of all further doses of 5-FU only by 20%
Hypercreatinemia	≥ Grade 1	Delay chemotherapy treatment until Grade 0, change cisplatin to carboplatin
Ototoxicity	Grade 2	Dose reduction of all further doses of cisplatin by 20%
	> Grade 2	Delay chemotherapy treatment until ≤ Grade 2, change cisplatin to carboplatin
	> Grade 3	Stop carboplatin
Hand-foot syndrome	Grade 2	Delay chemotherapy treatment until ≤ Grade 1
	> Grade 2	Delay chemotherapy treatment until ≤ Grade 1; dose reduction of all further doses of 5-FU by 20%
Other organ toxicity <sup>2</sup>	Grade 2	Delay chemotherapy treatment until Grade 1
	> Grade 2	Delay chemotherapy treatment until Grade 1 <sup>3</sup> ; dose reduction of all further doses of platinum-based treatment and 5-FU by 20% (or dose reduction of carboplatin to AUC 4 if applicable)
Sensory neuropathy	Grade 2	Dose reduction for all further doses of cisplatin by 20%
	> Grade 2	Stop cisplatin, change cisplatin to carboplatin
	> Grade 3	Stop carboplatin

5-FU: 5-fluorouracil.

- 1 Graded according to Common Terminology Criteria for Adverse Events, version 4.03.
- 2 Except asymptomatic increase in transaminases, cetuximab-induced skin reactions and medically irrelevant side effects (e.g., nausea, alopecia, altered taste).
- 3 Nonhematologic chemotherapy-related toxicities have resolved to ≤ Grade 1 or baseline (excluding weight loss, skin reactions, paronychia, fatigue, ototoxicity or neurotoxicity which must have resolved to ≤ Grade 2).

The results of hematology and blood biochemistry analyses must be available before the start of each cycle of chemotherapy.

## 6.4.2 Other Drugs

Subjects must be given an antihistamine and a corticosteroid at least 1 hour before receiving the first infusion of cetuximab (see [Section 6.2.1](#)). All pretreatment must be documented in the eCRF.

The prophylactic drugs will be prescribed via the hospital pharmacy at each trial center. The Investigator should administer the drugs in accordance with the information given in the product package insert with respect to dosage and administration, safety issues (warnings, precautions), adverse reactions, dose modifications and omissions. The Investigator should also follow any related local practices for the administration of such pretreatment. The Sponsor will not assume the costs for these pretreatment drugs.

Subjects must receive hydration treatment, medication to maintain urinary output and antiemetic prophylaxis for each cisplatin infusion as outlined in [Section 6.4.1.1.1](#). Centers should follow their related local practices and the approved local package insert or the scheme outlined in [Section 6.4.1.1.1](#). All of these drugs and infusions must be documented in the eCRF.

## 6.5 Concomitant Medications and Therapies

The following must be recorded in the eCRF:

- All medication administered during the trial until the safety follow-up visit or EOE visit, whichever is later, including the generic name, total daily dosage, and duration of treatment.
- All (neo-) adjuvant chemotherapy administered before inclusion in the trial, with start and stop dates, treatment, dose, and regimen.
- Any previous surgery on the underlying tumor (date, extent of surgical procedure).
- Any previous radiotherapy for the underlying tumor (date, dose).
- All diagnostic or therapeutic procedures performed during the trial period (i.e., from signing of informed consent onwards), including the date, indication, description of the procedures, and any clinical findings.
- Any change in the permitted concomitant medications being taken at the beginning of the clinical trial, with the type of medication, dose, duration, and indication.

### 6.5.1 Permitted Medicines

All subjects, male and female, must practice medically-accepted contraception throughout the trial if the risk of conception exists.

Sedatives, antiemetics, antibiotics, analgesics, antihistamines, steroids, granulocyte-colony stimulating factor, as well as red blood cells, erythropoietin, platelets or fresh frozen plasma transfusions may be given at the discretion of the Investigator according to local practices to assist in the management of pain, infection, and other complications of the malignancy. In the case of febrile neutropenia or documented infection, intravenous antibiotics may be administered for curative use (see [Section 6.4.1.2.1](#)). Prophylactic use of quinolone is also permitted in cases of recurrent febrile neutropenia despite dose reduction of chemotherapy.

For any skin AE of Grade 1–3, topical and/or oral antibiotics are permitted (see [Section 6.2.2.1](#)). Subjects with Grade 3 or higher reactions should be referred to a dermatologist for advice and management if needed. 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.

Localized radiation therapy for pain relief is permitted providing it is not directed towards an area in which the subject's only available target lesion is located. Any target or nontarget lesion assessed according to RECIST version 1.1 which will be radiated during the trial must not be further considered for response assessment. If any localized radiation therapy during trial treatment, e.g., due to increasing bone pain, is considered, it should always firstly be checked if the subject has PD according to RECIST version 1.1.

Bisphosphonates might be given for bone metastases. If any dose increase of an already ongoing bisphosphonate treatment or the start of bisphosphonate treatment due to increasing bone pain is considered, it should always firstly be checked if this subject might have PD according to RECIST version 1.1.

Any medications (other than those excluded by the protocol, see [Section 6.5.2](#)) that are considered necessary for the subject's welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations.

## 6.5.2 Prohibited Medicines

Additional concurrent chronic systemic immune treatment, chemotherapy, radiotherapy (except the situation described in [Section 6.5.1](#)), hormone treatment for treatment of cancer (other than corticosteroids as antiemetic treatment and gestagens for tumor cachexia which are allowed) or any other investigational agent may not be administered to subjects in this trial.

Any traditional Chinese medication with approval for use as anticancer treatment (regardless of the type of cancer) will not be permitted. Traditional Chinese medication for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator.

If the administration of a nonpermitted concomitant drug becomes necessary during the trial, e.g., for AEs or in an urgent medical situation, it is at the Investigator's discretion. In such a case, this subject has to be withdrawn from trial treatment and detailed information needs be recorded.

## 6.5.3 Other Trial Considerations

After the end of the trial, all subjects will receive further treatment based on local medical practice.

---

#### **6.5.4 Special Precautions**

Subjects enrolled in this clinical trial will be provided with an Emergency Medical Support Card during their trial participation. The Emergency Medical Support Card, which will be provided by the Sponsor, is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to provide any health care provider with access to the necessary information about their participation. This may be needed to determine the course of the subject's medical treatment. This service is designed to provide information to health care providers who are not part of the clinical trial. Clinical Trial Investigators, who are already aware of the protocol and treatment, have other means of accessing necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergency situations will be the Clinical Trial Investigator caring for the affected subject. The Investigator agrees to provide emergency contact information on the Emergency Medical Support Card for this purpose. If the Investigator is available when an event occurs, she/he will answer the question.

#### **6.6 Packaging and Labeling of the Investigational Medicinal Product**

The packaging, labeling, and documentation of the cetuximab will be in accordance with applicable local regulatory requirements and applicable GMP Guidelines, so that it shall be possible to retrace the composition and pharmaceutical quality. All labels are given in the Trial File.

#### **6.7 Preparation, Handling and Storage of the Investigational Medicinal Product**

Instructions for the handling and preparation of the cetuximab solution for infusion will be provided.

All cetuximab treatment boxes supplied to each trial center must be stored carefully, safely, and separately from other drugs. Cetuximab should be stored in a refrigerator at 2° to 8°C until use, with a temperature log maintained daily.

The IMP must not be used for any purpose other than the trial. The administration of IMP to subjects who have not been enrolled into the trial is not covered by the trial insurance for subjects.

The Investigator (or the pharmacist or another person who is designated by the Investigator) will maintain the following records for the IMP:

- Receipt of treatment boxes at the trial center.
- Inventory at the center.

- Administration to each subject.
- Destruction of unused IMPs.

It must be ensured that the IMPs are not used at each trial center:

- After the expiry date, or
- After the retest date unless the IMP is reanalyzed and its release date extended.

This is to be closely monitored by the trial monitor and trial manager.

Upon completion or termination of the trial, the Investigator/pharmacist will destroy all unused IMPs after approval by the monitor. The Investigator/pharmacist will provide the local monitor with a copy of the inventory record for filing and a record of the used, unused and destroyed clinical supplies, to facilitate inventory procedures. This form shall include information on:

- All administered units.
- All unused units.
- All units destroyed at the end of the trial.
- Date of destruction.
- Name and signature of the Investigator/pharmacist.

## 6.8 Investigational Medicinal Product Accountability

The Investigator (or designee) is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be carefully recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial center IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical trial and prepared at the center.
  - The use of each dose by each subject.
  - The disposition (including return, if applicable) of any unused IMP.
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the center), and the individual subject trial numbers.

The Investigator center should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a subject may be redispensed to a different subject.

A Trial Monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial center, or following the local hospital medical waste destruction practice for used containers.

## 6.9 Assessment of Investigational Medicinal Product Compliance

Cetuximab treatment and chemotherapy will be administered either by the Investigator or under his or her supervision in an inpatient setting.

The application dates and exact amounts of cetuximab, cisplatin, carboplatin, and 5-FU given at each infusion will be documented in the eCRF. If cetuximab and/or cisplatin and/or carboplatin and/or 5-FU treatment is interrupted during the actual infusion, the clinical staff will estimate the percentage of the dose received by the subject and document it in the eCRF.

Any reason for noncompliance should also be documented. Insufficient compliance is defined as a subject missing > 2 consecutive infusions of cetuximab or > 21 consecutive days chemotherapy infusion delay for nonmedical reasons. In the event of insufficient compliance, discontinuation of the trial treatment will be considered in mutual agreement between the Investigator and Sponsor on a case-by-case basis.

The IMP administration must be recorded in the eCRF.

## 6.10 Blinding

This trial will be an open-label trial as most subjects treated with cetuximab will experience skin reactions, facilitating their identification.

## 6.11 Emergency Unblinding

Not applicable.

## 6.12 Treatment of Overdose

CCI

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial ( $\leq 5\%$  more than planned dose will not be considered as overdose). Even if it does not meet other criteria for an SAE, any overdose

---

must be recorded in the trial medication section of the CRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in [Section 7.4](#). To date, there is limited experience with single cetuximab doses higher than 400 mg/m<sup>2</sup> BSA or weekly administrations of cetuximab doses higher than 250 mg/m<sup>2</sup> BSA. In clinical studies with cetuximab doses up to 700 mg/m<sup>2</sup> given every 2 weeks, the safety profile was consistent with that described in [Section 3.7.4](#). Any drug overdose (>10% of calculated dose per plan) occurring in the present trial must be reported as an SAE (see [Section 7.4.1.4](#)).

In the case of overdose of chemotherapy/cetuximab, the Investigator should provide all possible medical care and treatment in accordance with local medical practice.

### **6.13 Medical Care of Subjects after End of Trial**

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial center's standard of care and generally accepted medical practice and depending on the subject's individual medical needs. The Sponsor will provide trial treatment for free if the Investigator considers the subject is benefiting from it, until cetuximab is approved and marketed in China for the indication of SCCHN.

## **7 Trial Procedures and Assessments**

### **7.1 Schedule of Assessments**

Before performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in [Section 9.2](#).

This section summarizes the types of assessment to be performed by visit type. A complete schedule of assessments is given in [Table 1.1](#).

The trial will be terminated when the last subject has discontinued the trial treatment or OS cut-off, whichever is later. After OS cut-off and before the trial termination, only SAEs during treatment and at the EOEA visit will be reported, following the usual reporting procedure. Information collected in the EOEA forms will be limited to data on date of trial treatment completion, date of last treatment, subject status at end of trial, reason for discontinuation, disease progression (yes/no). From alive, but trial-treatment-discontinued subjects, no tumor response data, anti-cancer treatment and survival information will be collected.

#### **7.1.1 Screening Visit**

The screening visit (baseline) must take place in the 28 days before the start of trial treatment.

The following tests and procedures will be performed at this visit:

- Written informed consent.

- Primary tumor diagnosis (see [Section 7.2.2](#)).
- Documentation of AEs starting from the date of first signature of informed consent.
- Documentation of demographic data, height, and relevant medical history (see [Section 7.2.3](#)).
- Documentation of prior and concomitant medications (see [Section 6.5](#)).
- Check of inclusion and exclusion criteria (see [Section 5.3](#)).
- Physical examination, check of vital signs, and assessment of ECOG performance status (see [Section 7.4.4](#)).
- ECG (to be repeated if performed more than 7 days before the first dose of trial treatment) (see [Section 7.4.4.4](#)).
- Blood samples collected after fasting for at least 8 hours for safety laboratory assessments (hematology and biochemistry [see [Section 7.4.3](#)]), and to be repeated if performed more than 7 days before the first dose of trial treatment.
- Urinalysis (to be repeated if performed more than 7 days before the first dose of trial treatment) (see [Section 7.4.3](#)).
- If calculated creatinine clearance is <60 mL/min, 24 hour creatinine clearance might be requested by the Investigator for confirmation (see [Sections 7.1 and 7.2.7](#)).
- Serum pregnancy test (if applicable) (see [Section 7.2.5](#)).
- HBV antigen and antibody test, HCV antibody test, and HIV test (see [Section 7.2.4](#)).
- Collect HPV, tobacco, and alcohol consumptions status (if the subjects has done HPV test before the screening, the HPV data should be collected. Tobacco and alcohol consumptions status should also be documented) (see [Section 7.1](#)).
- Echocardiogram (see [Section 7.2.6](#)).
- Tumor assessment (see [Section 7.3](#)).

### 7.1.2 Weekly Cetuximab Administration Visit

For subjects in Arm A, the following procedures and investigations will be performed at weekly intervals ( $\pm$  3 days) until the last dose of cetuximab:

- Physical examination (see [Section 7.4.4](#)).
- Check of vital signs.
- Documentation of AEs and concomitant medications.
- Administration of cetuximab (based on BSA).

### 7.1.3 Start of Each Cycle Visit (Day 1 of Each 21-Day Cycle)

For all subjects in Arm A and B, the following procedures and investigations will be performed on Day 1 of each 21-day chemotherapy cycle. A visit window of 3 days is acceptable.

- Randomization (for Cycle 1 only, see [Section 6.3](#)).
- Physical examination, check of vital signs, and assessment of ECOG performance status (see [Section 7.4.4](#)).
- ECG (see [Section 7.4.4.4](#)).
- Blood samples collected after fasting for at least 8 hours for safety laboratory assessments (within 3 days before start of next cycle) (see [Section 7.4.3](#)).
- Urinalysis (within 3 days before start of next cycle) (see [Section 7.4.3](#)).
- Documentation of AEs and concomitant medications.
- Administration of cetuximab (based on BSA) only for subjects in Arm A.
- Administration of cisplatin (cisplatin may be replaced by carboplatin in subsequent cycles if there are cisplatin-related nonhematologic toxicities) and 5-FU (based on BSA) for subjects in Arm A and B.

**Note:** ECG and laboratory safety results must be available at start of each cycle visit.

**Note:** If the subject is not able to visit the Investigator for this evaluation or misses the scheduled visits, the Investigator should attempt to contact the subject or the referring physician by appropriate means to determine the subject's well-being.

### 7.1.4 6-Weekly Evaluation Visit

For all subjects in Arm A and B, the following procedures and investigations will be performed at 6-week intervals starting from the first dose of trial treatment until the EOE. A visit window of 3 days is acceptable.

- The evaluations which are completed within 7 days at 6-weekly evaluation visit for physical examination/weight; vital sign; ECG; hematology; biochemistry, and urinalysis can be accepted, and these evaluations at 6-weekly evaluation visit will be optional.
- Assessment of ECOG performance status (see [Section 7.4.4](#)).
- Documentation of AEs and concomitant medications.
- Tumor assessment (see [Section 7.3](#)).

### 7.1.5 End of Efficacy Assessment Visit

Subjects are to attend the EOEА visit on the day of the last efficacy assessment. A visit window of 3 days is acceptable. The following procedure and investigations will be performed:

- Physical examination, check of vital signs, and assessment of ECOG performance status (see [Section 7.4.4](#)).
- ECG (see [Section 7.4.4.4](#))\*.
- Blood samples collected after fasting for at least 8 hours for safety laboratory assessments (see [Section 7.4.3](#))\*.
- Urinalysis (see [Section 7.4.3](#))\*.
- Documentation of AEs and concomitant medications.
- Tumor assessment (see [Section 7.3](#)).

\*If the EOEА Visit is after the safety follow-up visit, these tests are optional.

### 7.1.6 Safety Follow-Up Visit

Subjects are to attend the Safety Follow-up visit 30 days ( $\pm$  3 days) after the last dose of trial treatment or immediately before commencing the start of any new anticancer treatment (see [Section 6.5.3](#) for details). The planned procedures and investigations, except tumor assessment, are the same as the EOEА visit (see [Section 7.1.5](#)).

### 7.1.7 Survival Follow-Up

The following assessments will be performed every 3 months after the EOEА visit until death or termination of the trial, whichever comes first. This follow-up can take the form of a telephone contact to the subject or the subject's family, or their referring doctor.

- Survival status.
- Documentation of subsequent antitumor treatment after the end of trial treatment.
- Outcome and resolution date of skin reactions.
- Resolution of ongoing SAEs (see [Section 7.4.1.6](#)).

## 7.2 Demographic and Other Baseline Characteristics

### 7.2.1 Demographic Data

At screening, the following demographic data will be collected: date of birth, sex, and ethnic origin data.

### 7.2.2 Diagnosis of Tumor

At the screening visit, the following data will be recorded for the tumor:

- Date of initial diagnosis and date of recurrence and/or metastasis.
- Histology.
- Localization.
- Recurrence or metastasis.
- Classification at initial diagnosis, according to TNM staging system, version 7, 2009.

### 7.2.3 Medical History

The following medical history data will be documented:

- Relevant previous and concomitant disease(s), other than SCCHN.
- Previous treatment for SCCHN.

### 7.2.4 Viral Serology

The antigen and antibody test for HBV, antibody test for HCV, and HIV test will be performed if clinically indicated. Subjects with known and declared HIV infection, as well as subjects with an active HBV or HCV infection resulting in an impaired liver function or cirrhosis will be excluded from the trial. These subjects will be identified during screening by either elevation of serum transaminases (i.e., not meeting inclusion criteria 8 for enrollment) ([Section 5.3.1](#)) and/or by the presence of a combination of markers of liver fibrosis (e.g., clinical, laboratory abnormalities, serologic markers, radiologic). Chronic asymptomatic HBV/HCV carriers are permitted into the trial.

### 7.2.5 Pregnancy Testing and Contraception

All female subjects of childbearing potential must have a negative blood pregnancy test at screening, which should be done within 7 days before the initiation of the trial treatment. Pregnancy testing must be repeated regularly throughout the trial if required by local legislation. All subjects, male or female, must practice medically-accepted contraception throughout the trial

---

if the risk of conception exists. The Investigator will decide together with the subject on adequate methods of contraception.

### **7.2.6 Echocardiogram**

The left ventricular ejection fraction will be measured at screening by echocardiogram. Subjects with left ventricular ejection fraction less than 45% will be excluded from the trial.

### **7.2.7 Creatinine Clearance**

The creatinine clearance will be calculated by trial centers based on serum creatinine according to local practices. Subjects with creatinine clearance less than 60 mL/minute will be excluded from the trial (24-hour creatinine clearance might be requested by the Investigator for confirmation, if calculated creatinine clearance is <60 mL/min).

### **7.2.8 Other Baseline Assessments**

Other baseline assessments include physical examination, measurement of vital signs, assessment of ECOG performance status, ECG, CT or MRI of the brain (only if clinically indicated), neck, chest, and abdomen, safety laboratory assessments (hematology, clinical chemistry, electrolytes, urinalysis).

As these assessments are also performed at subsequent visits during the trial, refer to the relevant subsections of [Sections 7.3](#) and [7.4](#) below for details of any method to be used.

## **7.3 Efficacy Assessment**

### **7.3.1 Documentation of Tumor Assessments**

A CT or MRI with contrast enhancement is recommended for tumor assessment.

Imaging, including CT or MRI of the brain (only if clinically indicated), neck (base skull to clavicles), chest, and abdomen, must be performed at baseline in order to review potential metastasis ( $\leq 28$  days before trial treatment is acceptable). A bone scan and/or positron emission tomography (PET) scan should be considered for subjects who have possible bone metastasis at baseline or if bone metastasis is suspected during the trial; however, CT/MRI must be used for tumor assessment at baseline and at subsequent visits. The bone scan or PET cannot be used for measurement of target lesions.

At baseline, the organs with metastatic disease and the target and nontarget lesions should be documented. Evaluation of lesions should be performed at baseline and then every 6 weeks ( $\pm 3$  days), regardless of any delays in trial treatment, until PD, as assessed by the Investigator. Tumor assessments should be conducted at each tumor assessment time point including a complete assessment of all target and nontarget lesions (see [Table 1.1](#)).

---

In the case of skin lesions, clinical evaluation should be made with a caliper and photos must be taken and made available.

All measurements should be recorded in metric notation.

Apart from trial center radiological reading to determine tumor responses, all images will also be assessed by an IRC. The IRC review will not interfere with the Investigator's judgment on tumor assessments.

Confirmation of progression needs to be based on radiological measurements. Clinical symptoms/signs suggestive of progression need radiological confirmation of PD. Subjects with a global deterioration of health status requiring discontinuation of treatment without radiological evidence of PD should be classified as "symptomatic deterioration". Any effort should be made to document the objective progression even after discontinuation of treatment (i.e., the subject needs to return for a final tumor assessment).

### 7.3.2 Criteria for Tumor Response Evaluation

Tumor response evaluation will be performed according to RECIST version 1.1 (see [Appendix I](#)) by using CT or MRI and other modalities at a 6-week interval starting from the first dose of trial treatment. In the case of symptoms suggesting progression, subjects should be evaluated by imaging thereafter for documentation and confirmation of the tumor responses.

Evaluation of lesions should be based on images obtained by either CT or MRI. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the trial. If a chest X-ray indicates metastatic disease while the subject is enrolled in this trial, a CT of the chest is required for confirmation. All assessments should be provided by the same physician or radiologist if possible during the trial.

Evaluation criteria for possible combination of tumor responses (e.g., target lesion, nontarget lesion, new lesion, and overall response) are provided in [Appendix I](#).

### 7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see [Section 7.4.1.2](#)). The reporting period of AEs is described in [Section 7.4.1.3](#).

## 7.4.1 Adverse Events

### 7.4.1.1 Adverse Event Definitions

#### Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE. Investigators will reference the National Cancer Institute - CTCAE, version 4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild.
- Grade 2 or Moderate.
- Grade 3 or Severe.
- Grade 4 or Life-threatening.
- Grade 5 or Death.

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

---

Investigators must also systematically assess the causal relationship of AEs to the IMP/trial treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP/trial treatments include, but may not be limited to, temporal relationship between the AE and the IMP/trial treatments, known side effects of IMP/trial treatments, medical history, concomitant medication, course of the underlying disease, trial procedures.

**Unrelated:** Not reasonably related to the IMP/trial treatments. The AE could not medically (pharmacologically/clinically) be attributed to the IMP/trial treatments under study in this clinical trial protocol. A reasonable alternative explanation must be available.

**Related:** Reasonably related to the IMP/trial treatments. The AE could medically (pharmacologically/clinically) be attributed to the IMP/trial treatments under study in this clinical trial protocol.

### **Abnormal Laboratory Findings and Other Abnormal Investigational Findings**

Abnormal laboratory findings (Grade 1-3) and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

For abnormal laboratory findings, which are recorded as AE, follow up measures should be performed.

### **Serious Adverse Event**

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (Note: The term “life-threatening” refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.)

Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE and described in [Section 7.4.1.4](#).

#### **Events that Do Not Meet the Definition of an SAE**

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related hydration treatment application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

#### **Events Not to Be Considered as AEs/SAEs**

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

In this trial, PD is the only medically anticipated clinical event which is considered as a clinical efficacy outcome rather than an AE. No other medically anticipated events are defined in this trial as efficacy outcomes.

However, if adverse signs or symptoms occur in association with PD then these should be recorded as AEs.

#### **AE/SAEs Observed in Association with Disease Progression**

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms should not be reported as AEs.

However, if adverse signs and symptoms occur in association with disease (tumor) progression, such as dyspnea, tumor pain, bleeding etc., then these should be recorded as AEs or reported as SAEs, if they meet criteria for seriousness.

### **7.4.1.2 Methods of Recording and Assessing Adverse Events**

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF.

---

All SAEs must be additionally documented and reported using the appropriate Report Form as described in [Section 7.4.1.4](#).

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose reduction or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

### **7.4.1.3 Definition of the Adverse Event Reporting Period**

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues until the Safety Follow-up visit.

Any SAE assessed as related to cetuximab must be reported whenever it occurs, irrespective of the time elapsed since the last administration of cetuximab.

### **7.4.1.4 Procedure for Reporting Serious Adverse Events**

#### **Serious Adverse Events**

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

For each SAE, all relevant medical information should be documented on the SAE report form.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the trial-specific SAE Report Form.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant medications). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the

---

Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

#### **7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators**

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable center-specific requirements related to the reporting of SAEs (particular deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor will inform the Investigator of “findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC’s/IRB’s approval/favorable opinion to continue the trial”. In particular, and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The Investigator should place copies of Safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or center-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

#### **7.4.1.6 Monitoring of Subjects with Adverse Events**

Any AEs are recorded and assessed continuously throughout the trial (see [Section 7.4.1.3](#)) and are assessed for final outcome at the Safety Follow-up visit. All SAEs ongoing at the Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”. Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

---

## 7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in [Section 7.4.1.3](#) must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner (within a maximum of 24 HOURS after becoming aware of the event) of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in [Section 7.4.1.4](#).

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in [Section 7.4.1.4](#), while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

## 7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for hematology, biochemistry, electrolytes, and urinalysis following the timing noted in the Schedule of Assessments ([Table 1.1](#)) and will include the following mentioned below in [Table 7.1](#). The results of all safety laboratory parameters must be available within 3 days before start of next chemotherapy cycle.

**Table 7.1 Standard Safety Laboratory Parameters**

Category	Parameters
Hematology	hemoglobin, red blood cell count, white blood cell count and differential count, platelet count
Biochemistry	creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, total bilirubin (including direct bilirubin if total bilirubin abnormal), total protein, albumin, alkaline phosphatase, glucose, blood urea, uric acid
Electrolytes	sodium, potassium, chloride, calcium, magnesium,
Urinalysis*	pH value, specific gravity, protein, glucose, red blood cell, white blood cell

\* Urinalysis dipstick will be followed by microscopic examination if results are abnormal.

All samples should be clearly identified. Blood samples will be collected after fasting for at least 8 hours. All laboratory assessments will be performed at local laboratories and will comply with local requirements. Analysis of additional laboratory parameters is at the discretion of the Investigator. Viral serology tests will be performed if clinically indicated (see [Section 7.2.4](#)).

At the screening visit, female subjects of childbearing potential including those who have had tubal ligation must additionally have a blood pregnancy test performed within 7 days before the first dose of trial treatment. Pregnancy testing must be repeated regularly throughout the trial if required by local legislation.

All laboratory test results obtained (including any potential repeat tests) must be documented in the eCRF.

Any laboratory result leading to an interruption or dose reduction of trial treatments will be considered as an untoward medical occurrence and therefore has to be documented as an AE (see [Section 7.4.1.1](#)).

The Sponsor should receive a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial should be forwarded to the Sponsor/designee.

#### **7.4.4 Vital Signs, Physical Examinations, and Other Assessments**

##### **7.4.4.1 Vital Signs**

Vital signs will be assessed at the time points outlined in [Table 1.1](#) and must include axillary temperature, heart rate and blood pressure (measured in a supine position after 5 minutes at rest), and respiratory rate. For those in Arm A, vital signs must be continuously monitored before, during, and up to 1 hour after each cetuximab infusion.

##### **7.4.4.2 Physical Examination**

Physical examination will be performed at the time points outlined in [Table 1.1](#) and must include the following: height (screening only), weight, general appearance, skin, head, neck, ears, eyes, nose, mouth, throat, respiratory/pulmonary, cardiovascular, gastrointestinal/abdominal, genito-urinary, neurological, musculoskeletal/extremities, and lymphatic systems, and any other that may be relevant.

For physical examinations after the screening visit, only new findings compared to the previous one have to be documented in the eCRF.

##### **7.4.4.3 Eastern Cooperative Oncology Group Performance Status**

The ECOG performance status of each subject will be reviewed at the time points outlined in [Table 1.1](#) and will be graded according to the following:

---

Grade 0	Fully active, able to carry on all pre-disease performance without restriction.
Grade 1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Grade 2	Ambulatory and capable of all self-care, but unable to carry out any work activities up and about more than 50% of waking hours.
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Grade 4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair.
Grade 5	Dead.

#### **7.4.4.4 Electrocardiogram**

A computerized 12-lead ECG must be obtained at the time points outlined in [Table 1.1](#) and as clinically indicated. An ECG should be performed after the subject has rested for 5 minutes. Each lead shall be recorded for at least 3 beats at a speed of 25 mm/second.

The following parameters will be recorded: rhythm, ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval.

At screening, the Investigator must assess the ECG for signs of cardiac disease that could exclude the subject from the trial. An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented in the eCRF. The ECG results must be available at start of each cycle visit.

#### **7.5 Pharmacokinetics**

Not applicable.

#### **7.6 Biomarkers/Pharmacogenetics**

Not applicable.

#### **7.7 Other Assessments**

Not applicable.

## 8 Statistics

### 8.1 Sample Size



### 8.2 Randomization

Subjects will be randomized to one of the 2 treatment arms, cetuximab plus chemotherapy versus chemotherapy alone, at a 2:1 ratio stratified by the following:

- ECOG performance status: 0 versus 1.
- Primary tumor site: oral cavity versus hypopharynx versus others.

A central stratified permuted block randomization procedure will be employed via IWRS to balance prognostic factors between treatment arms (see [Section 6.3](#)).

## 8.3 Endpoints

### 8.3.1 Primary Endpoint

The primary endpoint of this trial is PFS time, as assessed by an IRC. The primary endpoint is defined as the duration (in months) from the date of randomization until first observation of PD (based on imaging as assessed by IRC), or death due to any cause when death occurs within 60 days after the last tumor assessment or randomization (whichever is later). Any subject with neither assessment of tumor progression, nor death date within 60 days after last tumor assessment and randomization will be censored on the date of last tumor assessment or randomization. A subject who has not received trial treatment and for whom no date of progression or death is known will be censored on the date of randomization (Day 1) or date of last tumor assessment, whichever comes later.

### 8.3.2 Secondary Endpoints

The secondary endpoints include PFS time, as assessed by the Investigator, OS time, BOR, DCR, and duration of response.

- PFS time, as assessed by the Investigator, is defined as the duration (in months) from the date of randomization until first observation of radiologically confirmed PD (by the Investigator), or death due to any cause when death occurs within 60 days after the last tumor assessment or randomization (whichever is later). The same censoring rule as with the PFS time assessed by IRC is applied.
- OS time is defined as the time (in months) from the date of randomization to the date of death. If a subject is alive at the time of analysis, survival time will be censored at the last date when the subject is known to be alive.
- The BOR will be based on imaging and classified according to RECIST version 1.1 criteria. The BOR rate is defined as the number of subjects, whose BOR was either complete response (CR) or PR, relative to the number of subjects belonging to the trial set of interest.
- The DCR will be based on imaging and classified according to RECIST version 1.1 criteria. The DCR defined as the number of subjects whose BOR is either CR, PR or SD, divided by the number of subjects belonging to the trial set of interest.
- Duration of response will be determined for subjects whose BOR was either CR or PR. It is defined as the time from the first assessment of CR or PR until the event defining PFS time.

### 8.3.3 Safety Endpoints

The safety and toxicity of the treatment will be evaluated in terms of the following safety variables:

- Exposure to cetuximab, cisplatin or carboplatin, and 5-FU in terms of duration of therapy, cumulative dose, dose intensity and relative dose intensity, number of dose reductions, dose delays, and drug discontinuation.

- Incidence and type of AEs in terms of:
  - All treatment-emergent adverse events (TEAEs)
  - Related TEAEs
  - Treatment emergent SAEs
  - Related treatment emergent SAEs
  - CTCAE (version 4.03) Grade 3 and 4 TEAEs
  - Related CTCAE (version 4.03) Grade 3 and 4 TEAEs
  - TEAEs leading to withdrawal, dose modification, or drug discontinuation will be summarized by treatment arm.
- Incidence and reasons for deaths for each treatment arm.
- Safety laboratory tests graded by CTCAE (version 4.03) where applicable.
- Vital signs, physical examinations and ECOG performance status.

## 8.4 Analysis Sets

**All screened subjects:** The population of all screened subjects will include all subjects who signed the ICF.

**Safety population** (all treated subjects): All subjects who received at least 1 dose of any trial treatment (cetuximab, cisplatin, or 5-FU). Subjects will be allocated as treated.

**Intent to Treat (ITT) population** (full analysis set - all randomized subjects): All subjects who were randomized to trial treatment. Subjects will be allocated as randomized.

**Per protocol (PP) population:** All ITT subjects who do not have a clinically important protocol deviation. Further details on PP population will be specified in the Statistical Analysis Plan.

The following subgroups are considered of interest to comparatively explore the treatment effect for the definition of subgroups, data as documented in the eCRF will be taken.

- Age: <65 years versus  $\geq$  65 years.
- Sex: Male versus Female.
- Baseline ECOG performance status: 0 versus 1.
- Primary tumor site: oral cavity versus oropharynx versus hypopharynx versus larynx versus others.
- Time from initial SCCHN diagnosis: < median versus  $\geq$  median.
- Histology: well/moderately versus poorly differentiated.

- Extent of disease at trial entry: nonmetastatic recurrent versus nonrecurrent metastatic versus metastatic including recurrent.
- Prior antitumor therapy:
  - Any: yes versus no
  - Prior neoadjuvant/induction: yes versus no
  - Prior radiotherapy: yes versus no
  - Prior radiochemotherapy: yes versus no
  - Prior surgery: yes versus no
  - Prior platinum-containing treatment for SCCHN: yes versus no.

## 8.5 Description of Statistical Analyses

### 8.5.1 General Considerations

The ITT population will be primarily used in the analysis of baseline characteristics and efficacy. Selected efficacy analyses will be repeated for the PP population and for subgroups.

The Safety population will be considered for safety analyses.

This is a bridging trial. The hypothesis test will not be done and P-values will not be provided, unless otherwise specified. If CIs are to be calculated, these will be 2-sided with a confidence probability of 95%, unless otherwise specified.

Continuous variables will be summarized using descriptive statistics, i.e., number of subjects (N), mean, median, standard deviation, 25th and 75th percentiles (Q1, Q3), minimum and maximum.

Qualitative variables will be summarized by means of counts and percentages. Unless otherwise stated the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

#### Baseline

In general, the last measurement before or on the day of the first dose of trial treatment will serve as the baseline measurement. If such a value is missing, the last measurement before the first dose of trial treatment will be used as the baseline measurement.

### Handling of Dropouts and Missing Data

Unless otherwise specified, missing data will not be replaced. Incomplete AE-related dates will be handled as follows:

- In case the onset date is completely missing or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of trial treatment, then the onset date will be replaced by the minimum of start of trial treatment and AE resolution date.
- In all other cases the missing onset day or onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date. In all other cases, the incomplete stop date will not be imputed.

### Multicenter trial

- In order to provide overall estimates of the treatment effect data will be pooled across centers. The factor center will not be considered in statistical models or for subgroup analyses.

## 8.5.2 Analysis of Primary Endpoint

The primary endpoint of this trial is PFS time as assessed by IRC.

The PFS time by IRC is defined as the duration (in months) from the date of randomization until first observation of PD (based on imaging as assessed by IRC), or death due to any cause when death occurs within 60 days after the last tumor assessment or randomization (whichever is later). Any subject with neither assessment of tumor progression, nor death date within 60 days after last tumor assessment and randomization will be censored on the date of last tumor assessment or randomization. A subject who has not received trial treatment and for whom no date of progression or death is known will be censored on the date of randomization (Day 1) or date of last tumor assessment, whichever comes later.

The analysis will be performed on the basis of the ITT principle on the ITT population.

The treatment effect expressed as hazard ratio of cetuximab plus chemotherapy to chemotherapy alone including 95% CI on PFS time will be primarily evaluated using a stratified Cox proportional hazard model, including treatment and the randomization strata (as specified in the IWRS), ECOG performance status (0 versus 1) and primary tumor site (oral cavity versus hypopharynx versus others).

This is a bridging trial; in discussion with Chinese Health Authority, this trial would be regarded as positive if the point estimation of the stratified hazard ratio is less than or equal to 0.77 (retaining at least 50% of the estimated treatment effect of EXTREME trial, see [Section 8.1](#)).

The PFS time of the 2 treatment arms will be described by means of Kaplan-Meier survival curves (product-limit estimates) and associated summary statistics (e.g., median PFS time, 95% CI, survival estimates at certain time points, and number of subjects under risk).

### **Secondary Analyses of Primary Variable**

All secondary analyses of the primary variable will be performed to support the robustness of the primary confirmatory analysis and regarded as exploratory. Such analyses will comprise:

- Sensitivity Analyses.

Sensitivity analysis will be employed to explore the robustness of the primary confirmatory analyses to assess the impact of analysis populations, the validity of model assumptions by

- Executing per-protocol analysis. If PP population includes more than 90% of the ITT population, additional efficacy analyses on the PP population will be omitted.
- Subgroup analyses to investigate the effect in subgroups (see subgroup as given in [Section 8.4](#)).

Subgroup analyses will comprise univariable unstratified analysis considering the subgroups as defined in [Section 8.4](#). To assess the heterogeneity of treatment effects across the subgroups levels Cox proportional hazards model will be performed for PFS time as dependent variable and with subgroup type, the treatment arm assignment and with and without the treatment by subgroup type interaction as explanatory variables. P-values for the interaction test will be provided together with the hazard ratios and 95% CIs.

- Exploratory analyses to investigate the treatment effect when adjusted for explanatory variables of potential prognostic values.

Multivariable Cox regression analysis will be used to assess and adjust the treatment effect for potential baseline prognostic factors (see subgroup as given in [Section 8.4](#)). A stepwise selection procedure will serve to identify explanatory variables of potential prognostic values additional to the randomization strata (as documented in the eCRF) which will be included in all models during the selection procedure. The potential baseline prognostic factors variables used for this analysis will be specified before database lock.

### **8.5.3 Analysis of Secondary Endpoints**

The secondary efficacy analyses considered below are used as supporting evidence to underline the clinical benefit of cetuximab plus chemotherapy versus chemotherapy only. The analyses will be exploratory, and no adjustment for multiple comparisons will be made.

For the analysis of time-to-event variables (e.g., OS time, PFS time by Investigator), will follow standard methodology by employing Kaplan-Meier estimates (product-limit estimates), Cox's

proportional hazard model to estimate stratified hazard ratios and corresponding CI, subgroup analyses will be performed for predefined baseline factors (see subgroup as given in [Section 8.4](#)).

Duration of response will be presented descriptively.

For the analysis of dichotomous variables (e.g., BOR rate, DCR), counts and percentages will be summarized.

#### **8.5.4 Analysis of Safety**

Safety analyses will be performed according to the as-treated principle. Any TEAEs will be summarized, i.e., those events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state and with onset dates occurring within the first dosing day of trial treatment until 30 days after the last dose of trial treatment. No formal statistical comparisons are planned.

The extent of exposure for cetuximab, cisplatin or carboplatin, and 5-FU will be characterized by duration (weeks), cumulative dose, dose intensity, relative dose intensity (actual dose given/planned dose), number of dose reductions, and number of dose delays.

AEs will be coded according to the current Medical Dictionary for Regulatory Affairs (MedDRA). The severity of AEs will be graded using CTCAE toxicity grades. The incidence and type of AEs, SAEs, trial treatment-related AEs and SAEs, trial treatment-related AEs by CTCAE toxicity grade, CTCAE Grade 3 and 4 AEs, trial treatment-related CTCAE Grade 3 and 4 AEs, AEs leading to death, AEs leading to discontinuation of trial treatment, will be summarized in total and for each treatment arm according to the MedDRA system organ class and MedDRA preferred terms. Missing classifications concerning trial treatment relationship will be considered as related to the trial treatment.

All deaths, deaths within 60 days after date of first dose of trial treatment and deaths within 30 days after last dose of trial treatment as well as reasons for deaths will be tabulated.

Laboratory results will be classified according to the CTCAE (version 4.03) when applicable. The worst on trial grade after date of first dose of trial treatment will be summarized. Shifts in toxicity grading from treatment start to highest grade will be displayed. Results for variables that were not part of the CTCAE (version 4.03) will be presented as below, within, and above the normal limits of the local laboratory. Only subjects with post-baseline laboratory values will be included in these analyses. The last measurement before trial treatment will serve as the baseline measurement.

Vital signs (temperature, heart rate, blood pressure, respiratory rate) will be descriptively presented.

The baseline results of the physical examination will be presented. Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination during and after treatment will therefore not be provided.

---

Further details on safety analyses will be specified in the Statistical Analysis Plan.

## 8.6 Interim and Additional Planned Analyses

No interim analyses on efficacy will be conducted.

An IDMC will be established for this trial. The IDMC will be a group of independent experts consisting of clinicians with expertise in the relevant clinical specialties and at least one statistician. The IDMC will periodically review safety data and data quality for analysis during the trial. Descriptive interim safety and data quality analyses are scheduled but no formal statistical comparisons are planned. After each review, the IDMC will provide a recommendation to the Sponsor of how to proceed with the trial. Further details regarding the review process will be compiled in a trial-specific IDMC charter.

The main analysis will be based on all data recorded until the clinical cut-off date for PFS, e.g., defined at the date when the trial collects more than 144 events. The final analysis of OS at the OS cut-off date, will be presented in a report addendum. Safety data collected after the OS cut-off will be reported through patient profile. No additional statistical analyses will be conducted.

The OS cut-off will occur when the following conditions are met:

- Follow-up after the randomization of the last subject is at least 12 months, OR
- At least 180 deaths have been reported in this trial.

## 9 Ethical and Regulatory Aspects

### 9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the center and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

### 9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the

information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's center, and must be safely archived 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 ICF should be provided to the subject before participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IEC/IRB for review and opinion. Using the approved revised subject information sheet and other written information, The Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

### **9.3 Subject Identification and Privacy**

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the center. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

### **9.4 Emergency Medical Support and Subject Card**

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor/designee for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers

access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor/designee provides the appropriate means to contact a Sponsor physician/designee. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician/designee to assist with the medical emergency and to provide support for the events of the subject concerned.

## **9.5 Clinical Trial Insurance and Compensation to Subjects**

Insurance coverage shall be provided for the country participating to the trial. Insurance conditions shall meet good local practices, as applicable.

## **9.6 Independent Ethics Committee or Institutional Review Board**

Before commencement of the trial at a given trial center, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at Sponsor or designated organization.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see [Section 10.5](#)). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

## **9.7 Health Authorities**

The clinical trial protocol and any applicable documentation (for example, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each center.

---

## 10 Trial Management

### 10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely fashion. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. Portable Document Format files of the eCRFs will be provided to the Investigators at the completion of the trial.

### 10.2 Source Data and Subject Files

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight.
- Medical history and concomitant diseases.
- Prior and concomitant medications (including changes during the trial).
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number.
- Dates for entry into the trial (informed consent) and visits to the center.
- Any medical examinations and clinical findings predefined in this clinical trial protocol.
- All AEs.

- Date that the subject left the trial including any reason for early withdrawal from the trial or trial treatment (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the center.

### **10.3 Investigator Site File and Archiving**

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the center, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the center (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

### **10.4 Monitoring, Quality Assurance and Inspection by Health Authorities**

This trial will be monitored in accordance with the ICH GCP and any other applicable regulations. The center Monitor will perform visits to the trial center at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the center, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

## 10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the center. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires the subject's informed consent before implementation following the process as described in [Section 9.2](#).

## 10.6 Clinical Trial Report and Publication Policy

### 10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor/designee in consultation with the Coordinating Investigators following the guidance in ICH Topic E3.

### 10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial centers. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the center. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on [clinicaltrials.gov](http://clinicaltrials.gov) is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

## 11 References Cited in the Text

1. Mendelsohn J, Kawamoto T, Sato G, et al. Hybrid cell lines that produce monoclonal antibodies to epidermal growth factor receptor. United States Patent No 4,943,533. July 24, 1990
2. Goldstein NI, Prewett M, Zuklys K, et al. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. *Clin Cancer Res.* 1995;1:1311-8
3. Merck. Preclinical Report AB 01.2004. Binding competition between C225 and different epidermal growth factor ligands. November 26, 2003
4. Li S, Schmitz KR, Jeffrey PD, et al. Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. *Cancer Cell.* 2005;7:301-11
5. Waksal HW. Role of an anti-epidermal growth factor receptor in treating cancer. *Cancer Metastasis Rev.* 1999;18:427-36
6. Hadari YR, Doody JF, Wang Y, et al. The IgG1 monoclonal antibody cetuximab induces degradation of the epidermal growth factor receptor. *ASCO GI meeting 2004;Abstract 234*
7. Zhang W, Gordon M, Schultheis AM, et al. Two immunoglobulin G fragment C receptor polymorphisms associated with clinical outcome of EGFR-expressing metastatic colorectal cancer subjects treated with single agent cetuximab. *J Clin Oncol.* 2006;24(18S):Abstract 3028
8. Kimura H, Kazuko S, Arao T, et al. Antibody-dependent cellular cytotoxicity of cetuximab against tumor cells with wild- and mutant-EGFR. *Proc Amer Assoc Cancer Res.* 2006;47:Abstract 636
9. Yarden Y, Ullrich A. Growth factor receptor tyrosine kinases. *Ann Rev Biochem.* 1988;57:443-78
10. Harari PM, Allen GW, Bonner JA. Biology of interactions: Antiepidermal growth factor receptor agents. *J Clin Oncol.* 2007;25:4057-65
11. Chung CH, Ely K, McGavran L, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J Clin Oncol.* 2006;24:4170-6
12. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351:337-45

13. Salomon DS, Brandt R, Ciardiello F, et al. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol*. 1995;19:183-232
14. De Jong KP, Stellema R, Karrenbeld A, et al. Clinical relevance of transforming growth factor alpha, epidermal growth factor receptor, p53, and Ki67 in colorectal liver metastases and corresponding primary tumors. *Hepatology*. 1998;28:971-9
15. Grandis JR, Melhem MF, Barnes EL, et al. Quantitative immunohistochemical analysis of transforming growth factor-alpha and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer*. 1996;78(6):1284-92
16. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res*. 2002;62(24):7350-6
17. Hitt R, Castellano D, Ciruelos E, et al. Overexpression of epidermal growth factor receptor (EGFR) and p53 mutations levels as prognostic factors in patients with locally advanced head and neck cancer (LAHNC) treated with induction chemotherapy. *Proc Am Soc Clin Oncol*. 2002;22:Abstract 972
18. Magne N, Pivot X, Bensadoun RJ, et al. The relationship of epidermal growth factor receptor levels to the prognosis of unresectable pharyngeal cancer patients treated by chemo-radiotherapy. *Eur J Cancer*. 2001;37(17):2169-77
19. Liang K, Ang KK, Milas L, et al. The epidermal growth factor receptor mediates radioresistance. *Int J Radiat Oncol Biol Phys*. 2003;57(1):246-54
20. Rubin Grandis J, Melhem MF, Gooding WE, et al. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. *J Natl Cancer Inst*. 1998;90(11):824-32
21. Maurizi M, Almadori G, Ferrandina G, et al. Prognostic significance of epidermal growth factor receptor in laryngeal squamous cell carcinoma. *Br J Cancer*. 1996;74(8):1253-7
22. Huang SM, Harari PM. Epidermal growth factor receptor inhibition in cancer therapy: biology, rationale and preliminary clinical results. *Invest New Drugs*. 1999;17(3):259-69
23. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. *Endocr Relat Cancer*. 2004;11(4):689-708
24. Fan Z, Shang BY, Lu Y, et al. Reciprocal changes in p27 (Kip1) and p21 (Cip 1) in growth inhibition mediated by blockade or overstimulation of epidermal growth factor receptors. *Clin Cancer Res*. 1997;3:1943-8

25. Chou JL, Fan Z, DeBlasio T, et al. Constitutive overexpression of cyclin D1 in human breast epithelial cells does not prevent G1 arrest induced by deprivation of epidermal growth factor. *Breast Cancer Res Treat.* 1999;55:267-83
26. Wu X, Fan Z, Masui H, et al. Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. *J Clin. Invest.* 1995;95:1897-905
27. Kies MS, Arquette MA, Nabell L, et al. Final report of the efficacy and safety of the EGFR antibody Erbitux (IMC-C225) in combination with cisplatin in patients with recurrent squamous cell carcinoma of the head and neck refractory to cisplatin containing chemotherapy. *Proc Am Soc Clin Oncol.* 2002;Abstract 925
28. Baselga J, Trigo JM, Bourhis J, et al. Cetuximab (C225) plus cisplatin/carboplatin is active in patients with recurrent/metastatic squamous cell carcinoma of the head and neck progressing on a same dose and schedule platinum-based regimen. *Proc Am Soc Clin Oncol.* 2002;Abstract 900
29. Trigo JM, Hitt R, Koralewski P, et al. Cetuximab monotherapy is active in patients with platinum-refractory recurrent/metastatic squamous cell carcinoma of the head and neck. Abstract submitted to ASCO 2004
30. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008;359:1116-27
31. Burtneess B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: An Eastern Cooperative Oncology Group study. *J Clin Oncol.* 2005;23:8646-54
32. Bourhis J, Rivera F, Mesia R, et al. Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2006;24:2866-72
33. Misiukiewicz K, Winder L, Parides M, et al. Progression-free survival (PFS) as a measure of efficacy for anti-EGFR antibodies in recurrent/metastatic (R/M) squamous cell carcinoma of head and neck (SCCHN). *Journal of Clinical Oncology, 2013 ASCO Annual Meeting Abstracts.* Vol 31, No 15\_suppl (May 20 Supplement), 2013: 6078
34. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer.* 2011;19(8):1079-95
35. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a

pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28(8):1351-7

## 12 Appendices

### Appendix I Response Evaluation Criteria in Solid Tumors Version 1.1

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228-247.

#### Definitions

Response and progression will be evaluated in this trial using the international criteria proposed by the RECIST Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

#### Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

*Malignant lymph nodes:* To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

#### Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter  $\geq 10$  to  $< 15$  mm with conventional techniques or  $< 10$  mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

*Bone lesions:*

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

*Cystic lesions:*

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

*Lesions with prior local treatment:*

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm  $\times$  30 mm has a short axis of 20 mm and qualifies

---

as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis  $\geq 10$  mm but  $< 15$  mm) should be considered non-target lesions. Nodes that have a short axis  $< 10$  mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

### Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

## **GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

**Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

**Chest X-ray:** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

**CT, MRI:** CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on

---

the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article cited above, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

**Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the trial, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

**Endoscopy, laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

**Tumor markers:** Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

**Cytology, histology:** These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse event (AE) of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease (PD).

## RESPONSE CRITERIA

### Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

---

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). 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 1 or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

*Lymph nodes.* Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on trial. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Electronic case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

*Target lesions that become ‘too small to measure’.* While on trial, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

*Lesions that split or coalesce on treatment.* When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

### Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

*When the subject also has measurable disease.* In this setting, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

*When the subject has only non-measurable disease.* This circumstance arises in some phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

### New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought

---

to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the subject who has visceral disease at baseline and while on trial has a brain CT or MRI ordered which reveals metastases. The subject’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fludeoxyglucose positron emission tomography (FDG-PET) response assessments need additional trial, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

#### Evaluation of Best Overall Response

The best OR is the best response recorded from the start of the trial treatment until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of best OR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject’s best OR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the ‘best OR’.

The best OR is determined once all the data for the subject is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best OR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject’s best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	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
	Non-PD		
Not all evaluated		No	Not Evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; PD = progressive disease; and SD = stable disease.  
See text for more details.

**Note:**

When nodal disease is included in the sum of target lesions and the nodes decrease to ‘normal’ size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of ‘zero’ on the CRF.

In trials where confirmation of response is required, repeated ‘NE’ time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials, it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression even after discontinuation of treatment.

Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping trial therapy.

Conditions that define ‘early progression, early death and inevaluability’ are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. The use of FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

## **CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE**

### Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the trial protocol.

### Duration of Overall Response

The duration of OR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on trial).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

#### Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on trial (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of subjects achieving SD for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

## Appendix II Signature Pages and Responsible Persons for the Trial

### Signature Page – Protocol Lead

**Trial Title:** A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck

**Clinical Trial Protocol Date/Version:** 26 February 2018 / Final 3.0

**Protocol Lead responsible for designing the clinical trial:**

I approve the design of the clinical trial.

---

Signature

Date of Signature

Name, academic degree:

PPD

Function / Title:

PPD

Institution:

PPD

Address:

PPD

Telephone number:

PPD

Fax number:

PPD

E-mail address:

PPD

### Signature Page – Coordinating Investigator

**Trial Title:** A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck

**Clinical Trial Protocol Date/Version:** 26 February 2018 / Final 3.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

---

Signature	Date of Signature
Name, academic degree	PPD [Redacted]
Function / Title	PPD [Redacted]
Institution	PPD [Redacted]
Address	PPD [Redacted]
Telephone number	PPD [Redacted]
E-mail address	PPD [Redacted]

### Signature Page – Coordinating Investigator

**Trial Title:** A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck

**Clinical Trial Protocol Date/Version:** 26 February 2018 / Final 3.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

---

Signature	Date of Signature
Name, academic degree	PPD [Redacted]
Function / Title	PPD [Redacted]
Institution	PPD [Redacted]
Address	PPD [Redacted]
Telephone number	PPD [Redacted]
Fax number	PPD [Redacted]
E-mail address	PPD [Redacted]

## Signature Page – Principal Investigator

**Trial Title:** A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck

**Clinical Trial Protocol Date/Version:** 26 February 2018 / Final 3.0

Center Number:

Principal Investigator

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

---

Signature

---

Date of Signature

Name, academic degree

Function / Title

Institution

Address

Telephone number

Fax number

E-mail address

**Sponsor Responsible Person not Named on the Cover Page**

Name, academic degree PPD [redacted]  
Function / Title PPD [redacted]  
Institution PPD [redacted]  
Address PPD [redacted]  
Telephone number PPD [redacted]  
Fax number PPD [redacted]  
E-mail address PPD [redacted]

Name, academic degree PPD [redacted]  
Function / Title PPD [redacted]  
Institution PPD [redacted]  
Address PPD [redacted]  
Telephone number PPD [redacted]  
Fax number PPD [redacted]  
E-mail address PPD [redacted]



Appendix III Protocol Amendment 1.0 and List of Changes

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI

[Redacted text block]



CCI

[REDACTED]						
[REDACTED]						
[REDACTED]						
[REDACTED]						
[REDACTED]						
[REDACTED]						
[REDACTED]						

CCI

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



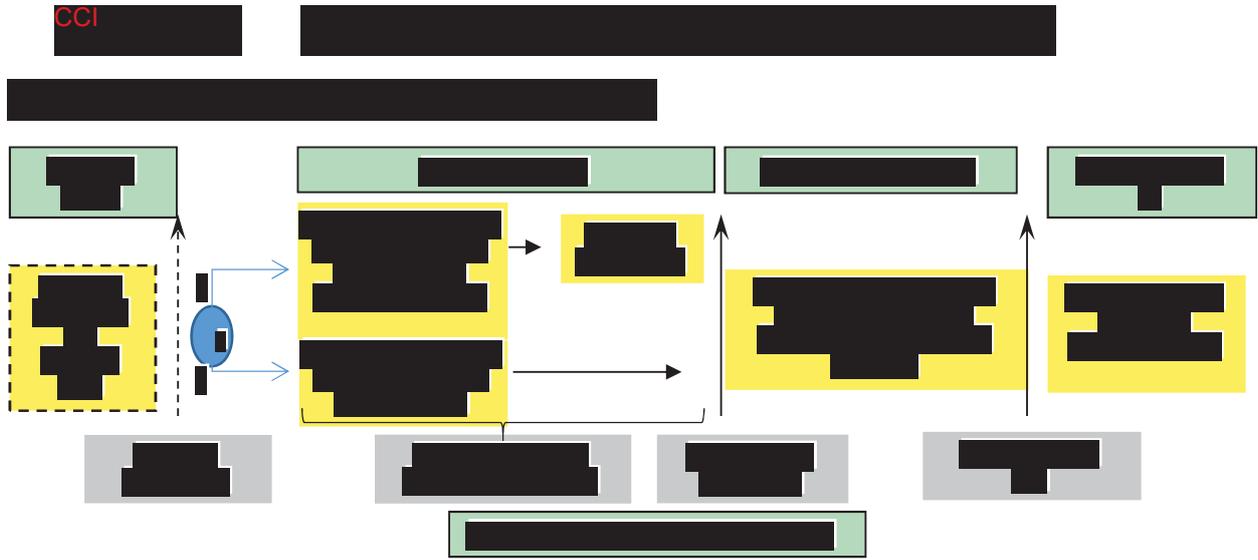
CCI

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]





[REDACTED]



CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]



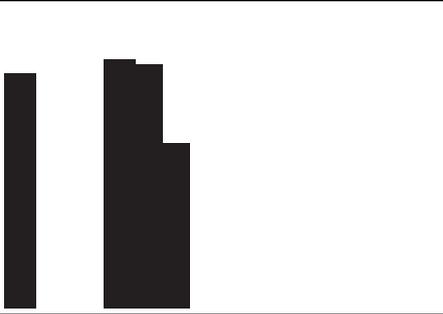
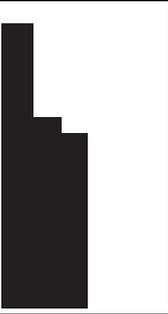
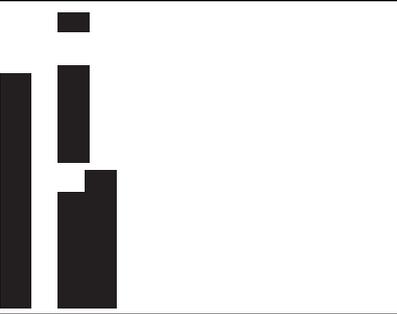
CCI

[Redacted]

[Redacted]

[Redacted]

<p>CCI</p>	<p>[Redacted]</p>													
------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------





[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
------------	------------	------------	------------	------------

[REDACTED]

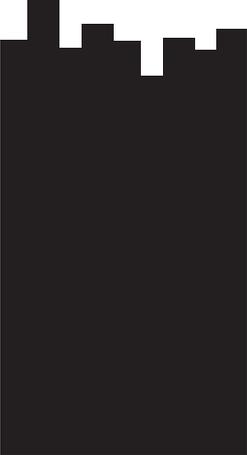




[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

CCI				



<p>CCI [Redacted]</p>			<p>[Redacted]</p>	<p>[Redacted]</p>
	<p>[Redacted]</p>	<p>[Redacted]</p>	<p>[Redacted]</p>	<p>[Redacted]</p>



<p>CCI [Redacted]</p>	<p>[Redacted]</p>								
-----------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------	-------------------

