Statistical Analysis Plan

Randomized, controlled, open label, multicenter, phase II study to evaluate the efficacy and safety of CetuGEX™ plus chemotherapy in comparison to cetuximab plus chemotherapy for the treatment of patients with stage III/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck

(The "RESGEX" Study)

SAP DATE: December 21, 2016

ClinicalTrials.gov Identifier: NCT02052960

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STATISTICAL ANALYSIS PLAN

Protocol Title:	Randomized, controlled, open label, multicenter, phase II study to evaluate the efficacy and safety of CetuGEX™ plus chemotherapy in comparison to cetuximab plus chemotherapy for the treatment of patients with stage III/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck
Protocol Number:	GEXMab52201 (Final Version 4.0 06-Feb-2015)
EudraCT Number:	2013-003695-13
IND Number:	118026
Compound:	CetuGEX™
Phase:	II
Sponsor:	Glycotope GmbH Robert-Rössle-Str. 10 D-13125 Berlin, Germany
SAP Author:	 Germany
SAP Version:	Final Version 1.0
SAP Date:	21-Dec-2016

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN DOCUMENT HISTORY

Version	Date	Author	Description
Final Version 1.0	21-Dec-2016		Original

SIGNATURE PAGE AND APPROVALS

Date

Date

Date

Date

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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
5-FU	5-fluorouracil
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC_{0-t}	Area under the concentration-time curve from zero up to a time t
$AUC0_{-\infty}$	Area under the concentration-time curve from zero up to ∞ w
$AUC_{\%extrap}$	Area under the concentration-time curve extrapolated in % of the total AUC
$AUC0_{-tau}$	Area under the concentration-time curve from zero up to the last concentration ≥ BLQ
BLQ	Below limit of quantification
AUC	Area under the curve
BMI	Body Mass Index
BO(R)	Best overall response (rates)
BSA	Body surface area
CB(R)	Clinical benefit (rate)
C_{avr}	Average serum concentration
CL	Clearance
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Oncology Research Trials Committee
EOS	End of study
FcγR	Fc-gamma receptor
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
HPV	Human Papilloma Virus
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
IRR	Infusion related reaction
irRC	Immune-related response criteria
ITT	Intention-to-treat
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCI	National Cancer Institute
NYHA	New York Heart Association
OR(R)	Objective response (rate)
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial response
PT	Preferred term
QLQ	Quality of life questionnaire
QoL	Quality of life
QTc	QT-interval for ECG corrected for heart rate
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAF	Safety population

SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
$t_{1/2}$	Terminal half-live
T_{max}	Time of maximum serum concentration
TTF	Time to treatment failure
UICC	Union for International Cancer Control
ULN	Upper limit of normal
V_z	Volume of distribution during terminal phase
V_{ss}	Apparent volume of distribution at equilibrium
WHO	World Health Organization

1. SYNOPSIS

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Glycotope protocol GEXMab52201 (Randomized, controlled, open label, multicenter, phase II study to evaluate the efficacy and safety of CetuGEX™ plus chemotherapy in comparison to cetuximab plus chemotherapy for the treatment of patients with stage III/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck), version 4.0 dated 06-Feb-2015.

This phase II study is being conducted to assess the efficacy, safety, tolerability, pharmacogenomics and pharmacokinetics of CetuGEX™.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH-E9) [1]. All work planned and reported in this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society, for statistical practice [3].

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol GEXMab52201 Final Version 4.0 dated 06-Feb-2015
- Electronic Case report forms (eCRFs) for Protocol GEXMab52201 Final Version 4.0, dated 14-May-2015
- ICH Guidance on Statistical Principles for Clinical Trials (E9)
- EORTC QLQ-C30 Scoring Manual and head and neck cancer module QLQ-H&N35 documentation

The reader of this SAP is encouraged to also read the clinical protocol and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to evaluate the efficacy of CetuGEX™ for the treatment of patients with stage III/IV recurrent and/or metastatic squamous cell carcinoma of the

head and neck (SCCHN) as compared to cetuximab (both in combination with platinum-based chemotherapy) in terms of progression-free survival (PFS).

2.1.2 Secondary Objectives

The secondary study objectives are:

- To evaluate further efficacy criteria, safety and quality of life (QoL) of patients with stage III/IV recurrent and/or metastatic SCCHN treated with CetuGEX™ as compared to cetuximab (both in combination with platinum-based chemotherapy)
- To assess pharmacokinetic (PK) parameters and profiles of CetuGEX™
- To assess efficacy and safety based on genetic markers for immune response (Fc-gamma receptor [FcγR] allotypes) and biomarkers

2.2 Efficacy and Safety Endpoints (Target Variables)

2.2.1 Efficacy Variables

Primary efficacy endpoint

The primary efficacy endpoint is PFS as assessed by the investigator.

PFS is defined as time from randomization until disease progression or death of any cause. Date of disease progression is defined as the date of imaging showing disease progression, as assessed by the investigator according to adapted immune-related RECIST 1.1 (modified irRC) [5]. The PFS time will be censored at the time of the last tumor assessment if the patient is alive and without progression at the last time of observation.

Secondary efficacy endpoints

If not otherwise specified, all response related secondary efficacy endpoints will derived according to the assessments of the investigator (modified irRC) as well as according to the independent centralized reading assessments (modified irRC and RECIST 1.1).

- PFS, as assessed by independent centralized reading
- Best overall response rates by response category (complete response [CR], partial response [PR], stable disease [SD] or progression [PD]) at the end of combination treatment
- Best overall response rates by response category (CR, PR, SD or PD) including maintenance therapy treatment
- Objective response rate (ORR; i.e., CR + PR) at the end of combination treatment
- Objective response rate (ORR; i.e., CR + PR) including maintenance therapy treatment
- Clinical benefit rate (CBR; i.e., CR + PR + SD) at the end of combination treatment

- Clinical benefit rate (CBR; i.e., CR + PR + SD) including maintenance therapy treatment
- Duration of response
- Overall survival (OS) defined as time from randomization until death of any cause
- Time to treatment failure (TTF)
- QoL as assessed by European Oncology Research Trials Committee (EORTC) QoL questionnaires (QLQ) EORTC-QLQ-C30 and EORTC-QLQ-H&N35
- Relationship of stratification factors, p16, epidermal growth factor receptor (EGFR) intensity and FcγRIIa allotypes to efficacy endpoints

2.2.2 Safety Variables

The safety endpoints are:

- Incidence of adverse events (AEs) and serious AEs (SAEs), including incidence of target/class-specific side effects (skin reactions, hypomagnesemia, neutropenia, gastrointestinal AEs, liver enzymes increases, conjunctivitis, mucositis)
- Infusion related reactions (IRRs)
- Physical assessments
- Laboratory assessments
- Vital signs
- Electrocardiogram (ECG)
- Relationship of FcγRIIa and FcγRIIIa-allotypes, occurrence of ADAs and PK parameters to safety endpoints

2.2.3 Pharmacokinetic Variables

Antibody trough levels and PK profiles of CetuGEX™ will be assessed throughout the study.

The PK samples for determining CetuGEX™ antibody concentrations will only be collected for the first-line treatment. No PK samples will be collected during the single-agent maintenance therapy, unless combination therapy has been prematurely terminated. There are 2 different groups of PK samples being collected during the first-line treatment.

For all patients randomized to CetuGEX™ treatment group for the first-line treatment, blood sampling for PK trough and maximum levels will be performed during Cycles 1, 2, 3 and 4. Blood samples will be collected before and at the end of each infusion on Day 1, 8, and 15 for Cycles 1, 2 and 3. On Cycle 4, blood samples will be collected before and at the end of each infusion but only on Day 1. Since the first dose of Cycle 1 will be split, there will also be blood samples collected before and at the end of the infusion on Day 0 (first infusion day of Cycle 1). Pre-infusion samples should be collected within 30 minutes prior to the start of the infusion. Post-infusion samples should be collected within 10 minutes following the end of the infusion and within 5 minutes would be ideal.

For a subset of patients, additional blood sampling will be collected on first infusion of Cycle 1 and Cycle 4 to gain a more fully PK profile for the first infusions from both of these cycles. The full profile of Cycles 1 and 4 PK blood samples will include pre- and post-infusion blood samples at 5 hour ± 5 min, 7 hours ± 15 min (Day 1), 24 ± 1 hour (Day 2), 48 ± 2 hours (Day 3), 72 ± 2 hours (Day 4), and 7 days (168 ± 2 hours; Day 8) after the start of the infusion on Day 1.

2.2.4 Exploratory Variables

Further exploratory variables include:

- Immunogenicity: incidence of anti-drug antibodies (ADAs)
- Immunological parameters: cytokine levels and immune cell counts
- FcγRIIa allotypes
- EGFR intensity and EGFR stained cancer cells

3. STUDY METHODS

3.1 Overall Study Design and Plan

This is a Phase 2, randomized, controlled, multicenter (approximately 40 sites in Europe and the USA) study with first line treatment (6 cycles of 5-FU and cisplatin in combination with CetuGEX™ vs. combination with cetuximab) followed by single-agent maintenance therapy (CetuGEX™ or cetuximab, respectively).

The study will include 3 separate study periods following screening:

Combination treatment phase

Eligible patients will be randomized to receive as first line treatment either CetuGEX™ or cetuximab in combination with 5-FU and cisplatin for the maximum duration of 6 cycles. In case of toxicity, the chemotherapy dose can be reduced, discontinued or, if later than the first cycle, switched to carboplatin. If discontinued earlier for any other reason apart from progression, patients will start the maintenance phase at that time.

As soon as at least 10 patients per treatment arm have completed the second cycle of combination therapy, patient safety data will be reviewed by an independent data safety monitoring board (DSMB).

Single-agent maintenance phase

After completion or discontinuation of combination chemotherapy for any other reason than progression, the treatment will be followed by maintenance therapy with CetuGEX™ alone or cetuximab alone, respectively. Single-agent maintenance therapy will be continued until progression of disease or limiting toxicity.

Follow-up

A Safety Visit must be performed 28 (+2) days after the last administration of the study drug for all randomized patients. In case of treatment discontinuation due to reasons other

than disease progression, patients will stay on the regular study schedule until disease progression is documented and will then attend a Final Examination Visit. In case of treatment discontinuation due to disease progression, the Safety Visit is identical to the Final Examination Visit.

After the Final Examination, patients will be followed-up by quarterly phone calls until death or for a maximum duration of 24 months after randomization of the last patient for assessment of overall survival.

3.2 Selection of Study Population

Patients aged at least 18 years at screening with stage III/IV recurrent and/or metastatic SCCHN will be enrolled. Inclusion and exclusion criteria are given in sections 8.2.1 and 8.2.2 of the protocol.

3.3 Method of Treatment Assignment and Randomization

Patients eligible for study participation will be randomized using a 1:1 ratio to either the CetuGEX™ or cetuximab arm. Randomization will be stratified by:

- FcγRIIIa status (FF or FV or VV)
- Oral cavity and oropharynx vs. other locations
- Locally recurrent vs. metastatic disease
- EGFR treatment naïve vs. EGFR treatment as part of multimodal therapy

A centralized randomization procedure, the interactive web response system (IWRS), will be used to assign a unique randomization number to each patient.

3.4 Treatment Masking (Blinding)

Blinding at the level of study treatment does not apply since the study is open label.

4. ANALYSES AND REPORTING

4.1 Interim Analyses

No formal interim analysis will be performed. An independent DSMB will periodically review the relevant safety data and provide advice on the continuation, modification or termination of the study. The DSMB will be comprised of 3 members, 2 of them being oncologists and one of them statistician. A study specific charter will define in detail the composition, responsibilities and procedures of the DSMB.

As soon as at least 10 patients per treatment arm have completed the second cycle of first line treatment, a first meeting of DSMB will be scheduled to review the patient safety data. After this meeting, regular 6-monthly meetings will be scheduled until all ongoing patients have been treated for at least 6 months. Starting at the second DSMB meeting, in addition to review of patient safety data a descriptive analysis on progression and survival, including point estimates and 95% confidence intervals of the hazard ratios, will be included to monitor a potential detrimental effect of the investigational compound. For

important reasons additional meetings may be scheduled by the coordinating investigator, sponsor, medical monitor or DSMB members as long as patients are at risk.

4.2 Final Analysis

No database may be locked or analyses completed until this SAP has been approved.

The database cut–off for the statistical analysis will be set to not earlier than 12 months after randomization of the last patient.

The efficacy analysis will be performed for all patients, regarding the patients still under observation as censored and applying the same rules as defined for missing assessments and loss to follow-up.

At this time, the safety analysis will be performed on all available data, including patients still under treatment.

All statistical results will be made available to Glycotope following database cut-off and compiled into the CSR. Final results accociated with OS will be added to the CSR after completion of follow-up for OS which is planned for 24 months after the last patient has been randomized.

Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

4.3 Pharmacokinetic Analysis

The PK samples will consist of 2 groups; samples from the PK profile group and samples from all patients of the CetuGEX™-arm before and at the end of each infusion (up to the 10th infusion).

The samples from the PK profile group will be used for noncompartmental analyses. Samples taken from all patients will be described by sampling time point. Further details are given in Section 11.5.

5. SAMPLE SIZE DETERMINATION

Approximately 240 patients will be randomized in this study.

The log-rank test will be used to test the hypothesis that patients assigned to the CetuGEX™ arm have increased PFS compared to patients assigned to the control arm. The sample size calculation is based on the following assumptions:

- The median PFS in the control arm is expected to be 5.6 months post randomization.
- It is expected that the median PFS in the CetuGEX™ arm can be increased to 8.4 months corresponding to a hazard ratio of 0.67.
- The overall trial duration will be approximately 36 months with an anticipated recruitment time of 24 months, anticipated treatment phase until PFS events are reached of approximately 12 months after randomization of the last patient (data

cut-off for main analysis) and ongoing follow-up for overall survival for at least 24 months after randomization of the last patient.

- Drop-outs are expected to occur at times following an exponential distribution and resulting in a drop-out rate of 10% at the cut-off for PFS analysis.
- Patients will be randomized in a 1:1 ratio.
- The overall two-sided significance level will be 0.05 and the power to be maintained 80%.

Based on these assumptions, approximately 240 patients have to be randomized to observe the required overall number of 192 events.

If the required number of events is not reached as planned after 12 months from last patient randomized, the main analysis will be postponed to obtain more events but not more than additional 6 months.

Assuming a corresponding effect on OS (hazard ratio 0.67) and a median overall survival of 10.6 months in the control group the number of survival events to be observed after a 24-months follow-up for survival will be 183.

6. ANALYSIS POPULATIONS

The analysis populations will include the following:

- The intention-to-treat (ITT) population will consist of all randomized patients. The ITT population will be the primary population for the efficacy analysis.
- The safety population (SAF) will include all patients who received at least one dose of trial medication. This population will be used for safety analyses.
- The per-protocol (PP) population will consist of all ITT patients who received at least one dose of trial medication and without major protocol deviations as defined in this SAP and finally decided in a Data Review Meeting before database lock.
- For PK analyses done in all patients the pharmacokinetic (PK) population will consist of all randomized patients who have at least one evaluable post dose concentration. For the PK profile analyses patients in the PK profile group will be included in the PK profile population who had blood samples collected for PK noncompartmental profiling and who had at least one measureable CetuGEX™ antibody concentration.

In the event that a patient is randomized incorrectly or is administered the incorrect study medication, analyses of the ITT population will be based on the assigned treatment whereas all other analyses will be based on the actual treatment.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the study variables. In general, disposition summaries will be completed for all patients; summaries of protocol violations will be presented for the ITT population. Analyses of demography and baseline variables, and all efficacy analyses will be performed on the ITT and PP population. Safety and exposure analyses will be done on the SAF. All summaries will be presented for each treatment arm and for the total population, unless otherwise specified. Where data are collected over time, both the observed data and the change from baseline will be summarized at each visit.

Continuous variable summaries will include the number of patients with non-missing values (N), mean, standard deviation, median, minimum and maximum, 1st and 3rd quartile.

Categorical variable summaries will include the frequency and percentage of patients who are in the particular category. In general the denominator for the percentage calculation will be based upon the total number of patients in the study population for the treatment arm, unless otherwise specified.

Any patient who does not complete the study per protocol will be included in the analysis with the data available. Response and benefit rates will be based on the observed assessments and the number of patients in the respective population as the denominator, assuming no response/benefit for patients without sufficient data. Other imputation of missing values will not be performed, unless specified in the relevant sections of the SAP.

The last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline. All data obtained on the eCRF and entered into the database will be provided in separate data listings showing individual patient values.

Free text specifications (“other”) of multiple choice items will be detailed in the listings, in the tables the frequency of “other” will be displayed.

All analysis will be performed using SAS® Software version 9.3 or later.

7.2 Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analysis of the primary and secondary target variables. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations required to support the analyses of primary and secondary target variables will be described in the CSR.

Disease will be evaluated by the investigator (modified irRC) and by independent

centralized reading (modified irRC and RECIST 1.1) and classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Tumor assessments will be performed by the investigator and independent centralized reading during the combination treatment phase and single-agent maintenance phase based on computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck region, chest, and abdomen. Subsequent assessments will include head, neck and chest; assessments of the abdomen will only be performed if at baseline metastases were confirmed or if clinical evidence suggests new lesions in these regions. Additional regions might be included if clinically indicated.

Tumor assessments in both study arms will be performed at Screening, every 6 weeks after day of randomization until Week 18 and every 8 weeks thereafter. The tumor evaluation will be performed pre-dose. Results of the assessments performed at Screening will be considered baseline values. The same type of imaging as for baseline assessments should be maintained throughout the study.

For time durations in days that need to be converted to months, the number of days will be divided by factor 30.4375. For time durations in days that need to be converted to years, the number of days will be divided by factor 365.25.

The following table describes the derivation of the primary and secondary efficacy variables related to response and survival in detail.

<table>
<tr><td colspan="4">Response Based Variables
Computation methods described below will be applied simultaneously to response criteria modified irRC (site, central review) and RECIST (central review)</td></tr>
<tr><td>Variable Name</td><td colspan="3">Computation Methods, Notes, or Equation(s)</td></tr>
<tr><td rowspan="6">PFSp

(primary definition)</td><td colspan="3">= Earliest date of progression or death - date of randomization + 1
The earliest date of PD will be used irrespective of PD confirmation</td></tr>
<tr><td>Finding</td><td>Date of PD of Censoring</td><td>Outcome</td></tr>
<tr><td>No PD or death</td><td>Pre and post-baseline imaging done: Date of last imaging</td><td>Censored</td></tr>
<tr><td></td><td>No baseline or no post-baseline imaging done: Date of randomization</td><td>Censored</td></tr>
<tr><td>Progression/death documented after a new anticancer treatment has started</td><td>Date of last imaging prior to new anticancer treatment</td><td>Censored</td></tr>
<tr><td>PD at scheduled visit

PD between scheduled visits</td><td>Date of imaging

Date of imaging</td><td>Event

Event</td></tr>
<tr><td rowspan="11">PFSs

(sensitivity definition)</td><td colspan="3">= Earliest date of progression or death - date of randomization + 1
The earliest date of PD will be used irrespective of PD confirmation</td></tr>
<tr><td>Finding</td><td>Date of PD of Censoring</td><td>Outcome</td></tr>
<tr><td>No PD or death</td><td>Pre and post-baseline imaging done: Date of last imaging</td><td>Censored</td></tr>
<tr><td></td><td>No baseline or no post-baseline imaging done: Date of randomization</td><td>Censored</td></tr>
<tr><td>Progression/death documented after a new anticancer treatment has started</td><td>Date of last imaging prior to new anticancer treatment.</td><td>Censored</td></tr>
<tr><td>PD at scheduled visit</td><td>Date of imaging</td><td>Event</td></tr>
<tr><td>PD between scheduled visits*</td><td>Date of next scheduled visit</td><td>Event</td></tr>
<tr><td>PD after 2 or more missing scheduled visits</td><td>Date of last imaging prior to first missing visit.</td><td>Censored</td></tr>
<tr><td>Death up to 16 weeks (112 days) after last imaging</td><td>Date of death</td><td>Event</td></tr>
<tr><td>Death later than 16 weeks (112 days) after last imaging</td><td>Date of last imaging</td><td>Censored</td></tr>
<tr><td>Best overall response</td><td colspan="3">Best modified irRC classification (CR, PR or SD) as assessed by the investigator or by the independent centralized review</td></tr>
</table>

(rates) (BO(R))	SD: follow-up measurements must have met the SD criteria at least once after randomization at a minimum interval of 8 weeks.
Objective response (rate) (OR(R))	Best response of CR or PR
Clinical benefit (rate) (CB(R))	Best response of CR or PR or SD. SD: follow-up measurements must have met the SD criteria at least once after randomization at a minimum interval of 8 weeks
Duration of response	= Date of first progression or death after initial response - date of first response + 1 Date of disease progression is defined as the date of imaging showing disease progression. Date of response is defined as the first date of imaging showing CR or PR. If no progression or death is observed after initial response, the duration of response will be censored at the last date of tumor assessment.
Duration of CR	= Date of first progression or death after initial response - date of first CR + 1 Date of disease progression is defined as the date of imaging showing disease progression. Date of CR is defined as the first date of imaging showing CR. If no progression or death is observed after initial CR, the duration of CR will be censored at the last date of tumor assessment.
Other variables	
Overall survival (OS)	Date of death – date of randomization + 1 If no death is observed, OS will be censored at the last date known to be alive.
Time to treatment failure (TTF)	Date of treatment discontinuation for any reason (including disease progression) as assessed by investigator, treatment toxicity, patient preference, or death) – date of randomization If no treatment discontinuation is observed, TTF will be censored at the date of last study treatment.
Body surface area (BSA)	BSA [m^2] = SQRT((weight [kg] × height [cm]/3600))
Number of combination treatment cycles	Number of treatment cycles with full combination treatment (3 doses of CetuGEX™/cetuximab, one dose of cisplatin/carboplatin, 4 doses of 5-FU) Only cycles in which all planned medication has been given will be counted as a full cycle. Dose reductions will however not prevent a cycle to be counted as full.
Overall treatment duration [weeks]	(Date of last treatment administration – date of first treatment administration) + 1 for CetuGEX™/cetuximab
Treatment duration [weeks] during combination treatment	(Date of last treatment administration within a combination cycle – date of first treatment administration) + 1 for CetuGEX™/cetuximab
Treatment duration [weeks] in maintenance phase	(Date of last treatment administration – date of first treatment administration after last Day 15 administration in combination treatment phase) + 1 for CetuGEX™/cetuximab

Total doses [mg]	Sum of actual doses administered for CetuGEX™/cetuximab cisplatin/carboplatin and 5-FU

* Scheduled visits are expected to be performed every 6 weeks after day of randomization until Week 18 and every 8 weeks thereafter. An assessment is considered "between scheduled visits" if it is performed more than 7 days before the next scheduled visit.

The following variable will be derived with respect to hospitalization:

Variable Name	Computation Methods, Notes, or Equation(s)
Percentage of days in hospital	(Number of days of hospitalization (sum of all: discharge date [or death date if died in hospital] – admission date +1) divided by number of days from randomization to EOS visit) * 100%

8. STUDY PATIENTS AND DEMOGRAPHICS

8.1 Disposition of Patients and Withdrawals

All patients who provide informed consent will be accounted for in this study.

Descriptive summaries of population data will include

- the frequency and percentage of patients in each study population, overall and by center
- the disposition of patients, including number of patients who gave informed consent for screening, number of screening failures, number of patients randomized, number of patients completing the clinical phase (EOS visit after observed progression), number of patients discontinuing treatment without preceding progression, reason for discontinuation from treatment
- study withdrawals by reason of withdrawal
- the frequency and percentage of patients in cross-sectional subgroups defined by the stratification factors at randomization
    - FcγRIIIa status (FF, FV or VV)
    - Oral cavity and oropharynx vs. other locations
    - Locally recurrent vs. metastatic disease
    - EGFR treatment naïve vs. EGFR treatment as part of multimodal therapy

and will be presented for all randomized patients, unless otherwise specified. Subgroups will also be detailed for the PP population.

8.2 Protocol Violations and Deviations

Clinical data will be checked for potential protocol violations before database lock in order to define the analysis populations. A data review meeting will be held after database soft lock. Cases and frequency of patients violating the criteria listed below will be analyzed and categorized as minor or major protocol violations. Patients with one or

more major protocol violation will be excluded from the PP population, patients with only minor or no violations will be included.

Violations of the following criteria may constitute a major protocol violation. Final decisions will however be made at a blinded data review meeting prior to data base lock:

- histologically confirmed recurrent and/or metastatic SCCHN not eligible for local treatment
- measurable disease according to RECIST 1.1
- at least 18 years of age at screening
- Eastern Cooperative Oncology Group (ECOG) at Screening ≤ 1
- negative pregnancy test at screening/prior to randomization (if female and of childbearing potential)
- no clinical evidence of brain metastasis or leptomeningeal involvement
- no nasopharyngeal tumors
- no myocardial infarction within 6 months prior to screening
- no symptomatic congestive heart failure (NYHA Grade 3 or 4), no unstable angina pectoris within 6 months prior to screening, no significant cardiac arrhythmia, no history of stroke or transient ischemic attack within 1 year prior to screening
- no prior allergic reaction to a monoclonal antibody, no grade 3 IRR or any grade 4 reaction to a monoclonal antibody
- no pregnancy during study
- treatment as randomized

Other issues which become obvious during data review may be considered as potential major violations as well.

Furthermore, data listings will be reviewed for prohibited previous and concomitant therapies (as defined in protocol sections 8.2.2 and 9.12.2).

Major and minor protocol violations will be summarized by type of violation and by treatment group for the ITT population. Individual patients with major protocol deviations will be listed.

8.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for the ITT and PP population.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics and baseline data (age, sex, race, height, weight, BMI, body surface area (BSA), smoking status, alcohol consumption, ECOG performance status)

- Tumor specific baseline characteristics: FcγRIIa allotypes, FcγRIIIa allotypes, p16 status, HPV status, EGFR expression, tumor location (oral cavity and oropharynx vs. other locations), stage of disease (locally recurrent vs. metastatic disease), EGRF pre-treatment (EGFR treatment naïve vs. EGFR treatment as part of multimodal treatment)
- SCCHN diagnosis and history
- Prior anti-cancer therapies (drug therapies, radiotherapy, surgeries)
- Echocardiogram (ECHO)/multiple-gated acquisition scan (MUGA) assessment
- Baseline physical examination
- General medical history
- Baseline signs and symptoms
- Prior medication
- Concomitant medication (at baseline / started after baseline / taken during study)
- Premedication

Baseline physical examination: Incidence of abnormalities will be summarized by body system.

Medical History: Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 16 or newer). Incidences of findings in medical history will be summarized by system organ class (SOC) and preferred term.

SCCHN diagnosis and history: Months since initial diagnosis, months since most recent recurrent/metastatic diagnosis, American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging at initial diagnosis, location of primary squamous cell carcinoma, metastatic disease and TNM classification at initial diagnosis will be displayed.

If the reported diagnosis dates are incomplete (year or year and month only), intervals will be calculated using the midpoint of the described period (15th in case of missing day only, 1st of July in case of missing day and month).

Baseline signs and symptoms: The number and percentage of patients with at least one baseline sign/symptom. Further details of the respective signs and symptoms will be listed.

Prior anti-cancer therapies: The number and percentage of patients with at least one prior therapy by type of therapy.

Prior and concomitant medication: All medication will be coded using the WHO-DRUG dictionary September 2013 edition (or newer). Incidences of prior and concurrent medications will be summarized by ATC level 2 and ATC level 4 if applicable.

Concomitant medication is defined as a medication other than study drug that was administered during the treatment period. The treatment period is defined as the time from day of first treatment to the EOS visit. Medication that has been classified as

premedication will be analyzed separately. Additionally the number of corticosteroids applications per patient will be analyzed.

Prior medication is defined as medication which was discontinued before start of study treatment. Medication which was started after the treatment period will be listed but not analyzed otherwise.

If the start date and stop date of medication are partially or completely missing, a medication will be assumed to be concomitant if it cannot be definitely shown that the medication was not administered during the treatment period. Missing dates will not be replaced.

Thus, the following approach will be taken for exclusion from concomitant medication because of discontinuation before start of treatment:

- If stop day is missing but month is complete, medication will only be excluded from concomitant medication if stop month is before month of treatment start.
- If stop day and month are missing but year is complete, medication will only be excluded from concomitant medication if stop year is before year of treatment start.
- If stop date is completely missing, medication will not be excluded.

For exclusion from concomitant medication because of late start after end of treatment period:

- If start day is missing but month is complete, medication will only be excluded from concomitant medication if start month is after end month of treatment period.
- If start day and month are missing but year is complete, medication will only be excluded from concomitant medication if start year is after end year of treatment period.
- If start date is completely missing, medication will not be excluded from concomitant medication.

8.4 Analysis of Exposure

The following variables will be summarized descriptively for the SAF population.

- Number of combination treatment cycles
- Number of infusions of CetuGEX™/cetuximab
- Overall treatment duration [weeks] for CetuGEX™/cetuximab
- Treatment duration [weeks] during combination treatment for CetuGEX™/cetuximab
- Treatment duration [weeks] in maintenance phase for CetuGEX™/cetuximab
- Total dose [mg] for CetuGEX™/cetuximab, cisplatin/carboplatin and 5-FU
- Dose changes/reductions: Number and percentage of dose reductions and reasons

per patient and per administration for CetuGEX™/cetuximab, cisplatin/carboplatin and 5-FU

- Dosing delays: Number and percentage of delays and reasons per patient and per administration for CetuGEX™/cetuximab, cisplatin/carboplatin and 5-FU
- Dosing interruptions: Number and percentage of interruption and reasons (AE/per-protocol/other) per patient and per administration for CetuGEX™/cetuximab, cisplatin/carboplatin and 5-FU
- Infusion rate changes: Number and percentage of infusions rate changes and reasons (AE/per-protocol/other) per patient and per administration for CetuGEX™/cetuximab
- Switches to carboplatin by reason for switch (AE/PI discretion) and first cycle of switch

Furthermore, details of study treatment termination will be tabulated, including reason for discontinuation of treatment and reason for chemotherapy termination and discontinued agent.

9. EFFICACY ANALYSIS

Efficacy analyses will be performed based on the treatment group the patient was randomized to unless otherwise specified.

9.1 Primary Efficacy Analysis

The primary efficacy analysis for PFS as assessed by the investigator will be based on the ITT population using the PFSp definition as described in Section 7.2.

A two-sided log-rank test will be used to test the null hypothesis of equal treatment effects at an overall significance level of 0.05. The Kaplan-Meier method will be used to estimate the survival functions. Median survival times together with their 95%-confidence intervals will be retrieved from the survival functions. PFS rates at 6, 12, 15 and 18 months and associated 95%-confidence intervals and graphs of the Kaplan-Meier curves by treatment arm will also be presented.

The primary efficacy analysis will not be stratified by the factors used for stratification at randomization in order to preserve the estimated power considering the high number of strata.

To investigate the influence of the stratification factor on the primary endpoint a Cox regression model will be applied as a sensitivity analysis based on the ITT population. This model will include the treatment effect and the stratification factors

- FcγRIIIa allotypes (FF, FV or VV)
- Oral cavity and oropharynx vs. other locations
- Locally recurrent vs. metastatic disease
- EGFR treatment naïve vs. EGFR treatment as part of multimodal treatment

The hazard ratios, the corresponding 95% confidence intervals and the p-values of the Wald test (using adjustment for ties according to Efron) will be presented for all factors. The Kaplan-Meier analyzes will be repeated separately within the subgroups formed by the stratification factors. Corresponding figures will combine the curves for all treatment group/factor level combinations on one page per factor. Factor levels maybe combined if the sample size per level is < 15.

Further sensitivity analyses will be done as follows

- The analyses will be repeated using the PFSs definition as described in Section 7.2
- The analyses will be repeated for the PP Population
- It has been recognized that not all sites had strictly applied modified irRC for response assessment. To investigate the influence of deviating response criteria on PFS a log rank test will performed stratifying sites according to strict adherence to modified irRC (yes/no).

9.2 Secondary Efficacy Analysis

Secondary efficacy analyses will be based on the ITT and PP population.

9.2.1 Progression-free Survival Based on Independent Central Review

PFS as assessed by independent centralized reading (irRC and RECIST 1.1) will be analyzed based on the PFSp definition applying a not stratified log rank test. Kaplan-Meier estimates will be presented and Cox regression models be applied as described in Section 9.1.

9.2.2 Tumor Response Rates

ORR and CBR according to different criteria (irRC, RECIST) and sources (investigator, central review) will be analyzed using Chi-square tests to evaluate the effects of treatment on ORR and CBR for the combination treatment period as wells for the entire treatment period including maintenance treatment. 95%-confidence intervals will be calculated for the rates and their treatment differences based on normal approximation.

Logistic regression models will be used to investigate the influence of the stratification factors on the response variables. These models will include the treatment effect and the randomization stratification factors. The odds ratios, the corresponding 95% confidence intervals and the p-values of the Wald test will be presented for all factors.

Absolute and relative frequencies of tumor response categories will be tabulated by time point and for the best response. Waterfall plots to illustrate individual maximum percentage change of target lesion size form baseline will be presented by treatment group.

Duration of response will be analyzed by Kaplan-Meier methods. Duration of CR will be described case by case.

9.2.3 Time to Treatment Failure

TTF will be analyzed applying a not stratified log rank test. Kaplan-Meier estimates will be presented and Cox regression models be applied as described in Section 9.1.

9.2.4 Overall Survival

OS will be analyzed applying a not stratified log rank test and a proportional hazards regression model including the stratification factors in addition to the study treatment Kaplan-Meier estimates will be presented as described in Section 9.1 factor. Survival rates at 12, 18 and 24 months and associated 95%-confidence intervals will be presented.

A further proportional hazards regression model will be applied including the study treatment factor, the stratification factors and a dichotomous variable for second line treatment. This model maybe further modified or supplemented to account for different classes of second line treatments.

9.3 Explorative Efficacy Analysis

9.3.1 Landmark Analyses

To explore the effect of the single-agent maintenance treatment on PFS a landmark analysis will be performed based on the primary endpoint definition. The landmark will be set to the start of the maintenance therapy. Only ITT patient still at risk for progression and death at this time point will be used for the analysis. The landmark PFS will be calculated from the start of maintenance treatment using the PFSp definition accordingly. Cox regression model will be applied including the treatment effect and the stratification factors. Kaplan-Meier analyzes will be presented.

Corresponding landmark analyses will be presented for OS.

9.3.2 Influence of Baseline Tumor Characteristics on Treatment Effects

To investigate the influence of covariables on treatment effects as assessed by the primary PFS endpoint Cox regression models will be applied including the covariable in addition to the treatment and the stratification factors based on the ITT and PP population. The following prognostic variables will be investigated

- FcγRIIa allotype (HH, HR, RR)
- p16 status (+/-)
- EGFR intensity
- EGFR stained cancer cells (%, continuous)

Classes may be combined if the number of patients within a class is lower than 15. The hazard ratios, the corresponding 95%-confidence intervals and the p-values of the Wald test will be presented for all factors. Kaplan-Meier analyzes will be repeated separately within the subgroups formed by discrete factors. Corresponding figures will combine the curves for all treatment group/factor level combinations on one page per factor.

Corresponding analyses will be performed for OS.

Similarly logistic models will be applied including the covariable in addition to the treatment and the stratification factors based on the ITT and PP population to evaluate the effects of treatment on CBR.

9.3.3 Correlation of Pharmacokinetic Parameters with PFS and CBR

The following PK parameters of CetuGEX™ serum concentrations will be investigated concerning their impact on efficacy outcomes in the subgroup of patients who were treated with CetuGEX™

- Trough levels after 1st, 2nd and 3rd infusion (= pre-infusion concentrations at 2nd, 3rd and 4th infusion)
- Post-infusion concentration after 1st, 2nd and 3rd infusion.

Cox regression models including the PK parameter as continuous covariable will be fit to the primary PFS endpoint. Separate analyses will be performed for each of the 6 PK parameters. Hazard ratios, the corresponding 95%-confidence intervals and the p-values of the Wald test will be presented. A forest-plot will be provided to illustrate the hazard ratios and confidence interval for all 6 PK parameters in one figure.

Logistic regression models including the PK parameters as continuous covariable will be fitted to the CBR as assessed by the central review (RECIST). Separate analyses will be performed for each of the 6 PK parameters. Odds ratios, the corresponding 95%-confidence intervals and the p-values of the Wald test will be presented. Moreover, sample statistics of the PK parameters grouped by CB response (yes/no) will be presented including p-values of the Wilcoxon rank test. A forest-plot will be provided to illustrate the odd ratios and confidence interval for all 6 PK parameters in one figure.

These analyses will be based on PK population.

10. SAFETY AND TOLERABILITY ANALYSES

The safety analysis will be performed for the SAF population.

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data:

- AEs (including IRRs)
- Clinical laboratory investigations (biochemistry, hematology, urinalysis)
- Vital signs
- ECG investigations
- ECOG performance status

Findings in post-baseline physical examinations will be documented as AE and analyzed as part of the general AE analysis.

10.1 Adverse Events

Adverse Events will be coded using MedDRA version 16 or newer.

An AE is defined as treatment emergent (TEAE), if the first onset or worsening is at or after the first administration of IMP (CetuGEX^{TM} or cetuximab) and within 28 days after last administration.

If the start date or time of an AE is partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment emergent period (worst case approach). Missing dates and times will not be replaced for display in listings and further calculations.

Thus, the following approach will be taken:

- If the start time of an AE is missing, but the start date is complete, an AE will only be excluded from treatment-emergent AEs if the start day is before day of first treatment or the start day is after end day of the treatment-emergent period.
- If the start time and day are missing but the start month is complete, an AE will only be excluded from treatment emergent AEs if the start month is before month of first treatment or the start month is after end month of treatment-emergent period or if the stop date/time information is sufficient to show the event ended before the start of treatment.
- If the start day and months are missing but the start year is complete, an AE will only be excluded from treatment-emergent AEs if the start year is before year of first treatment or if the start year is after end year of treatment-emergent period or if the stop date/time information is sufficient to show the event ended before the start of treatment.
- If start date is completely missing, an AE will not be excluded from treatment-emergent AEs unless the stop date/time information is sufficient to show the event ended before the start of treatment.

Time from first treatment to onset of AEs [days] and duration of AEs [days] will be calculated for complete dates only and will be included in listings.

In the following infusion related reactions (IRRs) are defined as AE marked as infusion related reactions (IRRs) by the investigator and/or specific AEs which occurred at or the day after an infusion. The relevant AEs will be identified as a list of Preferred Terms which will be compiled before data base lock.

An AE summary table will be presented including rows with the number of patients with

- AEs
- TEAEs
- SAEs
- Any Deaths (NCI CTCAE V4.0 Grade 5 TEAEs and/or with an outcome of death)
- NCI CTCAE Grade 4, 3, 2, 1 TEAEs
- Adverse drug reactions (ADRs) (related or possibly related TEAEs)
- TEAEs leading to withdrawal of study treatment

- TEAEs leading to drug interruption or infusion rate reduction
- TEAEs requiring additional medication
- TEAEs constituting IRRs
- TEAEs marked as disease related symptoms

Incidences of TEAEs will be presented for all TEAEs and separately for the combination treatment (TEAE which occurred before first maintenance treatment) and maintenance treatment (TEAE which occurred at or after first maintenance treatment).

Incidences of TEAEs will be calculated on Preferred Term level, on System Organ Class level (SOC) and globally by treatment group. On each analysis level, a patient will be counted only once. Summaries of incidence rates (frequencies and percentages) of individual TEAEs by MedDRA SOC and Preferred Term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity graded according to NCI-CTCAE (Version 4.03), TEAEs by strongest relationship to study treatment, and TEAEs by strongest relationship to chemotherapy. In the SOC/PT tables, events with missing grade or relationship information will be classified into the worst category. No statistical tests will be performed. In addition, separate summaries of incidence rates of IRRs and all TEAEs without IRRs by SOC and PT will be given.

IRRs will be linked to the last infusion administered before the occurrence of the IRR. Incidence rates will be calculated by SOC and PT on a per infusion basis. Moreover the first infusion per patient with a least one IRR will be identified and summarized in frequency tables.

Also, a summary of incidence rates of TEAEs by SOC and PT and of incidence rates of IRRs by FcγRIIIa-allotype subgroups (FF, FV and VV), by FcγRIIa allotypes (HH, HR, RR) the occurrence of ADAs (no/yes) and the CetuGEX™ concentration (C_{max}) after the 3rd infusion (≤ median/>median) will be prepared.

In the AE listings all recorded AEs will be included, TEAEs will be identified by a flag variable.

10.1.1 Adverse Events Leading to Withdrawal of Study Drug, Drug Interruption or Dose Adjustments

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by SOC, and Preferred Term, will be prepared for the SAF population.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the events captured on the eCRF.

Similar table and listings will be presented for TEAEs leading to drug interruptions/infusion rate reductions or dose reductions.

10.1.2 Serious Adverse Events

SAE Reconciliation will be performed by the Data Manager prior to database lock according to the SAE Reconciliation Plan.

A summary of incidence rates (frequencies and percentages) of SAEs by SOC, and Preferred Term will be prepared for the SAF Population.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the eCRF.

10.1.3 Adverse Events of Special Interest

The times to the first occurrence of neutropenia (CTC-grade ≥ 3), liver enzymes increases (CTC-grade ≥ 3), (hypomagnesemia (CTC-grade ≥ 3), skin reactions (SOC="Skin and subcutaneous tissue disorders"), gastrointestinal symptoms (SOC='Gastrointestinal disorders), mucositis (PT='Mucositis') and conjunctivitis (PT='Conjunctivitis') will be investigated by Kaplan-Meier methods. Patients who did not experience this AE will be censored at the Safety Follow-up visit.

Logistic regression models including the CetuGex plasma concentration after the 3rd infusion as continuous covariable will be fitted to the incidences of AEs of special interest. Separate analyses will be performed for each of the AEs. Odds ratios, the corresponding 95%-confidence intervals and the p-values of the Wald test will be presented. Moreover, sample statistics of the CetuGex plasma concentration after the 3rd infusion grouped by the occurrence of these AEs (yes/no) will be presented including p-values of the Wilcoxon rank test.

AEs of special interest will be omitted from these analyses if their overall incidence is < 5%.

10.2 Clinical Laboratory Evaluations

Safety laboratory data (hematology including coagulation panel, biochemistry, urinalysis) will be collected from the respective local laboratories of each involved site.

The analysis of laboratory parameters will be presented for the SAF population, separated into blood parameters (hematology, biochemistry) and urine parameters (urinalysis). All data will be listed.

For hematology and biochemistry the laboratory values will be transformed to SI values based on SI units to make laboratory parameters comparable between different local laboratories. The relevant reference ranges supplied by each laboratory will also be transformed to SI reference ranges for each laboratory.

For hematology and biochemistry variables, descriptive summaries of absolute values and changes from baseline will be presented by visit and treatment arm. Visits with less than 10 values will be omitted. The description will include two derived visits: "Last Value under Combination Therapy" and "Last Value".

Each abnormal value will be flagged to show whether it is a value below or above the reference range. For the assessment of laboratory variables, five categories will be used taking into account the investigator's assessment of clinical relevance: 'abnormal high – clinically relevant', 'abnormal high – not clinically relevant', 'within normal limits', 'abnormal low – not clinically relevant', 'abnormal low – clinically relevant'.

The assessment of laboratory variables will be tabulated by study visit for each clinical laboratory parameter by treatment arm (frequency tables). Additionally, for each laboratory parameter, shifts in assessments from Baseline to last combination therapy visit and overall last visit will be presented by treatment arm (shift tables).

If NCI-CTCAE grades are available for a clinical laboratory analyte, these will be derived according to Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) and used to present additional frequency and shift tables based on NCI-CTCAE grades.

The assessment of categorical urinalysis variables (within normal limits, abnormal – not clinically significant, abnormal – clinically significant) will be tabulated by visit for each urine parameter by treatment arm (frequency tables). Additionally, for each of these urine parameters, shifts in assessments from Baseline to EOS visit will be presented by treatment arm (shift tables).

Laboratory values that are outside the reference range will also be flagged in the data listings, along with corresponding reference ranges.

10.3 Vital Signs

Descriptive summaries of observed values and changes from baseline will be calculated for weight, temperature, systolic blood pressure, diastolic blood pressure, and pulse rate. These summaries will be presented by visit and treatment arm.

10.4 Electrocardiogram

The summary ECG assessment (categories: normal, abnormal – not clinically significant, abnormal – clinically significant) will be tabulated by visit (frequency tables). Additionally, shifts in assessments from baseline to EOS visit will be presented by treatment arm (shift tables).

Descriptive summaries of actual values and changes from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (Bazett), and HR (heart rate) by visit and treatment arm.

If not available in the clinical database, Bazett's Correction (QTc_b) will be derived as follows:

Bazett's Correction (QTc_b) $$QTc_b = \frac{QT_{msec}}{\sqrt{RR}}$$

where: Relative Rate: RR = 60 / HR
HR = heart rate obtained from ECG.

Also, the number and percentage of patients in each treatment group with QTc values 451 - 480 ms, 481 - 500 ms or >500 ms and the number and percentage of patients in each treatment group who experienced a change >30 ms or a change >60 ms will be presented by visit.

10.5 ECOG Performance Status

ECOG assessments will be tabulated by visit and treatment arm (frequency tables). Additionally, shifts in assessments from Baseline to EOS visit will be presented by treatment arm (shift tables). These analyses will be performed for the SAF population.

11. OTHER PLANNED ANALYSES

11.1 Comparison of Investigator and Centralized Tumor Response Assessments

Cross-tables comparing case-by-case the best overall investigator and centralized tumor response assessments (irRC) based on the entire treatment phase will be presented.

11.2 Anti-drug Antibodies

The incidence of ADAs will be summarized by sampling time point in frequency tables for the SAF population.

11.3 Hospitalization

Descriptive summaries of the percentage of days of hospitalization, based on the period between randomization and EOS, will be presented by treatment arm for the SAF population for all hospitalizations as well as broken down by reason.

11.4 Cytokines Release and Immune Cell Status

Cytokine release and immune cell counts ($CD4^+$ T cells, $CD8^+$ T cells, B cells, NK cells from FACS results and eosinophils, neutrophils and monocytes from blood count) analyses will include descriptive summaries of measured values and changes from baseline (absolute and percent changes, fold change for cytokines). All analyses will be performed by sampling time point and treatment arm for the respective subset of the ITT population. The time courses of cytokines and immune cell count will be displayed graphically (scatter plot overlaid by corresponding medians and interquartile ranges) . The change of cytokines/serum factor from pre-first infusion to end of first infusion will be summarized by grades of timely related IRRs.

11.5 Pharmacokinetic Analysis

Derivation of pharmacokinetic parameters and statistical analyses will be performed by the xxxxxxxxxxxxxxx Clinical Pharmacokinetics Department. Summaries of serum concentration data by sampling time point and derived PK parameters will be presented.

Serum Concentrations

For all patients treated with CetuGEX™ its concentration will be analyzed in serum samples.

For serum concentration data, all values below the limit of quantification (BLQ) will be set to BLQ/2 for summary statistics and graphs. Individual serum CetuGEX™ concentrations will be summarized at each time point using descriptive statistics. Individual concentration plots and mean data graphs will be produced. All graphs will be presented using both linear and semilogarithmic scales. All CetuGEX™ concentrations

will be presented in a by-subject listing.

Pharmacokinetic Parameters

Serum PK samples at pre-dose and at the end of each infusion will be collected from all patients. In addition, serum PK samples will be collected at 5 hours ± 5 min, 7 hours ± 15 min, 24 hours ± 1 hour, 48 hours ± 2 hours, 72 hours ± 2 hours and 168 hours ± 2 hours after the start of the 1st infusion on Day 1 from a subgroup of approximately 30 patients dosed with CetuGEX™. The same sampling regimen will also be taken after the 10th infusion. The resulting pharmacokinetic profiles obtained from this subgroup will be subjected to noncompartmental analysis, as data permit.

Pharmacokinetic parameter estimation will be performed using Phoenix WinNonlin® (Version 6.4 or later; Pharsight, Cary, NC) on individual serum concentration-time data. For the PK parameter calculation, BLQ serum concentrations occurring before Tmax will be set to BLQ/2 (50 ng/mL) with the exception of a BLQ value occurring between two measurable concentrations, in which case it will be set to missing. BLQ serum concentrations occurring after Tmax will be set to missing. Pharmacokinetic parameter estimates and summaries will be completed for subjects in the PK Population having sufficient measurable concentrations to define the profile. The calculation of terminal half-life will only be performed if at least three data points are available.

Pharmacokinetic parameter estimates, including C_{max}, C_{min}, C_{avg}, T_{max}, MRT, AUC_{0-t}, $AUC0_{-\infty}$, $AUC_{\%extrap}$, AUC_{0-tau}, λz, $t_{1/2}$, V_z, V_{ss}, and CL, will be summarized using descriptive statistics, including arithmetic and geometric means, SD, %CV, median, minimum, and maximum. For Tmax, only the median and the range will be reported, as it is a categorical variable.

Values of $AUC0_{-\infty}$ for which the extrapolated part exceeded 20% will be flagged for possible exclusion from descriptive statistics.

The steady state will be assessed by visual observation of the mean trough (pre-dose) concentrations over time. Only trough concentrations for which the actual sampling time did not deviate by more than 2 hours from the nominal (planned) sampling time will be included in the steady state assessment. If the steady state is reached, mean accumulation ratio and fluctuation (%fluctuation) will also be calculated.

All pharmacokinetic calculations will be performed per WinNonlin standard noncompartmental algorithms, using actual sampling times elapsed from the start of the first infusion. Actual sampling times elapsed from the start of the 10th infusion will also be included in the PK input file

The correlation between PK parameters (AUC_{0-t}, C_{max}, C_{min}, CL and $t_{1/2}$) with body weight, body surface area and BMI will be explored in scatter plots and by calculating correlations coefficients.

11.6 Quality of Life Analysis

To assess the QoL of each patient, patient-reported disease-related symptoms and health related QoL will be measured using the EORTC-QLQ-C30 questionnaire and the head and neck module (H&N35; according to the availability of the validated translations).

The QoL questionnaires EORTC QLQ-C30 version 3.0 and QLQ-H&N35 are collected at Baseline and several post-baseline visits. The following scores will be derived:

- Global health status/QoL (revised): items 29 to 30

Functional scales (QLQ-C30)

- Physical functioning (revised): items 1 to 5
- Role functioning (revised): items 6 to 7
- Emotional functioning: items 21 to 24
- Cognitive functioning: items 20 and 25
- Social functioning: items 26 to 27

Symptom scales / items (QLQ-C30)

- Fatigue: items 10, 12, 18
- Nausea and vomiting: items 14, 15
- Pain: items 9, 19
- Dyspnea: item 8
- Insomnia: item 11
- Appetite loss: item 13
- Constipation: item 16
- Diarrhea: item 17
- Financial difficulties: item 28

Symptom scales / items (QLQ-H&N35)

- Pain: items 1 to 4
- Swallowing: items 5 to 8
- Senses problems: items 13 and 14
- Speech problems: items 16, 23 and 24
- Trouble with social eating: items 19 to 22
- Trouble with social contact: items 18 and 25 to 28
- Less sexuality: items 29 and 30
- Teeth: item 9
- Opening mouth: item 10
- Dry mouth: item 11
- Sticky saliva: item 12

- Coughing: item 15
- Felt ill: item 17
- Pain killers: item 31
- Nutritional supplements: item 32
- Feeding tube: item 33
- Weight loss: item 34
- Weight gain: item 35

Each of the scores will be derived individually if at least half of the required items are available. In general, the mean score will be derived first and then be linearly transformed in a way that 0 is the lowest and 100 is the highest possible value. Functional scores for QLQ-C30 will be reversed so that a value of 100 represents the highest level of functioning. Global and symptom scores will not be reversed so that 100 represents the highest possible QoL and the highest level of problems, respectively.

Summary statistics of all scores and their changes from baseline will be tabulated by cycle including p-values of a Wilcoxon rank test for the changes. The time courses of means scores will be presented as boxplots.

In addition, for the QLQ-C30 scales, the difference with respect to baseline will be classified as $\leq$ -10, -10 – 10, $\geq$ 10. The rates of patients within these ranges will be presented by treatment group and visit. The time from randomization to the first occurrence of a deterioration of at least 10 points ($\leq$ -10 for global and functional scales, $\geq$ 10 for symptom scales) will be analyzed by Kaplan-Meier methods. Patients without occurrence of deterioration will be censored at the last assessment. The estimate of the quartiles of the time to deterioration as well as the associated 95%-confidence intervals will be tabulated by treatment arm together with the p-value of a log rank test.

12. CHANGES COMPARED TO THE CLINICAL TRIAL PROTOCOL

All planned statistical analyses are in agreement with the clinical trial protocol.

13. REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

13.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in landscape orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item

displayed.

- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g. μ, α, β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, listings, and graphs.
- All footnotes will be left justified and at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned, then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format. A four-digit year is preferred for all dates.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- Time durations will be reported in HH:MM:SS notation. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figure, and data listings will have the name of the program and a date stamp on the bottom of each output.

13.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "Population: <name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) Full Analysis or ITT, (b) All Patients, (c) PP or Per-Protocol, (d) Efficacy, (e) Safety, or (f) Pharmacokinetic.

- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
- All population summaries for continuous variables will include: N, mean, standard deviation, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x%).
- Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). All p-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.001 should be reported as <0.001 not 0.000.

14. REFERENCES

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15. TABLES, LISTINGS, AND FIGURES

15.1 Planned Table Descriptions

The following are planned summary tables for protocol GEXMab52201. Tables will be numbered according to the nomenclature used to support the clinical study report.

Tables will be repeated according to population adding an additional table extension digit.

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14.3.5.4.1	Safety	Exposure (CetuGEX™/cetuximab) Number of Cycles, Number of Infusions, Treatment Duration and Total Dose	16.2.5.1
14.3.5.4.2	Safety	Exposure (CetuGEX™/cetuximab) Dose Changes, Dosing Delays, Dosing Interruptions and Infusion Rate Changes (Per Patient)	16.2.5.1
14.3.5.4.3	Safety	Exposure (CetuGEX™/cetuximab) Dose Reductions, Dosing Delays, Dosing Interruptions and Infusion Rate Changes (Per Administration)	16.2.5.1
14.3.5.5.1	Safety	Exposure (5-Fluorouracil) Number of Cycles and Total Dose	16.2.5.3
14.3.5.5.2	Safety	Exposure (5-Fluorouracil) Dose Reductions, Dosing Delays, Dosing Interruptions (Per Patient)	16.2.5.3

Table Number	Population	Table Title / Summary	Supporting Listing
14.3.5.5.3	Safety	Exposure (5-Fluorouracil) Dose Reductions, Dosing Delays, Dosing Interruptions (Per Administration)	16.2.5.3
14.3.5.6.1	Safety	Exposure (Cisplatin/Carboplatin) Number of Cycles and Total Dose	16.2.5.4
14.35.6.2	Safety	Exposure (Cisplatin/Carboplatin) Dose Reductions, Dosing Delays, Dosing Interruptions (Per Patient)	16.2.5.4
14.3.5.6.3	Safety	Exposure (Cisplatin/Carboplatin) Dose Reductions, Dosing Delays, Dosing Interruptions (Per Administration)	16.2.5.4
14.3.5.7.1	Safety	Switch to Carboplatin Reason	16.2.5.4
14.3.5.7.2	Safety	Switch to Carboplatin First Cycle of Switch	16.2.5.4

Table Number	Population	Table Title / Summary	Supporting Listing
14.4 PHARMACOKINETIC DATA			
14.4.1.1	PK	Pharmacokinetic – Summary of CetuGEX Serum Concentrations Before and After Infusions Sample Statistics	16.2.5.3
14.4.1.2	PK	Pharmacokinetic - Summary of CetuGEX Serum Concentrations from Extended PK Evaluation Sample Statistics	16.2.5.3
14.4.1.3	PK	Pharmacokinetic - Summary of Parameters of CetuGEX Serum Concentrations Sample Statistics	16.2.5.4
14.4.1.4	PK	Pharmacokinetic - Correlation of Parameters with Body Weight, BSA and BMI Correlation Coefficients	16.2.5.4

14.4.2.1	PK	Effect of CetuGEX Trough Levels After 1st, 2nd and 3rd Infusion on PFS Cox Regression Model	16.2.5.3 and 16.2.6.3
14.4.2.2	PK	Effect of CetuGEX Post-infusion Concentrations After 1st, 2nd and 3rd Infusion on PFS Cox Regression Model	16.2.5.3 and 16.2.6.3
14.4.2.3	PK	Effect of CetuGEX Trough Levels After 1st, 2nd and 3rd Infusion on CBR Logistic Regression Model	16.2.5.3 and 16.2.6.3
14.4.2.4	PK	Effect of CetuGEX Post-infusion Concentrations After 1st, 2nd and 3rd Infusion on CBR Logistic Regression Model	16.2.5.3 and 16.2.6.3
14.4.2.5	PK	Pharmacokinetic Parameter by Clinical Benefit Sample Statistics	16.2.5.3 and 16.2.6.3

Table Number	Population	Table Title / Summary	Supporting Listing
14.5 OTHER DATA ANALYSES			
14.5.1	ITT	Investigator and Centralized Tumor Assessment – Comparison of Best Overall Response Results	16.2.6.1.4 and 16.2.6.2.4
14.5.2	Safety	Anti-drug Antibodies	16.2.9.7
14.5.3	Safety	Hospitalization (Percentage of Individual Study Duration)	16.2.10..1
14.5.4.1	ITT	Cytokine Release Absolute Values	16.2.9.8 – 16.2.9.9
14.5.4.2	ITT	Cytokine Release Absolute Changes from Baseline	16.2.9.8 – 16.2.9.9

14.5.4.3	ITT	Cytokine Release Fold Changes from Baseline	16.2.9.8 – 16.2.9.9
14.5.4.4	ITT	Change of Cytokine Release from Cycle 0 Pre-Infusion to Cycle 0 Post-Infusion by Grades of Timely Related IRRs Sample Statistics	16.2.7 and 16.2.9.8
14.5.5.1	ITT	Immune Cell Counts Absolute Values	16.2.9.8 – 16.2.9.9
14.5.5.2	ITT	Immune Cell Counts Absolute Changes from Baseline	16.2.9.8 – 16.2.9.9
14.5.5.3	ITT	Immune Cell Counts Percentage Changes from Baseline	16.2.9.8 – 16.2.9.9
14.5.6.1	ITT	Quality of Life EORTC QLQ-C30 Global Health Status – Absolute Values	16.2.10.1
14.5.6.2	ITT	Quality of Life EORTC QLQ-C30 Global Health Status – Changes from Baseline	16.2.10.1
14.5.6.3	ITT	Quality of Life EORTC QLQ-C30 Global Health Status – Classified Changes from Baseline	16.2.10.1
14.5.6.4	ITT	Quality of Life EORTC QLQ-C30 Functional Scales – Absolute Values	16.2.10.1
14.5.6.5	ITT	Quality of Life EORTC QLQ-C30 Functional Scales – Changes from Baseline	16.2.10.1
14.5.6.6	ITT	Quality of Life EORTC QLQ-C30 Functional Scales – Classified Changes from Baseline	16.2.10.1

14.5.6.7	ITT	Quality of Life EORTC QLQ-C30 Symptom Scales – Absolute Values	16.2.10.1
14.5.6.8	ITT	Quality of Life EORTC QLQ-C30 Symptom Scales – Changes from Baseline	16.2.10.1
14.5.6.9	ITT	Quality of Life EORTC QLQ-C30 Symptom Scales – Classified Changes from Baseline	16.2.10.1
14.5.6.10	ITT	Quality of Life EORTC QLQ-C30 – Time (Months) to First Deterioration of at Least 10 Points - Log-Rank Test and Kaplan-Meier Analysis	16.2.10.1
14.5.7.1	ITT	Quality of Life EORTC QLQ-H&N35 Symptom Scales – Absolute Values	16.2.10.3
14.5.7.2	ITT	Quality of Life EORTC QLQ- H&N35 Symptom Scales – Changes from Baseline	16.2.10.3

15.2 Planned Listing Descriptions

The following are planned data and patient listings for protocol GEXMab52201. Listings will be numbered according to the nomenclature used to support the clinical study report. Listings will be ordered by patient. In addition the unique patient identification number will be displayed on all listings.

Listings may be split if more space is required using an additional last digit.

Listing Number	Listing Title / Summary
16.2.1.1	Study Completion and Discontinuation Status
16.2.1.2	Analysis Populations
16.2.1.3	Stratification Factors
16.2.2.1	Inclusion and Exclusion Criteria

Listing Number	Listing Title / Summary
16.2.2.2	Major Protocol Deviations
16.2.3	Patients Excluded From Analysis Populations
16.2.4.1	Demographic Data
16.2.4.2	Tumor Tissue
16.2.4.3	ECHO/MUGA Assessment, EGFR Expression, p16 Status, FcγRIIa and IIIa Allotypes
16.2.4.4	Physical Examination (Screening)
16.2.4.5	Medical History
16.2.4.6	SCCHN Diagnosis and History
16.2.4.9	Baseline Signs and Symptoms
16.2.4.10	Prior Anti-Cancer Drug Therapies
16.2.4.11	Prior Anti-Cancer Surgeries
16.2.4.12	Prior Anti-Cancer Radiotherapy
16.2.4.13	Visit Dates
16.2.5.1	Study Treatment Administration
16.2.5.2	Study Treatment Termination
16.2.5.3	5-Fluorouracil Administration
16.2.5.4	Cisplatin/Carboplatin Administration
16.2.5.5	Chemotherapy Termination
16.2.5.6.1	Pharmacokinetics - CetuGEX™ Serum Concentration
16.2.5.6.2	Pharmacokinetics - CetuGEX™ Serum Derived Parameters
16.2.6.1.1	Tumor Assessment (Investigator) – Target Lesions
16.2.6.1.2	Tumor Assessment (Investigator) – Non-Target Lesions

Listing Number	Listing Title / Summary
16.2.6.1.3	Tumor Assessment (Investigator) –New Lesions
16.2.6.1.4	Tumor Response Evaluation (Investigator)
16.2.6.2.1	Tumor Assessment (Independent Centralized Reading) – Target Lesions
16.2.6.2.2	Tumor Assessment (Independent Centralized Reading) – Non-Target Lesions
16.2.6.2.3	Tumor Assessment (Independent Centralized Reading) – New Lesions
16.2.6.2.4	Tumor Response Evaluation (Independent Centralized Reading)
16.2.6.3	Derived Efficacy Variables (BOR, Duration of Response, PFS, TTP, OS)
16.2.7	Adverse Events
16.2.8.1	Laboratory Data - Hematology
16.2.8.2	Laboratory Data - Biochemistry
16.2.8.3	Laboratory Data - Urinalysis
16.2.8.4	Pregnancy Test
16.2.9.1	Prior and Concomitant Medication
16.2.9.2	Pre-Medication
16.2.9.3	Post-Study Anti-Tumor Therapies
16.2.9.4	Vital Signs
16.2.9.5	ECG
16.2.9.6	ECOG Performance Status
16.2.9.7	ADAs
16.2.9.8	Cytokines
16.2.9.9	Immune Cell Status
16.2.10.1	Hospitalization

Listing Number	Listing Title / Summary
16.2.10.2	Quality of Life Questionnaire EORTC-QLQ-C30
16.2.10.3	Quality of Life Questionnaire EORTC-QLQ-H&N35

15.3 Planned Figure Descriptions

The following are planned summary figures for protocol GEXMab52201. Figures will number according to the nomenclature used to support the clinical study report.

Figure Number	Population	Figure Title / Summary	Supporting Table Number
14.5.1.1	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Investigator Assessment)	14.2.1.1
14.5.1.2	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on irRC)	14.2.2.1
14.5.1.3	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on RECIST 1.1)	14.2.2.1
14.5.2.1	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Investigator Assessment) by FcγRIIIa Receptor Status Subgroup	14.2.10.1
14.5.2.2	ITT/PP	Kaplan-Meier Plot of Progression Free Survival Independent Centralized Reading based on irRC) by FcγRIIIa Receptor Status Subgroup	14.2.10.2
14.5.2.3	ITT/PP	Kaplan-Meier Plot of Progression Free Survival Independent Centralized Reading based on RECIST 1.1) by FcγRIIIa Receptor Status Subgroup	14.2.10.2
14.5.3.1	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Investigator Assessment) by FcγRIIa Receptor Status Subgroup	14.2.11.1

Figure Number	Population	Figure Title / Summary	Supporting Table Number
14.5.3.2	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on irRC) by FcγRIIa Receptor Status Subgroup	14.2.11.2
14.5.3.3	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on RECIST 1.1) by FcγRIIa Receptor Status Subgroup	14.2.11.2
14.5.4.1	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Investigator Assessment) by p16 Status Subgroup	14.2.12.1
14.5.4.2	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on irRC) by p16 Status Subgroup	14.2.12.2
14.5.4.3	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on RECIST 1.1) by p16 Status Subgroup	14.2.12.2
14.5.5.1	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Investigator Assessment) by EGFR Intensity Subgroup	14.2.13.1
14.5.5.2	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on irRC) by EGFR Intensity Subgroup	14.2.13.2
14.5.5.3	ITT/PP	Kaplan-Meier Plot of Progression Free Survival (Independent Centralized Reading based on RECIST) by EGFR Expression Subgroup	14.2.13.2
14.5.5.4	ITT	Kaplan-Meier Plot of Progression Free Survival Landmark Analysis	14.2.13.2

Figure Number	Population	Figure Title / Summary	Supporting Table Number
14.5.6.1	ITT/PP	Kaplan-Meier Plot of Duration of Response (Investigator Assessment)	14.2.6.1
14.5.7	ITT/PP	Kaplan-Meier Plot of Overall Survival	14.2.8.1
14.5.8.1	ITT/PP	Kaplan-Meier Plot of Overall Survival by FcγRIIIa Allotypes Subgroup	14.2.14
14.5.8.2	ITT/PP	Kaplan-Meier Plot of Overall Survival by FcγRIIa Allotypes Subgroup	14.2.15
14.5.8.3	ITT/PP	Kaplan-Meier Plot of Overall Survival by p16 Status Subgroup	14.2.16
14.5.8.3	ITT/PP	Kaplan-Meier Plot of Overall Survival by EGFR Intensity Subgroup	14.2.17
14.5.8.4	ITT	Kaplan-Meier Plot of Overall Survival Landmark Analysis	14.2.17
14.5.9	ITT/PP	Kaplan-Meier Plot of Time to Treatment Failure	14.2.9.1
14.5.10	ITT	Maximum Percentage Change of Target Lesion Sizes From Baseline Waterfall Plots	14.2.6.1
14.5.11.1	PK	Correlation of Pharmacokinetic Parameters with Progression-free Survival Forest plot	
14.5.11.2	PK	Correlation of Pharmacokinetic Parameters with Clinical Benefit Forest plot	
14.5.12.1	ITT/PP	Cytokine Release – Absolute Values Scatterplot with Median and Interquartile Range	14.5.4.1

Figure Number	Population	Figure Title / Summary	Supporting Table Number
14.5.12.2	ITT/PP	Cytokine Release – Absolute Changes From Baseline Scatterplot with Median and Interquartile Range	14.5.4.1
14.5.12.3	ITT/PP	Cytokine Release – Fold Changes From Baseline Scatterplot with Median and Interquartile Range	14.5.4.1
14.5.13.1	ITT/PP	Immune cell counts –Absolute Values Scatterplot with Median and Interquartile Range	14.5.4.1
14.5.13.2	ITT/PP	Immune cell counts – Absolute Changes From Baseline Scatterplot with Median and Interquartile Range	14.5.4.1
14.5.13.3	ITT/PP	Immune cell counts – Percent Changes From Baseline Scatterplot with Median and Interquartile Range	14.5.4.1
14.5.14.1	PK	Extended Pharmacokinetic - Individual Time Courses of CetuGEX™ Concentrations	14.4.1
14.5.14.2	PK	Extended Pharmacokinetic - Individual Time Courses of CetuGEX™ Concentrations (log scale)	14.4.1
14.5.14.3	PK	Extended Pharmacokinetic - Individual Time Courses of CetuGEX™ Concentrations (log scale)	14.4.1
14.5.15.1	PK	Extended Pharmacokinetic – Parameters and Body Weight Scatterplots	14.4.1

Figure Number	Population	Figure Title / Summary	Supporting Table Number
14.5.15.2	PK	Extended Pharmacokinetic – Parameters and BMI Scatterplots	14.4.1
14.5.15.3	PK	Extended Pharmacokinetic – Parameters and BSA Scatterplots	14.4.1
14.5.16.1	PK	Pharmacokinetic CetuGEX™ - Concentrations in All Patients Boxplots	14.4.1
14.5.16.1	PK	Pharmacokinetic CetuGEX™ - Concentrations in All Patients (log scale) Boxplots	14.4.1