Study Protocol

# 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)

PROTOCOL DATE: February 06, 2015

ClinicalTrials.gov Identifier: NCT02052960

GLYCOTOPE

# PROTOCOL

**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)**

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| PRODUCT NAME/NUMBER: | CetuGEX™ |
| PROTOCOL NUMBER: | GEXMab52201 |
| EUDRACT NUMBER: | 2013-003695-13 |
| IND NUMBER: | 118026 |
| DEVELOPMENT PHASE: | Phase II |
| PROTOCOL DATE: | Final Version 4.0, 06 February 2015 |
| SPONSORED BY: | Glycotope GmbH<br>Robert-Rössle-Str. 10<br>D-13125 Berlin, Germany<br>Phone: +49 30 9489 2600<br>Fax: +49 30 9489 2609 |
| COORDINATING INVESTIGATOR | |
| CONTRACT RESEARCH ORGANIZATION: | |

# 1 APPROVAL SIGNATURES

PROTOCOL NUMBER: GEXMab52201

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. (The "RESGEX" Study)

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

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Date

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# 2 SYNOPSIS

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| PRODUCT NAME/NUMBER | CetuGEX™ |
| PROTOCOL NUMBER | GEXMab52201 |
| EUDRACT NUMBER | 2013-003695-13 |
| IND NUMBER | 118026 |
| DEVELOPMENT PHASE | Phase II |
| 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. (The "RESGEX" Study) |
| INDICATION | First line systemic treatment for stage III/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) |
| SPONSOR | Glycotope GmbH<br>Robert-Rössle-Str. 10<br>D-13125 Berlin, Germany |
| COORDINATING INVESTIGATOR | |
| OBJECTIVES | Primary:<br>To evaluate the efficacy of CetuGEX™ for the treatment of patients with stage III/IV recurrent and/or metastatic SCCHN as compared to cetuximab (both in combination with platinum-based chemotherapy) in terms of progression-free survival (PFS).<br>Secondary:<br>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).<br>To assess pharmacokinetic (PK) parameters and profiles of CetuGEX™.<br>To assess efficacy and safety based on genetic markers for immune response (Fc-gamma receptor [FcγR] allotypes) and biomarkers. |
| STUDY DESIGN | Randomized, controlled, multicenter, phase II study with first line treatment (six cycles of 5-fluorouracil and cisplatin in combination with CetuGEX™ vs. combination with cetuximab) followed by single-agent maintenance therapy (CetuGEX™ or cetuximab respectively). Following the first cycle, substitution of cisplatin by carboplatin is allowed in case of toxicity. Randomization to CetuGEX™ vs. cetuximab will be performed using a 1:1 ratio.<br>Randomization will be stratified by:<br>• FcγRIIIa status (FF or FV or VV)<br>• Oral cavity and oropharynx vs. other locations<br>• Locally recurrent vs. metastatic disease |

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| | • Epidermal growth factor receptor (EGFR) treatment naïve vs. EGFR treatment as part of multimodal therapy. |
| DATA SAFETY MONITORING BOARD | 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). After this, regular 6-monthly meetings will be scheduled until all ongoing patients have been treated for at least 6 months. For important reasons additional meetings may be scheduled by sponsor, medical monitor, coordinating investigator or DSMB as long as patients are at risk. |
| PLANNED NUMBER OF PATIENTS | A total of approximately 240 randomized patients. |
| STUDY ENTRY CRITERIA | Inclusion criteria:<br>1. Patients with histologically confirmed recurrent and/or metastatic SCCHN not eligible for local treatment.<br>2. Patients with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.<br>3. Patients aged at least 18 years at screening.<br>4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.<br>5. Minimum life expectancy of 3 months.<br>6. Tissue samples available for specific disease and therapy related biological assessments.<br>7. If female and of childbearing potential, is non-lactating and has negative pregnancy test results at screening and prior to randomization.<br>8. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or willing to use highly effective contraceptives during study participation until 6 months after last administration of any study medication, particularly cisplatin or carboplatin, with a failure rate < 1% according to the Note for Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (CPMP/ICH/286/95) of the European Medicines Agency (EMA).<br><br>Male patients who have partners of childbearing potential have to confirm adequate use of highly effective contraceptives during study participation until 6 months after last administration of any study medication, particularly cisplatin or carboplatin, as well.<br>9. Willing and able to comply with the protocol.<br>10. Willing and able to provide written informed consent.<br>Exclusion criteria:<br>1. Prior systemic chemotherapy, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to randomization.<br>2. Cetuximab or other EGFR targeting agent treatment, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to randomization.<br>3. Surgery (other than minor interventions like diagnostic biopsy or intravenous port implantation) or irradiation within 30 days before randomization. |

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| | 4. Concomitant anti-tumor therapy or concomitant immunotherapy, live vaccines including yellow fever vaccination (as per cisplatinum Summary of Product Characteristics [SmPC]).<br>5. Concomitant corticosteroid treatment unless specified within the protocol.<br>6. Clinical evidence of brain metastasis or leptomeningeal involvement.<br>7. Patients with nasopharyngeal tumors.<br>8. Concomitant malignant disease, except for adequately treated tumors with high likelihood of being cured (e.g., basal cell cancer of the skin, cervical cancer or breast cancer in situ). Patients with other previous malignancies but without evidence of disease for at least 5 years will be allowed to enter the study.<br>9. Patients with renal or hepatic impairment (serum creatinine and bilirubin > 1.5 fold above the upper limit of normal ranges, creatinine clearance < 60 ml/min, and transaminase > 5 fold above the upper limit of normal ranges) and patients with hematology parameters outside the normal ranges (hemoglobin < 9 g/dl, absolute neutrophil count < $1500/mm^3$ and platelet count < $10^5/mm^3$) at screening as well as patients with impaired auditory function or platinum-related neuropathy.<br>10. Clinically active infections ≥ Grade 2 using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4 and/or requiring intravenous antibiotics.<br>11. Known active hepatitis B or C.<br>12. Known human immunodeficiency virus (HIV) infection.<br>13. Myocardial infarction within 6 months prior to screening.<br>14. Symptomatic congestive heart failure (New York Heart Association [NYHA] Grade 3 or 4), unstable angina pectoris within 6 months prior to screening, significant cardiac arrhythmia, history of stroke or transient ischemic attack within 1 year prior to screening.<br>15. History of keratitis requiring medical interventions within the last 5 years or interstitial lung disease.<br>16. Patients with any other disorder that, in the opinion of the investigator, might interfere with the conduct of the study.<br>17. Patients with an unstable condition (e.g., psychiatric disorder, a recent history of drug or alcohol abuse, interfering with study compliance, within 6 months prior to screening) or otherwise thought to be unreliable or incapable of complying with the requirements of the protocol.<br>18. Patients institutionalized by official means or court order.<br>19. Receipt of any other investigational medicinal product within the last 30 days before randomization or any previous CetuGEX™ administration.<br>20. Prior allergic reaction to a monoclonal antibody, grade 3 infusion related reaction (IRR) or any grade 4 reaction to a monoclonal antibody.<br>21. Known sensitivity to any component of the investigational medicinal product (IMP) and medication used in this study. |
| INVESTIGATIONAL PRODUCT | Active substance: CetuGEX™, a chimeric monoclonal immunoglobulin G (IgG) antibody binding to the EGFR which is glyco-optimized and fully human glycosylated with an enhanced antibody-dependent cell-mediated |

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| | cytotoxicity (ADCC) activity against tumor cells.<br>Dose, route, frequency: Solution for infusion, to be administered once weekly. The initial dose will be 990 mg; subsequent doses will be 720 mg once weekly. The initial dose will be given as split-dose over 2 days with a priming dose of 60 mg on Day 0 and the remaining dose of 930 mg on Day 1. |
| REFERENCE PRODUCT | Active substance: cetuximab, a chimeric monoclonal IgG antibody binding to the EGFR.<br>Dose, route, frequency: Solution for infusion, to be administered once weekly. The initial dose will be 400 mg/m$^2$ body surface area (BSA), subsequent doses will be 250 mg/m$^2$ BSA each. The maximum infusion rate for the initial dose must not exceed 5 mg/min. The maximum infusion rate for subsequent doses must not exceed 10 mg/min. |
| NON-INVESTIGATIONAL PRODUCTS | Active substance: 5-Fluorouracil (5-FU)<br>Dose, route, frequency: Solution for intravenous injection. Doses of 1000 mg/m$^2$ BSA per day will be administered every 3 weeks (1 cycle of cisplatin or carboplatin treatment) as continuous intravenous infusion on Days 1-4 of each cycle.<br>Active substance: Cisplatin<br>Dose, route, frequency: Solution for infusion. Doses of 100 mg/m$^2$ BSA will be administered every 3 weeks (1 cycle), on Day 1 of each cycle.<br>Active substance: Carboplatin<br>Carboplatin may substitute cisplatin following the first cycle of therapy in case of toxicity.<br>Dose, route, frequency: Solution for infusion, to be administered at an area under the curve (AUC) of 5 mg/mL/min (using the Calvert formula for calculation) as a 1-hour intravenous infusion every 3 weeks (1 cycle), on Day 1 of each cycle. As per SmPC, carboplatin may not be used in patients with bleeding tumors.<br>Cisplatin (which is allowed to be substituted by carboplatin following the first cycle in case of toxicity) in combination with 5-FU will be administered for a maximum of 6 cycles, starting approximately 1 hour after CetuGEX™/cetuximab infusion on Day 1 of each cycle. |
| TREATMENT REGIMENS | <u>Combination treatment phase:</u><br>Eligible patients will be randomized to receive as first line treatment either CetuGEX™ or cetuximab in combination with chemotherapy (5-FU and cisplatin) for the maximum duration of 6 cycles of combined treatment. In case of toxicity, chemotherapy can be dose reduced, discontinued or, if later than the first cycle, switched to carboplatin. If corticosteroids are required, e.g., as premedication to prevent infusion related reactions, dexamethasone is to be used (unless contraindicated). If chemotherapy is discontinued earlier for any other reason apart from progression, patients will start the maintenance phase at that time.<br><u>Single-agent maintenance phase:</u><br>After completion or discontinuation of combination chemotherapy for any other reason apart from progression, the treatment will be followed by maintenance therapy receiving single agent CetuGEX™ or cetuximab, respectively. Single-agent maintenance therapy will be continued until progression of disease.<br><u>Follow-up:</u> |

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| | 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 regular treatment discontinuation due to disease progression, the Safety Visit is identical to the Final Examination Visit.<br>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. |
| PLANNED STUDY SITES | Approximately 40 study sites in Europe and the USA. |
| CRITERIA FOR EVALUATION | Primary efficacy endpoint:<br>Progression-free survival (PFS) as assessed by the investigator.<br><br>Secondary endpoints<br><br>Efficacy endpoints:<br>• PFS as assessed by independent centralized reading<br>• Objective response rate (ORR; i.e., complete response [CR] + partial response [PR]) at the end of combination treatment<br>• Best overall response rates (including maintenance therapy treatment)<br>• Clinical benefit rate (CBR; i.e., CR + PR + stable disease [SD])<br>• Duration of response<br>• Overall survival (OS)<br>• Time to treatment failure (TTF)<br>• QoL scores as assessed by European Oncology Research Trials Committee (EORTC) quality of life questionnaires (QLQ) EORTC-QLQ-C30 and EORTC-QLQ-H&N35.<br><br>In addition, PFS and all secondary efficacy endpoints listed above will be analyzed by FcγRIIIa-allotype subgroups (i.e., FF, FV, and VV), by p16 status, by EGFR status, and other potential parameters, unless the sample sizes in subgroups are too low.<br><br>Pharmacokinetic endpoints:<br>Antibody trough levels and PK profiles of CetuGEX™ will be assessed throughout the study.<br><br>Safety endpoints:<br>• Incidence of adverse events (AEs) and serious AEs, including incidence of target/class-specific side effects (skin reactions, diarrhea)<br>• IRRs<br>• Physical and laboratory assessments<br>• Vital signs<br>• Electrocardiogram (ECG)<br>In addition, the incidence of AEs will be analyzed by FcγRIIIa-allotype subgroups (FF, FV, VV).<br><br>Exploratory endpoints:<br>• Immunogenicity: incidence of anti-drug antibodies (ADAs)<br>• Immunological parameters: cytokine levels and immune cell status. |

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| STATISTICAL METHODS | Analysis Populations<br>• Intention-to-treat (ITT) population – all randomized patients<br>• Safety Population – all patients having received treatment at least once.<br>• Per-protocol (PP) Population – all patients in the ITT population and who have received treatment at least once without major protocol deviations as defined in the statistical analysis plan and finally decided in a Data Review Meeting before data base lock.<br>• Pharmacokinetic Population – all randomized patients including the subset of patients who had blood samples collected for PK non-compartmental profiling, who had at least one measureable CetuGEX™ antibody concentration.<br>Efficacy Analyses<br>Primary endpoint of the trial is PFS defined as time from randomization until disease progression (as assessed by the investigator) or death of any cause. If the patient is alive and without progression at the last time of observation, the PFS time will be censored at the time of the last tumor assessment.<br>The primary efficacy analysis for PFS will be based on the ITT population. A log-rank test will be used to test the null hypothesis of equal treatment effects at an overall significance level of 0.05. 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. As a sensitivity analysis, a proportional hazards regression model will be applied and the effects of the stratification factors, the p16 status, and the EGFR status will be estimated.<br>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.<br>The analysis will be repeated for the PP population as a sensitivity analysis.<br>A Chi-squared test will be performed to evaluate the effects of treatment on response rates according to RECIST. A logistic regression model will be fit to estimate odds ratios for the association of stratification factors, the p16 status, and the EGFR status with response categories. 95%-confidence intervals will be calculated for the treatment differences in response rates.<br>Overall survival and TTF will be analyzed analogously to PFS on an ITT basis.<br>If subgroup sample sizes allow, analyses of the primary and secondary efficacy endpoints will be repeated for the FcγRIIIa-allotype subgroups (i.e., FF, FV, and VV), the p16 status subgroups as well as the EGFR status subgroups s, omitting the FcγRIIIa factor, the p16 status and the EGFR status factor, respectively.<br>Pharmacokinetic Analyses<br>A population PK analysis will be performed with samples from all patients. In addition, non-compartmental analyses to evaluate the PK profile will be performed for a subgroup of approximately 30 patients.<br>Safety Analyses<br>All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and analyzed on Preferred Term (PT) and System Organ Class (SOC) level.<br>Treatment emergent adverse events (TEAEs) are defined as any AE which started or deteriorated at or after start of treatment. Incidences for TEAE will be calculated on PT level, on SOC level and globally by treatment group. On |

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| | each analysis level, a patient will be counted only once. Frequencies for TEAE will also be given for causality and severity graded according to Common Toxicity Criteria (NCI-CTC; AE criteria Version 4.0). In addition, toxicity as evaluated via incidence of AEs will be analyzed by Fc-gamma receptor allotype subgroups (FF, FV, VV) The incidences of ADA will be summarized in frequency tables per treatment arm.<br>For biomarkers as well as hematology and biochemistry laboratory variables, descriptive summaries of observed values and changes from baseline will be presented by treatment arm. The assessments of laboratory variables concerning reference ranges and clinical relevance will be tabulated by visit for each clinical laboratory parameter by treatment arm (frequency tables). Additionally, for each laboratory parameter, shifts in assessments from baseline to the last on-study value will be presented by treatment arm (shift tables).<br>Descriptive summaries of observed values and changes from baseline will be calculated for vital signs. These summaries will be presented by visit and treatment arm.<br>Descriptive summaries of observed values and changes from baseline will be calculated for ECG variables. QT will be corrected according to Bazett. Frequency and shift tables will be presented for the classified values of $QT_c$ as given by the International Conference on Harmonisation (ICH)-E14, as well as for the overall clinical assessment.<br>Finding in post-baseline physical examinations will be documented as AE and analyzed as part of the general AE analysis. |
| SAMPLE SIZE DETERMINATION | 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:<br>• The median PFS in the control arm is expected to be 5.6 months post randomization.<br>• It is expected that the median PFS in the CetuGEX™ arm can be increased to 8.4 months corresponding to a hazard rate of 0.67.<br>• The anticipated recruitment time is 24 months, anticipated time until PFS events are reached is 12 months after randomization of the last patient, follow-up for OS for at least 24 months after randomization of the last patient.<br>• 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.<br>• Patients will be randomized in a 1:1 ratio.<br>• The overall two-sided significance level will be 0.05 and the power to be maintained 80%.<br>Based on these assumptions, approximately 240 patients have to be randomized to observe the required overall number of 192 events.<br>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. |
| STUDY AND TREATMENT | The overall study duration is expected to be approximately 48 months, assuming 24 months for recruitment and follow-up of the patients for at least |

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| DURATION | 24 months after randomization of the last patient).<br>The sequence and maximum duration of the study periods and treatment for each patient will be as follows:<br>1. Screening: to be performed within 28 days prior to first infusion to assess general eligibility for this study.<br>2. Combination treatment phase: maximum of 6 treatment cycles of combination treatment.<br>3. Single-agent maintenance treatment: until disease progression.<br>4. Follow-up: at least 24 months after randomization of the last patient.<br>The patients will be treated until disease progression. |

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# 4 LIST OF ABBREVIATIONS

| | |
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| ADA | Anti-drug antibody |
| ADCC | Antibody dependent cell cytotoxicity |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AUC | Area under the curve |
| BMI | Body mass index |
| BSA | Body surface area |
| BUN | Blood urea nitrogen |
| CBR | Clinical benefit response |
| CR | Complete response |
| CRA | Clinical research associate |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTC | Common Toxicity Criteria |
| DSMB | Data safety monitoring board |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EGFR | Epidermal growth factor receptor |
| EORTC | European Oncology Research Trials Committee |
| FcγR | Fc-gamma receptor |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| IgG | Immunoglobulin G |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IRR | Infusion-related reaction |
| irRC | Immune-related response criteria |
| ITT | Intention-to-treat |
| IWRS | Interactive web response system |
| KRAS | Kirsten rat sarcoma viral oncogene |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MUGA | Multiple gated acquisition scan |

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| nIMP | Non-investigational medicinal product |
| NCI | National Cancer Institute |
| NYHA | New York Heart Association |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progression disease |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PP | Per-protocol |
| PR | Partial response |
| QLQ | Quality of life questionnaire |
| QoL | Quality of life |
| 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 |
| SmPC | Summary of product characteristics |
| TEAE | Treatment emergent adverse event |
| TTF | Time to treatment failure |
| UADR | Unexpected adverse drug reaction |
| 5-FU | 5-fluorouracil |

# 5 INTRODUCTION

## 5.1 Background

Cetuximab (Erbitux®) is a chimeric immunoglobulin G (IgG) 1 mouse-human antibody targeted against the extracellular domain of the epidermal growth factor receptor (EGFR) with high specificity and affinity and is produced in the murine myeloma cell line SP2/0. Cetuximab is approved and marketed for clinical use as a single agent or in combination with chemotherapy for the treatment of EGFR-expressing, KRAS-non mutated, metastatic colorectal cancer. Cetuximab is also approved for use in combination with radiation therapy for treating squamous cell carcinoma of the head and neck (SCCHN) or in combination with platinum-based chemotherapy and 5-fluorouracil (5-FU) for the treatment of recurrent and/or metastatic SCCHN.

CetuGEX™ is an improved second-generation antibody, designed to fully retain the antigen binding properties of cetuximab, e.g., affinity, specificity and EGFR inhibition, and is improved by fully human glycosylation and glycosylation optimization in its anti-tumor efficacy mediated by antibody dependent cell cytotoxicity (ADCC) and its lack of potentially immunogenic carbohydrate chains in order to improve drug efficacy and to reduce side effects. To obtain the fully human and optimized glycosylation, CetuGEX™ is produced in a cell line of the GlycoExpress™ system. Improvement of ADCC-mediated anti-tumor efficacy against EGFR positive tumor cells was demonstrated in *in vitro* studies in comparison to cetuximab. Adverse effects are likely to be reduced since non-human carbohydrate structures of cetuximab which result from its rodent cell based production system do not occur on CetuGEX™. The Gal-Gal carbohydrate and also other non-human structures present on cetuximab such as the neuraminic acid NeuGc are potentially immunogenic and known to be responsible for hypersensitivity reactions following cetuximab therapy.

Glycotope GmbH intends to develop CetuGEX™ in various tumor indications, based on target expression and patient experience starting in patients with recurrent/metastatic SCCHN.

### 5.1.1 Study Drug – Mode of Action

CetuGEX™ specifically binds to the EGFR and acts as a competitive antagonist at the ligand binding site of EGFR. The antigen specificity is exactly the same as for cetuximab.

An increasing body of data from various anti-tumor antibodies, such as rituximab (MabThera®), trastuzumab (Herceptin®) and cetuximab, indicates that the ADCC activity is the key mode of action of therapeutic anti-tumor antibodies in patients. Glycosylation structure especially the absence of core fucose and the presence of bisecting GlcNAc within the antibody Fc part are known key structures for an increased ADCC activity. Core fucose is present and bisecting GlcNAc absent on the Fc part glycans produced in rodent systems such as CHO and SP2/0 as it is the case for cetuximab. Therefore, CetuGEX™ was glyco-optimized to contain bisecting GlcNAc and largely reduced core fucose of Fc glycans in order to achieve improved ADCC activity in a fully human

glycosylation setting. *In vitro* assays show that glyco-optimization of CetuGEX™ leads to a higher binding affinity of the molecule to the Fc-gamma receptor IIIa (FcγRIIIa) on natural killer cells, thereby enhancing ADCC activity and probably broadening the subpopulations per indication benefitting from such an antibody.

Two allotypes of this receptor are known which have different affinities to human IgG1 depending on the glycosylation of the Fc tail of IgG1. While antibodies with core fucose such as rituximab, trastuzumab and cetuximab bind to the V allotype inducing some ADCC activity in homozygous patients, they show a strongly reduced binding to the F allotype with little or no ADCC activity in homozygous (FF) or heterozygous (FV) patients. Addition of bisecting GlcNAc and/or reduction of core fucose at the Fc part glycan results in an increase of the binding affinity to the FcγRIIIa and an increase in ADCC activity. This increase is most pronounced for F allele types thereby broadening the patient coverage for the ADCC-mediated anti-tumor effect of antibodies[1, 2, 3, 4]. This is also reflected by studies showing that patients with the higher affinity FcγRIIIa V allotype (VV) have a better clinical outcome than those with the lower affinity FcγRIIIa F allotype[5, 6, 7, 8].

The key mode of action of ADCC-mediated killing is improved for CetuGEX™ compared to cetuximab as tested in human assay systems. The degree of ADCC increase depends on the FcγRIIIa polymorphism status of the effector cells. The ADCC increase compared to cetuximab is higher for effector cells from donors comprising the FcγRIIIa F variant (~50-fold on FF, ~20-fold on FV) than for effector cells being homozygous for the V variant (~10-fold on VV). By achieving a ~10-fold improvement of anti-tumor ADCC activity with homozygous FcγRIIIa V alleles (the one best working for cetuximab) CetuGEX™ even reaches comparable absolute tumor cell killing rates with all receptor variants including the F allotypes. Thereby, the suitable patient spectrum is potentially broadened by making effective anti-tumor ADCC activities available also for the 80% of the patients bearing the lower affinity FcγRIIIa (FV and FF).

It is expected that due to improved ADCC activity for all FcγRIIIa allotypes CetuGEX™ will show comparable anti-tumor activity against tumor cells largely independent on KRAS status (KRAS wild types and mutants) because the downstream effector mechanisms mediated by EGFR are less relevant for the therapeutic effect.

### 5.1.2 GlycoExpress™ (GEX™)

The anti-tumor activity of cetuximab was improved manifold by glycolization-optimization using the proprietary production system GlycoExpress™ (GEX™). GlycoExpress™ is a toolbox consisting of a series of newly developed human glyco-engineered cell lines biotechnologically optimized not only for product optimization but also for high yield protein expression and fully reproducible quality from batch to batch. The GlycoExpress™ system is fully serum and virus free and well documented, rendering it suitable for pharmaceutical production. Three antibodies and 1 non-antibody manufactured using GlycoExpress™ are currently being tested in human clinical studies.

## 5.2 Clinical Experience

A phase 1 study has been performed at 5 sites in Germany, Italy and Switzerland. This was a dose escalation, multicenter study evaluating the safety, tolerability and pharmacokinetics of CetuGEX™ after intravenous administration in patients with locally advanced and/or metastatic solid cancers. The effect of CetuGEX™ on the development of anti-drug antibodies and on tumor response was also evaluated. This was an open-label, dose-escalation study in a 3 + 3 design, in which 3 to 6 eligible patients were enrolled into each of the sequential ascending dosing cohorts. CetuGEX™ was administered in 500 ml physiologic saline solution by intravenous infusion over a 2 or 3 hour-period, later amended to a more complex scheme.

Until the relevant cut-off date for the clinical study report, 40 patients were treated on a weekly (8 dose levels from 12 to 1370 mg flat dose), or once-every-two-weeks (990 mg flat) schedule. Twenty-four patients had received at least 8 weekly doses and were thus evaluable for activity. The most frequently observed related treatment-emergent adverse events (TEAEs), all grades, apart from infusion related reactions (IRRs), were acneiform dermatitis (25%), skin rash (28%), asthenia (15%), fatigue (13%) and nausea (10%). Observed IRRs, all grades, (70%), virtually restricted to the first infusion and most of mild or moderate grade, were associated with cytokine secretion: IL-6, IL-8, TNFα, IFNγ and IP-10 as marker of macrophage activation. An optimized infusion scheme and premedication reduced the incidence of IRRs. Activity was seen over all dose levels. One patient with non-small cell lung cancer achieved a complete response. Another 2 patients with esophageal and gastric cancer without measurable disease at study entry had marked improvement of symptoms and normalization of tumor markers. Additional 15 patients had stable disease lasting from 8 weeks to over a year, including several minor responses, leading to a clinical benefit rate of 45% (18/40) in the overall and 75% (18/24) in the PP population. Pharmacokinetics (PK) supports weekly and bi-weekly dosing. One additional patient was included into the study after the cut-off date and results of this patient are not yet included within the summary presented above.

## 5.3 Summary of Potential Risks and Benefits

As an optimized (bio-superior) second-generation antibody of the marketed product cetuximab, CetuGEX™ has the potential to become a considerably more active anti-EGFR antibody due to its significantly higher tumor-specific ADCC activity caused by the humanized and optimized glycosylation in the production process. At the same time the removal of non-human immunogenic Gal-Gal carbohydrate structures is expected to avoid the severe hypersensitivity reactions reported to be caused by non-human carbohydrate structures of cetuximab (in some geographical regions in about 22% of patients treated with cetuximab). Furthermore, CetuGEX™ opens the chance of therapeutic activity in otherwise unsuitable patients. As the key anti-tumor mode of action, ADCC is expected to be not only pronounced in patients with FcγRIIIa receptor allele status VV (8 - 27 % of the population) but also in those with FF and FV allotypes (73 - 92 % of the population), while the latter show no or very low anti-tumor ADCC activity with cetuximab. Therefore extended patient populations may benefit from the potential anti-tumor activity of CetuGEX™ in the clinic. The well-known cutaneous

toxicity occurring in up to 90% of patients treated with the approved anti-EGFR antibodies cetuximab and panitumumab (Vectibix®) is clearly linked to the EGFR inhibition in the skin and correlates with the anti-tumor efficacy of the antibody. This was also observed in the patients treated with CetuGEX™, although from first evidence with lower incidence and grade. The phase 1 study showed reasonable tolerability with an expected high incidence of IRRs (mostly grades 1 and 2, few grade 3 and no grade 4) in conjunction with a considerable activity, given the far advanced cancer population.

Immediate allergic infusion reactions are unlikely; however IRRs of low grade were very common with this compound. As in general, although it didn't happen in the reported study, any infusion reaction has the potential to occur as life threatening severe reaction like a hypertensive crisis associated with neurologic signs and symptoms, wheezing, oxygen desaturation, chest pain, headaches, rigors, and diaphoresis, cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, or hypotension, monitoring for these events will be cautiously undertaken.

In conclusion, the benefit-risk balance is deemed positive.

## 5.4 Rationale

Cancers of the head and neck, primarily tumors of the oral cavity, pharynx and larynx, account for > 5% of all malignancies. Most head and neck cancers, approximately 90% in Western societies, are SCCHN. Tobacco and alcohol use are the most important risk factors for the development of head and neck cancers. Beside cigarette smoke, chewing of tobacco increases the risk for cancers of the oral cavity. Smoking pipes may lead to cancer of the lip and tongue. The detrimental effect of tobacco is further enhanced by alcohol abuse and by poor oral hygiene. Further risk factors are virus infections caused by Epstein-Barr virus and human papilloma viruses. Due to the drinking and smoking habits, many patients also suffer from concomitant diseases such as coronary artery disease, chronic bronchitis or liver cirrhosis.

Treatment of head and neck cancer varies depending on localization, spread and histological subtype. The primary therapy option is surgery with excision of the primary tumor combined with extensive neck dissection. For advanced-stage disease, surgery and radiotherapy are often combined with chemotherapy usually delivered postoperatively. For unresectable disease, combined chemotherapy and radiotherapy has become the standard of care. The majority of patients presenting in a more advanced disease stage will eventually relapse either loco regional and/or at distant sites[9,10]. Patients with recurrent and/or metastatic disease who are not candidates for local therapies are usually offered chemotherapy, with the goal of prolonging survival and controlling symptoms. Platinum based chemotherapy is the current standard of care in patients with recurrent and/or metastatic SCCHN and since 2008 a new targeted therapy, cetuximab, showed benefit by prolonging overall survival in addition to platinum-based chemotherapy and 5-FU without modifying the characteristic AE profile of platinum-based chemotherapy and without negative impact on quality of life (QoL). Platinum based chemotherapy plus cetuximab is the current standard of care in patients with recurrent and/or metastatic SCCHN[9]. Recurrent and metastatic SCCHN still carries a poor prognosis. The median

survival of patients with recurrent and/or metastatic SSCHN is 6-9 months and the 1-year survival is 20-40%[9].

The clinical conduct of this study is planned in accordance to the guidance document of the International Conference of Harmonization (ICH) on Good Clinical Practice (GCP) and study design is chosen in accordance with the published guidelines on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIgs) (EMA/CHMP/BPWP/94033/2007), on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) and on the evaluation of anticancer medicinal products in man (CHMP/EWP/205/95).

# 6 OBJECTIVES

## 6.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of CetuGEX™ for the treatment of patients with stage III/IV recurrent and/or metastatic SCCHN as compared to cetuximab (both in combination with platinum-based chemotherapy) in terms of PFS.

## 6.2 Secondary Objectives

Secondary objectives are as follows:

1. To evaluate further efficacy criteria, safety and 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).
2. To assess PK parameters and profiles of CetuGEX™.
3. To assess efficacy and safety based on genetic markers for immune response (FcγR allotypes) and biomarkers.

# 7 STUDY DESIGN

## 7.1 Overall Study Design and Plan

### 7.1.1 Overview

This is a phase II, randomized, controlled, multicenter 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 randomization to CetuGEX™ vs. cetuximab will be performed using a 1:1 ratio and 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.

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 chemotherapy (5-FU and cisplatin) for the maximum duration of 6 cycles of combined treatment. In case of toxicity, chemotherapy can be dose 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 apart from 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.

An overview on the duration of each study period as well as the overall study duration is provided in Section 10.2.

### 7.1.2 Endpoints

The primary efficacy endpoint is the progression-free survival (PFS) as assessed by the investigator.

Secondary endpoints are:

Efficacy endpoints:

- PFS as assessed by independent centralized reading
- Objective response rate (ORR; i.e., complete response [CR] + partial response [PR]) at the end of combination treatment
- Best overall response rates (including maintenance therapy treatment)
- Clinical benefit rate (CBR; i.e., CR + PR + stable disease [SD])
- Duration of response
- Overall survival (OS)
- Time to treatment failure (TTF)
- QoL scores as assessed by European Oncology Research Trials Committee (EORTC) QoL questionnaires (QLQ) EORTC-QLQ-C30 and EORTC-QLQ-H&N35.

In addition, PFS and all secondary efficacy endpoints listed above will be analyzed by FcγRIIIa-allotype subgroups (i.e., FF, FV and VV), by p16 status, by EGFR status, and other potential parameters, unless the sample sizes in subgroups are too low.

Pharmacokinetic endpoints:

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

Safety endpoints are:

- Incidence of AEs and serious AEs, including incidence of target/class-specific side effects (skin reactions, diarrhea)
- IRRs
- Physical and laboratory assessments
- Vital signs
- Electrocardiogram (ECG)

In addition, the incidence of AEs will be analyzed by FcγRIIIa-allotype subgroups (FF, FV, VV).

Exploratory endpoints are:

- Immunogenicity: incidence of anti-drug antibodies (ADAs)
- Immunological parameters: cytokine levels and immune cell status.

## 7.2 Discussion of Study Design

The study is designed as a 2-arm study in patients with SCCHN to assess the efficacy and safety of CetuGEX™ as compared to cetuximab, both in combination with platinum-based chemotherapy and thereafter as single-agent maintenance therapy until progression of disease (PD) in patients with recurrent or metastatic SCCHN.

Cetuximab as well as CetuGEX™ are chimeric monoclonal IgG antibodies binding to the EGFR, which is overexpressed in more than 95% of SCCHN patients. Both cetuximab and CetuGEX™ are acting as competitive agonists at the ligand-binding site of EGFR and thus interrupt the signaling pathways and induce apoptotic cell death to EGFR expressing tumor cells. Cetuximab has received marketing authorization for the treatment of patients with SCCHN, either in combination with radiation therapy for locally advanced disease or in combination with platinum-based chemotherapy for patients with recurrent or metastatic SCCHN and therefore was selected as active control treatment in this study.

Antibody dependent cellular cytotoxicity, one of the main antitumor mechanisms of monoclonal antibodies of the IgG1 class, is mediated by surface receptors on immune-effector cells belonging to the FcγR family. The activity of cetuximab is strongly related to the V allotype of the FcγRIIIa and most prevalent when homozygously expressed (VV allotype). CetuGEX™ does not show this dependency on FcγRIIIa phenotypes from pre-clinical experience and may as well be effective in patients with FF and FV-allotypes. This is most probably depending on the glycosylation status of the Fc part of the antibody, which has been improved for CetuGEX™ in contrast to cetuximab. One goal of this study is to confirm this pre-clinically observed independency on FcγRIIIa phenotypes in clinical practice.

Eligible study population are patients aged at least 18 years at screening, with metastatic and/or recurrent, stages III or IV SCCHN, not eligible for local treatment.

## 7.3 Study Site(s)

The study will take place at approximately 40 sites in Europe and the USA. Each site is anticipated to screen a sufficient number of patients to be able to randomize a total of approximately 240 patients.

## 7.4 Point of Contact

A point of contact will be identified to provide information to patients about where to obtain information on the study, the rights of the patient, and whom to contact in case of study-related injury. This information will be provided in the patient information and informed consent form (ICF).

# 8 PATIENT POPULATION

## 8.1 Selection of Study Population and Diagnosis

It is planned to randomize approximately 240 adult patients with stage III/IV recurrent and/or metastatic SCCHN. An enrollment log of enrolled patients must be maintained at each study site.

## 8.2 Study Entry Criteria

### 8.2.1 Inclusion Criteria

A patient will be eligible for study participation if the patient meets all of the following criteria:

1. Patients with histologically confirmed recurrent and/or metastatic SCCHN not eligible for local treatment.
2. Patients with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
3. Patients aged at least 18 years at screening.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
5. Minimum life expectancy of 3 months.
6. Tissue samples available for specific disease and therapy related biological assessments.
7. If female and of childbearing potential, is non-lactating and has negative pregnancy test results at screening and prior to randomization.
8. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or willing to use highly effective contraceptives during study participation until 6 months after last administration of any study medication, particularly cisplatin or carboplatin, with a failure rate < 1% according to the Note for Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (CPMP/ICH/286/95) of the European Medicines Agency (EMA).
   Male patients who have partners of childbearing potential have to confirm adequate use of highly effective contraceptives during study participation until 6 months after last administration of any study medication, particularly cisplatin or carboplatin, as well.
9. Willing and able to comply with the protocol.
10. Willing and able to provide written informed consent.

### 8.2.2 Exclusion Criteria

A patient will be excluded from the study if the patient meets any of the following criteria:

1. Prior systemic chemotherapy, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to randomization.
2. Cetuximab or other EGFR targeting agent treatment, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to randomization.
3. Surgery (other than minor interventions like diagnostic biopsy or intravenous port implantation) or irradiation within 30 days before randomization.
4. Concomitant anti-tumor therapy or concomitant immunotherapy, live vaccines including yellow fever vaccination (as per cisplatinum Summary of Product Characteristics [SmPC, Appendix F]).
5. Concomitant corticosteroid treatment unless specified within the protocol.
6. Clinical evidence of brain metastasis or leptomeningeal involvement.
7. Patients with nasopharyngeal tumors.
8. Concomitant malignant disease, except for adequately treated tumors with high likelihood of being cured (e.g., basal cell cancer of the skin, cervical cancer or breast cancer in situ). Patients with previous malignancies but without evidence of disease for at least 5 years will be allowed to enter the study.
9. Patients with renal or hepatic impairment (serum creatinine and bilirubin > 1.5 fold above the upper limit of normal ranges, creatinine clearance < 60 ml/min, and transaminase > 5 fold above the upper limit of normal ranges) and patients with hematology parameters outside the normal ranges (hemoglobin < 9 g/dl, absolute neutrophil count < 1500/$mm^3$ and platelet count < $10^5$/$mm^3$) at screening as well as patients with impaired auditory function or platinum-related neuropathy.
10. Clinically active infections ≥ Grade 2 using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4 and/or requiring intravenous antibiotics.
11. Known active hepatitis B or C.
12. Known human immunodeficiency virus (HIV) infection.
13. Myocardial infarction within 6 months prior to screening.
14. Symptomatic congestive heart failure (New York Heart Association [NYHA] Grade 3 or 4), unstable angina pectoris within 6 months prior to screening, significant cardiac arrhythmia, history of stroke or transient ischemic attack within 1 year prior to screening.
15. History of keratitis requiring medical interventions within the last 5 years or interstitial lung disease.

16. Patients with any other disorder that, in the opinion of the investigator, might interfere with the conduct of the study.
17. Patients with an unstable condition (e.g., psychiatric disorder, a recent history of drug or alcohol abuse, interfering with study compliance, within 6 months prior to screening) or otherwise thought to be unreliable or incapable of complying with the requirements of the protocol.
18. Patients institutionalized by official means or court order.
19. Receipt of any other investigational medicinal product within the last 30 days before randomization or any previous CetuGEX™ administration.
20. Prior allergic reaction to a monoclonal antibody, grade 3 IRR or any grade 4 reaction to a monoclonal antibody.
21. Known sensitivity to any component of the investigational medicinal product (IMP) and medication used in this study.

## 8.3 Premature Patient Withdrawal

All patients will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep patients in the study; however, patients must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact patients who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a patient due to protocol violations or other reasons.

The investigator also has to withdraw patients from the study at any time for the following reasons:

- Unacceptable toxicity
- More than 3 weeks delay of scheduled infusion of CetuGEX™/cetuximab (i.e., missing more than 2 consecutive infusions)
- Intercurrent illness interfering with study procedures
- Noncompliance with study procedures, or
- Pregnancy.

If a patient is withdrawn from treatment prior to PD due to unacceptable toxicity or any other reasons as detailed above except noncompliance with study procedures, the patient will remain on regular study schedule until progression of disease unless this might interfere with the patient's best interest.

If a patient is withdrawn from the complete study before documented progressive disease, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate electronic case report form (eCRF). Whenever possible, the evaluations that were to be conducted at the Final Examination should be performed at the time of premature discontinuation.

### 8.4 Replacement of Withdrawn Patients

No replacement procedure of withdrawn patients is planned or accepted for this study.

## 9 TREATMENTS

### 9.1 Identification of Investigational Medicinal Products (IMPs)

Investigational medicinal products (IMPs) of this study are CetuGEX™ and the active comparator cetuximab.

In addition to CetuGEX™ or cetuximab, all patients will receive 5-FU and cisplatin or, in case of unacceptable toxicity, carboplatin. These drugs are non-investigational medicinal products (nIMPs) in this study and will be used according to general standard of care.

#### 9.1.1 Investigational Medicinal Products

**CetuGEX™**

CetuGEX™ is a chimeric monoclonal glyco-optimized IgG antibody with fully human glycosylation. CetuGEX™ binds to the EGFR and shows an enhanced ADCC activity against tumor cells.

| | |
|---|---|
| Name of the drug: | CetuGEX™ |
| Active substance: | Chimeric monoclonal IgG antibody |
| Dosage form: | Solution for intravenous infusion, provided in single-use vials |
| Strength: | 240 mg |
| Volume: | 48 mL |
| Excipients: | Sodium citrate, sodium chloride, Tween 80, glycine, water for solution for infusion |

CetuGEX™ will be manufactured in accordance with Good Manufacturing Practice (GMP) requirements by Glycotope Biotechnology, Heidelberg, Germany.

**Cetuximab**

Cetuximab, a chimeric monoclonal IgG antibody binding to the EGFR, will be the reference drug used in this study. The authorized product will be sourced from the European or US market as applicable and will be provided by Glycotope GmbH or its delegate for the European sites.

| | |
|---|---|
| Name of the drug: | Cetuximab |
| Active substance: | Chimeric monoclonal IgG antibody |
| Dosage form: | Solution for infusion, 2 mg/mL or 5mg/mL in vials with volumes as applicable for the corresponding market. |

For more detailed information, please refer to the Summary of Product Characteristics (SmPC) for cetuximab[11].

### 9.1.2 Non-Investigational Medicinal Products

**5-Fluorouracil**

The chemotherapy drug 5-FU, a thymidylate synthase inhibitor, will be administered to all patients for the first line treatment phase (a maximum of 6 cycles).

**Cisplatin (or, in case of unacceptable toxicity, Carboplatin)**

The platinum-salt that will be used in this study is cisplatin. It will be administered as intravenous infusion for the first line treatment phase (maximum of 6 cycles) according to the routine standard of care at each site, avoiding corticosteroids as far as possible. If corticosteroids are required, dexamethasone is to be used (unless contraindicated). Carboplatin may be administered in the same fashion in case cisplatin is not tolerated and dose reduction of cisplatin is not deemed to be the appropriate measure. However, cisplatin is mandatory for the first therapy cycle.

## 9.2 Labeling and Packaging

### 9.2.1 Labeling

The medication labels for the IMPs and nIMPs will comply with the requirements of local laws and regulations as well as with GMP Annex 13 and ICH-GCP. Master labels will be filed within the Trial Master File (TMF).

### 9.2.2 Packaging

The packaging and supply to the study sites of CetuGEX™ and cetuximab will be performed by Glycotope GmbH or a delegate company contracted and authorized by Glycotope GmbH.

## 9.3 Treatments Administered

The treatment period will consist of a first line treatment phase followed by maintenance therapy. CetuGEX™, cetuximab, 5-FU, cisplatin and carboplatin must be administered under the supervision of an investigator experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

Prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and dexamethasone (or another corticosteroid if dexamethasone is

contraindicated). According to the SmPC[11] this premedication is recommended prior to all subsequent infusions of cetuximab.

Prior to the first two infusions of CetuGEX™ (Day 0 and Day 1 of 990mg initial loading dose) patients must receive premedication consisting of paracetamol (acetaminophen) 1 g per os (PO) the evening before the infusion as well as paracetamol 1g PO, dexamethasone (or another corticosteroid if dexamethasone is contraindicated) and antihistamines approximately 60 minutes before the start of infusion. Premedication should be avoided during subsequent cycles. However, premedication might be applied after the occurrence of an IRR in relation to the previous infusion.

During administration of CetuGEX™/cetuximab, IRRs might occur. For a more detailed description of possible IRRs and dose adjustment procedures to be followed in case of IRRs, please refer to Section 9.9.

Combination Treatment Phase

Patients who fulfill all inclusion criteria and do not meet any of the exclusion criteria will be randomized in a 1:1 ratio to receive either CetuGEX™ or cetuximab in combination with 5-FU and cisplatin (or carboplatin later than the first cycle, in case of unacceptable toxicity), for a maximum of 6 chemotherapy cycles.

During the combination treatment phase, even if the chemotherapy is delayed for any reason (e.g., see Sections 9.9.3 and 9.9.4), the IMP (CetuGEX™ or cetuximab) administration may not be withheld and needs to be continued with weekly infusions as scheduled.

**CetuGEX™**

The study drug CetuGEX™ will be administered as infusion to all patients randomized to the CetuGEX™ arm, once weekly, starting with Day 0. Starting with the second infusion (Day 8 of Cycle 1), a time window of ± 1 day will be allowed for the weekly infusions (calculated from the previous infusion).

The initial dose will be 990 mg and subsequent doses will be 720 mg once weekly. The initial loading dose will be given as split-dose over 2 days with a priming dose of 60 mg on Day 0 diluted to a total volume of 100 mL (administered over 2 hours with a 30-minute break) and the remaining dose of 930 mg on Day 1 diluted to a total volume 500 mL (the intravenous infusion will last for approximately 4 hours). Infusion on Day 1 should be started within 24 ± 2 hours after start of infusion on Day 0. The exact timing, total volumes of infusions, steps for increasing infusion flow rates and duration of each flow rate for first and subsequent infusions can be found in Table 9-1. If clinically indicated, timely discontinuation of the infusion will be possible in order to prevent serious side effects.

**Table 9-1: CetuGEX™ Infusion Scheme and Dosage**

| Infusion/Timing | Dose [mg] (Total Volume) | Duration [min] | Flow rate [(mL/h] | Dose in mg/h |
|---|---|---|---|---|
| **Infusion 1 (Cycle 1)** | 990 | | | |
| Day 0 | 60 (100 mL) | 60 | 35 | 21 |
| | | Break (30) | NA | |
| | | 60 | 65 | 39 |
| Day 1 | 930 (500 mL) | 30 | 20 | 37 |
| | | 60 | 40 | 74 |
| | | ≈ 164 | 165 | 306 |
| **Infusion 2* (Day 8 of Cycle 1)** | 720 (500 mL) | 60 | 30 | 43 |
| | | 60 | 55 | 79 |
| | | ≈ 116 | 215 | 310 |
| **Infusion 3* (Day 15 of Cycle 1) and subsequent weekly infusions** | 720 (500 mL) | 90 | 333 | 480 |

* Starting with the second infusion (Day 8 of Cycle 1), a time window of ± 1 day will be allowed for the weekly infusions (calculated from the previous infusion).

### Cetuximab

Cetuximab will be administered once weekly as infusion to all patients randomized to the cetuximab arm. Starting with the second infusion (Day 8 of Cycle 1), a time window of ± 1 day will be allowed for the weekly infusions (calculated from the previous infusion). The initial dose will be 400 mg/m$^2$ body surface area (BSA) and each subsequent dose will be 250 mg/m$^2$ BSA. The maximum infusion rate for the initial dose must not exceed 5 mg/min. The maximum infusion rate for subsequent doses must not exceed 10 mg/min. The BSA will be calculated using the Mosteller formula:

$$\text{BSA } [m^2] = (\text{Weight } [kg] \times \text{Height } [cm]/3600)^{1/2}$$

The following information related to the infusion of CetuGEX™ and cetuximab will be recorded for each infusion:

- Infusion start time
- Infusion stop time
- Time, duration and reason of any infusion interruptions, if applicable
- Adjustments to infusion rate, if applicable

### Concomitant Platinum-based Chemotherapy

During the combination treatment phase, all randomized patients will receive 5-FU as continuous intravenous infusion, in combination with cisplatin (or carboplatin in case of required substitution of cisplatin in further cycles). This platinum-based chemotherapy will be administered for a maximum of 6 cycles of 3 weeks each, starting approximately 1 hour after CetuGEX™/cetuximab infusion on Day 1 of each cycle. If the CetuGEX™/cetuximab infusion is administered in the afternoon, the concomitant

platinum-based chemotherapy may be administered the next morning; however, all drugs should be given within 24 hours.

5-fluorouracil will be administered in doses of 1000 mg/m$^2$ BSA per day every 3 weeks (one cycle of cisplatin or carboplatin treatment) as continuous intravenous infusion on Days 1 to 4 of each cycle.

Cisplatin will be administered as a dose of 100 mg/m$^2$ BSA by infusion every 3 weeks, on Day 1 of each cycle, according to current standards and prescribing guidelines including hydration before and after cisplatin treatment, as required (please refer to the instructions in the corresponding SmPC [Appendix F]). In case cisplatin has to be replaced by carboplatin for toxicity reasons, Carboplatin will be administered at an area under the curve (AUC) of 5 mg/mL/min (using the Calvert formula for calculation[12]) as a 1-hour intravenous infusion every 3 weeks, on Day 1 of each cycle. As per SmPC (Appendix H), carboplatin may not be used in patients with bleeding tumors.

In case of related relevant toxicity, each compound of the chemotherapy treatment can be discontinued prior to completion of 6 cycles of chemotherapy, and patients will continue with the remaining compounds of the combination therapy. After all chemotherapy has been discontinued, irrespective if the 6 cycles are completed or discontinued prematurely for any other reason apart from progression, patients will directly enter the maintenance phase.

Single-Agent Maintenance Treatment Phase

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

## 9.4 Dispensing and Storage

The IMPs and nIMPs supplied by Glycotope GmbH are to be used exclusively in the clinical study according to the instructions of this protocol. The investigator and the dispensing study team member(s) are responsible for dispensing the study medications according to the dosage scheme and for ensuring proper storage of the IMPs and nIMPs. The study medication and the nIMPs will be administered at the study site, under strict surveillance of experienced study team members.

All study medication must be stored in accordance with the manufacturer's instructions and separately from normal hospital/practice stocks in a securely locked area, only accessible to authorized study personnel.

CetuGEX™ and cetuximab have to be stored by 2-8°C and should not be frozen.

5-fluorouracil and cisplatin have to be stored at 15-25°C and protected from light.

Carboplatin has to be stored not exceeding 25°C and protected from light.

Dispensing will only be performed by authorized study team members and according to the interactive web response system (IWRS) for randomization. IWRS will be performed

by Perceptive. Receipt and dispensing of study medication must be recorded by an authorized person at the investigator´s site.

Detailed instructions concerning the storage, preparation and administration of IMPs and nIMPs will also be described in a separate Drug Handling Manual.

All unused study medication should be returned to Glycotope GmbH or its designee for destruction or can be destroyed at the study site upon sponsor's request after the drug accountability check has been performed.

## 9.5 Method of Assigning Patients to Treatment Groups

Patients eligible for study participation will be randomized using a 1:1 ratio to either the CetuGEX™ or cetuximab arm. The randomization may take place within 3 days prior to Day 0 of the first treatment cycle for the patients randomized in CetuGEX™ arm or prior to Day 1 of the first treatment cycle.

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 IWRS will be used assigning a unique randomization number to each patient.

## 9.6 Blinding and Unblinding Treatment Assignment

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

## 9.7 Selection of Doses in the Study

Doses for cetuximab, 5-FU, cisplatin and carboplatin are chosen based on routine standard of care and according to the instructions of the corresponding SmPCs and product information leaflets for the treatment of SCCHN.

The dosage of CetuGEX™ has been chosen based on the results of former studies and PK simulations, indicating that an initial dose of 990 mg followed by subsequent infusions of 720 mg are well tolerated and safe.

## 9.8 Selection of Timing of Dose for Each Patient

Timing of dose for each patient has been chosen according to current standard of care and based on the instructions in the corresponding SmPCs and product information leaflets. According to the instructions for treatment of recurrent or metastatic SCCHN, platinum-based chemotherapy in combination with 5-FU should not start prior to 1 hour after end of cetuximab. The same timing has been chosen for CetuGEX™. The platinum-based chemotherapy should be given within 24 hours after the infusion of

CetuGEX™/cetuximab. Administration of 5-FU should be started within 24 hours after the infusion of CetuGEX™/cetuximab.

## 9.9 Dose Adjustment Criteria

Adjustment of the study drug doses is performed according to the rules described in this section.

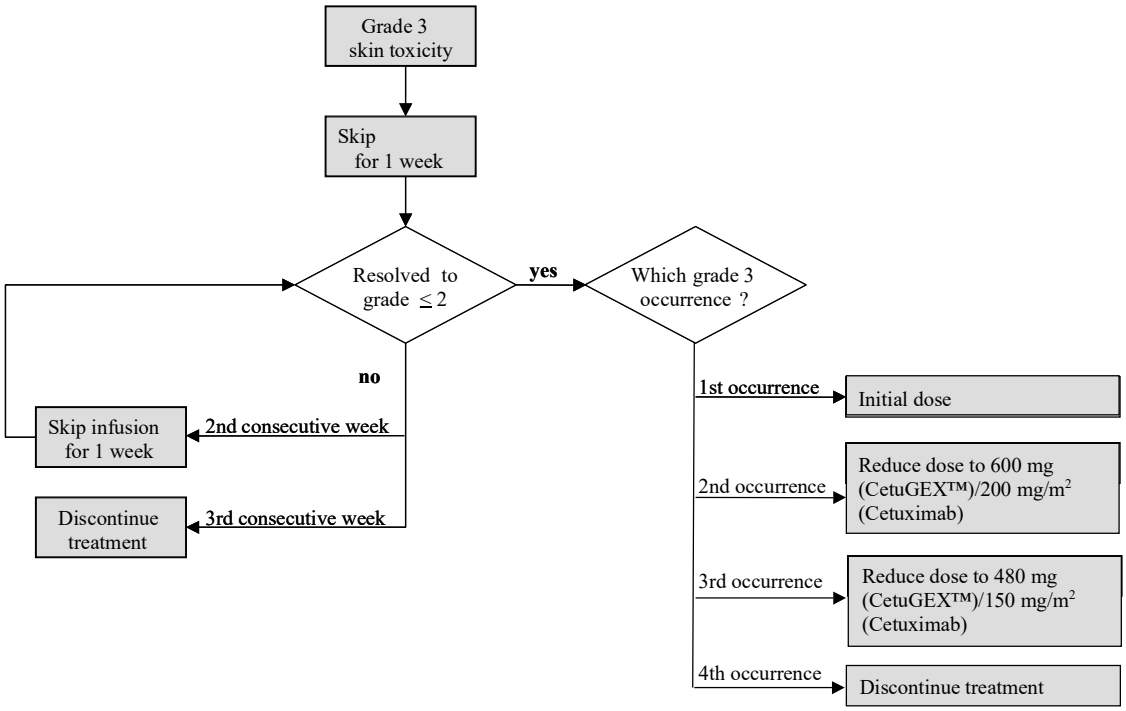
Mild or moderate IRRs are very common comprising symptoms such as fever, chills, dizziness, or dyspnea that occur in a close temporal relationship mainly to the first CetuGEX™/cetuximab infusion.

Severe IRRs also may commonly occur, in rare cases with fatal outcome.

In case of IRRs requiring dose adjustment, this should be performed as described in following sections.

The dose of CetuGEX™/cetuximab will be adjusted for CetuGEX™/cetuximab-related grade 3 skin toxicities only as displayed in Figure 9-1 and described in sections 9.9.1 and 9.9.2. CetuGEX™/cetuximab therapy will not be withheld for chemotherapy-related toxicities.

**Figure 9-1: Treatment Modification in the Event of Grade 3 Skin Toxicity Considered to be Related to Weekly Administration of CetuGEX™/Cetuximab.**



### 9.9.1 CetuGEX™

There were no severe IRRs in the Phase 1 study of CetuGEX™. It was also noted that decreasing the infusion rate did not influence the symptom control of mild to moderate IRRs. At this time it is recommended that CetuGEX™ infusions should be temporarily interrupted where necessary until improvement.

Whilst no severe IRRs have occurred to date in early clinical trials with CetuGEX™, it should be noted that severe IRRs may occur, in rare cases with fatal outcome, and investigators should be vigilant of similar reactions like observed for cetuximab (see Section 9.9.2).

In case of a severe IRR, the CetuGEX™ infusion needs to be discontinued immediately, and infusion tubing has to be disconnected from the patient. Emergency treatment (epinephrine, broncho-dilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated) might be necessary.

**Patients must be withdrawn immediately from the treatment and must not receive any further CetuGEX™ treatment**.

**Skin toxicities**: If a patient experiences a grade 3 skin toxicity (as defined in the US NCI-CTC, Version 4.0), CetuGEX™ therapy may be skipped for up to two consecutive infusions without changing the dose level. Patients with grade ≥3 reactions should be referred to the dermatologist for advice and management. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may resume. With the second and third occurrences of grade 3 skin toxicity, CetuGEX™ therapy may again be skipped for up to two consecutive infusions, with concomitant dose reductions to 600 mg and 480 mg, respectively. CetuGEX™ dose reductions are permanent. Patients should discontinue CetuGEX™ if more than two consecutive infusions are withheld or a fourth occurrence of grade 3 skin toxicity occurs despite appropriate dose reduction.

**Table 9-2: Treatment Adjustment in the Event of CetuGEX™ Caused Allergic/Hypersensitivity Reaction**

| **CTC Grade Allergic/ Hypersensitivity Reaction** | **Treatment CetuGEX™** |
|---|---|
| Grade 1 | Infusions should be temporarily interrupted where necessary until improvement of mild IRRs. |
| Grade 2 | Infusions should be temporarily interrupted where necessary until improvement of moderate IRRs. |
| Grade 3 or Grade 4 | Stop the CetuGEX™ infusion immediately and disconnect infusion tubing from the patient. Administer epinephrine, broncho-dilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. **Patients must be withdrawn immediately from the treatment and must not receive any further CetuGEX™ treatment.** |

### 9.9.2 Cetuximab

In case of mild to moderate IRRs, the infusion rate of cetuximab might be decreased and it is recommended to maintain the reduced infusion rate for all subsequent infusions.

During treatment with cetuximab, severe IRRs usually develop during or within 1 hour of the initial 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, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

In case of severe IRRs (grade 3 and 4), the cetuximab infusion requires immediate and permanent discontinuation and emergency treatment might be necessary.

**Skin toxicities:** In case of skin toxicities like grade 1 or 2 acne –like rash, pruritus or dry skin due to cetuximab treatment, events should be treated according to the instructions given in the cetuximab SmPC (Appendix E). If a patient experiences a grade 3 skin toxicity (as defined in the US NCI-CTC, Version 4.0), cetuximab therapy may be skipped for up to two consecutive infusions without changing the dose level. Patients with grade ≥3 reactions should be referred to the dermatologist for advice and management.

With the second and third occurrences of grade 3 skin toxicity, cetuximab therapy may again be skipped for up to two consecutive infusions (one infusion during maintenance) with concomitant dose reductions to 200 mg/m$^2$ and 150 mg/m$^2$ respectively. Cetuximab

dose reductions are permanent. Patients should discontinue cetuximab if more than two consecutive infusions are withheld or a fourth occurrence of grade 3 skin toxicity occurs despite appropriate dose reduction (see Figure 9-1).

**Allergic/hypersensitivity reactions:** In each case of allergic/hypersensitivity reaction, the investigator should implement treatment measures according to the best available medical practice. Based on previous experience with cetuximab allergic/hypersensitivity reactions, the treatment guidelines as described in Table 9-3 may be applicable.

**Table 9-3: Treatment Adjustment in the Event of Cetuximab Caused Allergic/Hypersensitivity Reaction**

| **CTC Grade Allergic/ Hypersensitivity Reaction** | **Treatment** |
|---|---|
| Grade 1 | Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.<br>The total infusion time for cetuximab should not exceed 4 hours. |
| Grade 2 | Stop cetuximab infusion.<br>Administer bronchodilators, oxygen, etc. as medically indicated.<br>Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening |
| Grade 3 or Grade 4 | Stop the cetuximab infusion immediately and disconnect infusion tubing from the patient.<br>Administer epinephrine, broncho- dilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated.<br>**Patients must be withdrawn immediately from the treatment and must not receive any further cetuximab treatment**. |

**Retreatment following allergic/hypersensitivity reactions:** Once a cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. For patients having a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped, and the patients should be removed from the study. If a patient experiences a Grade 3 or 4 allergic/hypersensitivity reactions at any time, cetuximab should be discontinued.

If therapy must be withheld for a longer period of time than defined above, the patient will be removed from the study treatment. In special cases, the investigator may request that the patient continues to receive cetuximab (the investigator must ask permission from the legal representative of the sponsor).

### 9.9.3 Cisplatin

Prior to each cisplatin infusion the following criteria should be fulfilled:

- Leucocytes $\geq$3.5 x $10^9$/L or neutrophils $\geq$1.5 x $10^9$/L
- Platelets $\geq$100 x $10^9$/L
- Creatinine $\leq$1.5 mg/100ml
- Urea <25mg/100ml

If the above mentioned criteria are not fulfilled at the planned day of infusion, chemotherapy will be delayed until the criteria are fulfilled. If the chemotherapy is delayed, the IMP (CetuGEX™ or cetuximab) administration may not be withheld and needs to be continued with weekly infusions as scheduled. If chemotherapy is delayed for more than 3 weeks (i.e., more than 6 weeks between 2 consecutive Day 1 platinum-based chemotherapy infusions), the chemotherapy will be stopped and the patient will continue with the single-agent maintenance therapy.

The patient's subsequent chemotherapy doses will all be **reduced to 75 % of the initial dose** if any of the following toxicity occurs at any time during a chemotherapy cycle:

- Febrile neutropenia (ANC <1.0 x $10^9$/L, fever $\geq$38.5°C)
- ANC <0.5 x $10^9$/L
- Platelets <25 x $10^9$/L
- Non-hematological toxicity grade 3 (NCI-CTC version 4.0): dose may be reduced at the discretion of the investigator

Once a chemotherapy dose modification has occurred, the dosage may not be re-escalated for this patient.

Patients with febrile neutropenia or a delay in therapy due to myelosupression will be treated with G-CSF on subsequent cycles.

Switching from cisplatin to carboplatin has to be considered if the following toxicity occurs at any time during a chemotherapy cycle:

- Creatinine increase > Grade 1 (NCI-CTC version 4.0)
- Ototoxicity > Grade 2 (NCI-CTC version 4.0)
- Sensory neuropathy > Grade 2 (NCI-CTC version 4.0)

If any of the above mentioned occurs again under carboplatin, chemotherapy has to be discontinued and the patient will enter the single-agent maintenance phase.

For more detailed information, please refer to the SmPCs for cisplatin (Appendix F) and carboplatin (Appendix H).

### 9.9.4 5-Fluorouracil

Prior to each 5-fluorouracil infusion the following criteria should be fulfilled:

- Leucocytes $\geq$3.5 x $10^9$/L or neutrophils $\geq$1.5 x $10^9$/L
- Platelets $\geq$100 x $10^9$/L

If the above mentioned criteria are not fulfilled at the planned day of infusion, chemotherapy will be delayed until the criteria are fulfilled. If the chemotherapy is delayed, the IMP (CetuGEX™ or cetuximab) administration may not be withheld and needs to be continued with weekly infusions as scheduled. If chemotherapy is delayed for more than 3 weeks (i.e., more than 6 weeks between 2 consecutive Day 1 platinum-based chemotherapy infusions), the chemotherapy will be stopped and the patient will continue with the single-agent maintenance therapy.

**Diarrhea:** For patients with grade 3 diarrhea for several days, **a reduction to 80% of the initial dose of 5-FU** is required. If grade 3 diarrhea does recur on a subsequent cycle, then a **further reduction of 20% in the 5-FU dose** is recommended.

**Mucositis:** For patients with the first episode of mucositis grade 3 lasting several days, **a reduction of the daily dose to 80% of the initial dose of 5-FU** is required. If grade 3 mucositis does recur on a subsequent cycle, then **no further cycle of 5-FU will be given**.

Once a chemotherapy dose modification has occurred, the dosage may not be re-escalated for this patient.

For more detailed information, please refer to the SmPC for 5-FU (Appendix G).

## 9.10 Drug Accountability

Shipment of study medication will be performed by Glycotope GmbH or an authorized delegate including a shipment record and approval form. Each delivery of study medication must be inspected and acknowledged by an authorized team member of the study personnel and must be kept in a secure locked location only accessible by authorized study personnel.

Clinical supplies are to be dispensed only in accordance with the study protocol. Dispensing of study medication to the patients must be recorded on drug accountability logs and in the eCRF.

The inventory will be available to the monitor to verify the drug accountability during the study. Any unused bottles will be returned to Glycotope GmbH or its designee or can be destroyed at the study site upon sponsor's request after the drug accountability check has been performed. Empty or partially used bottles must not be returned and should be destroyed at the study site following local policies, after the monitor has reviewed the remaining volumes versus the eCRF and accountability records.

## 9.11 Treatment Compliance

Treatment compliance will be confirmed by maintenance and close reviews of the drug accountability records.

## 9.12 Concomitant and Prohibited Therapies

### 9.12.1 Concomitant Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and in the eCRF. Furthermore, each change in concomitant medication (e.g., new treatment, discontinuation of treatment, change in dosage/route, etc.) during the study should be documented in the same way. Previous medication taken within the last 6 months prior to screening has to be recorded as well.

If patients received any previous treatment which is part of an exclusion criterion (for details, please refer to Section 8.2.2) they will not be eligible for study participation. Patients on ongoing treatment with phenytoin will be closely monitored (blood plasma level) due to the drug-drug interaction with cisplatin and 5-FU.

### 9.12.2 Prohibited Therapies

The following co-medication/therapies are not allowed during participation in the study:

- EGFR targeting agents apart from randomly assigned study medication until end of treatment.
- Any other immunotherapy until end of treatment.
- Any anti-cancer treatment other than described in this protocol until end of treatment.
- Ongoing regular doses of hydrocortisone and steroids (except for topical/inhaled) other than corticosteroids used for precaution of IRR.
- Immunosuppressive agents until end of treatment.
- Radiation therapy (except palliation of existing bone metastasis pain).
- Erythropoietin (Epo).
- Other medications that are contraindications to 5-FU and cisplatin or carboplatin respectively as per SmPC 4.3 “Contraindications” and 4.5 “Interaction with other medicinal products and other forms of interaction” (see Appendices F, G, H).

## 9.13 Treatment After End of Study

After the end of the study, i.e., in case of progression of disease or if other withdrawal criteria are met, patients will be treated by their physician according to most appropriate and best supportive standard of care.

# 10 STUDY PROCEDURES

Patients will provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For an overview on the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 18.1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each patient.

## 10.1 Study Periods and Schedule of Visits

### 10.1.1 Screening Visit

The patient must be screened within 28 days prior the day of first infusion.

The following records and assessments will be performed at screening:

- Obtain written informed consent.
- Contact the IWRS to obtain patient identification number.
- Check of inclusion/exclusion criteria.
- Check availability of pre-existing tumor tissue sample for EGFR and p16 status assessment.
- Demographic information (including age, race, smoking status and alcohol consumption).
- Diagnosis of SCCHN, including oncological information, previous chemotherapy and radiotherapy and other oncological regimens.
- Medical history apart from SCCHN, including current therapies (e.g., prescription and non-prescription medication).
- Record ECOG performance status.
- Physical examination including underlying disease, weight, height and BMI.
- Vital signs (blood pressure, heart rate and body temperature).
- 12-lead ECG.
- Echocardiogram (ECHO)/Multiple Gated Acquisition (MUGA) scan for confirmation of eligibility (exclusion criterion 13).
- Evaluation of tumor size by computed tomography (CT) or magnetic resonance imaging (MRI) (head and neck region, chest, and abdomen).
- Blood and urine sampling for safety laboratory (hematology, coagulation panel, blood chemistry and urinalysis). Please note that creatinine clearance needs to be assessed at screening unless previous results not older than 6 weeks are available.

- Blood sampling for genotyping (FcγRIIIa status; only in case the patient will enter the study, the blood sample might also be used at a later time point for further analyses like FcγRII status).
- Recording of previous and concomitant medication.

### 10.1.2 Randomization

If the patient is eligible to participate in this study (i.e., if all inclusion criteria are met and no exclusion criteria apply), the investigator will contact the IWRS for randomization information within 1 to 3 days prior to the next scheduled visit of the corresponding patient. The patient will be randomly assigned to receive either CetuGEX™ or cetuximab by receiving a unique randomization number (as detailed in Section 9.5). The patients do not need to visit the study site for this procedure but can be informed by phone.

Additionally, the pre-existing tissue sample will be sent to the central laboratory for the following analyses:

- EGFR expression by immunohistochemistry at a central laboratory. Further immunohistochemical assessments may be performed on the tumor sample if deemed necessary by the sponsor, e.g. tissue micro arrays to further characterize the tumor.
- p16 tumor suppressor gene status, indicative for high risk of Human Papilloma Virus (HPV) in the tumor (remaining tissue needs to be stored for further analysis in case of eligibility).
- Assessment of HPV status at a central laboratory.

These analyses may be performed at a later time point during the study.

### 10.1.3 Combination Treatment Phase

During the combination treatment phase, the patients will receive the study medication (CetuGEX™ or cetuximab) in combination with chemotherapy (cisplatin and 5-FU) for a maximum of 6 cycles of combined treatment. In case of toxicity of cisplatin, carboplatin may substitute cisplatin, but after completion of the first cycle at the earliest.

During the combination treatment phase, even if the chemotherapy is delayed for any reason (e.g., see Sections 9.9.3 and 9.9.4), the IMP (CetuGEX™ or cetuximab) administration may not be withheld and needs to be continued with weekly infusions as scheduled. Additionally, all assessments related to the weekly administration of CetuGEX™/cetuximab should be performed as scheduled (see *). Only assessments relevant for the determination of whether the patient is eligible to continue the chemotherapy treatment (i.e., vital signs measurements and safety laboratory tests) have to be repeated in relation to the next administration of chemotherapy (see also Schedule of Events, Section 18.1).

If the administration of CetuGEX™ or cetuximab is skipped for any reason (see Sections 9.9.1 and 9.9.2), e.g., on Day 8, all assessments scheduled for this study visit

day are to be performed as planned (i.e., including collection of blood samples for the determination of ADA and pre-dose samples for PK).

Table 10-1 displays the ideal treatment schedule for the combination treatment phase.

**Table 10-1: Ideal treatment schedule – combination treatment phase**

| Treatment cycle | Week | Chemotherapy [a] | IMP [b,c] | |
|---|---|---|---|---|
| **1** | Week 1 | D1 [d] | D1 | |
| | | D2 – D4 | | |
| | Week 2 | | D8 | |
| | Week 3 | | D15 | |
| **2** | Week 4 | D1 [d] | D1 | |
| | | D2 – D4 | | |
| | Week 5 | | D8 | |
| | Week 6 | | D15 | |
| **3** | Week 7 | D1 [d] | D1 | |
| | | D2 – D4 | | |
| | Week 8 | | D8 | |
| | Week 9 | | D15 | |
| **4** | Week 10 | D1 [d] | D1 | |
| | | D2 – D4 | | |
| | Week 11 | | D8 | |
| | Week 12 | | D15 | |
| **5** | Week 13 | D1 [d] | D1 | |
| | | D2 – D4 | | |
| | Week 14 | | D8 | |
| | Week 15 | | D15 | |
| **6** | Week 16 | D1 [d] | D1 | |
| | | D2 – D4 | | |
| | Week 17 | | D8 | **Start of maintenance phase** |
| | Week 18 | | D15 | |

a) If the chemotherapy is delayed, the IMP (CetuGEX™ or cetuximab) administration needs to be continued with weekly infusions as scheduled.
b) Starting with the second IMP infusion (Day 8 of Cycle 1), a time window of ± 1 day will be allowed for the weekly infusions (calculated from the previous infusion).
c) If the administration of CetuGEX™ or cetuximab is skipped for any reason (see Sections 9.9.1 and 9.9.2), e.g., on Day 8, all assessments scheduled for this study visit day are to be performed as planned (i.e., including collection of blood samples for the determination of ADA and PK).
d) The platinum-based chemotherapy should be given within 24 hours after the infusion of CetuGEX™/cetuximab. Administration of 5-FU should be started within 24 hours after the infusion of CetuGEX™/cetuximab.
D = day, W = week

**Day 0, Cycle 1 (Week 1)**

On Day 0 of Cycle 1, eligible patients randomized to receive CetuGEX™ will visit the study site to receive their unique randomization number and perform baseline assessments as listed below and to receive a priming dose of 60 mg on this visit, after all baseline/safety assessments have been performed. The Day 0 visit is not applicable for patients randomized to receive cetuximab. General baseline assessments scheduled for Day 0 will be performed on Day 1 for those patients randomized to cetuximab.

The following assessments will be performed on Day 0 for patients in the CetuGEX™ treatment arm:

- Confirmation of inclusion/exclusion criteria.
- Physical examination.
- Vital signs (blood pressure, heart rate and body temperature), body weight and BMI.
- 12-lead ECG, if not done within 7 days prior start of study medication administration during screening phase.
- Record ECOG performance status.
- Blood and urine sampling for safety laboratory (hematology, coagulation panel, blood chemistry and urinalysis).
- Pregnancy test for female patients of childbearing potential.
- Quality of life questionnaires EORTC-QLQ-C30 and EORTC-QLQ-H&N35 (to be performed prior to any other assessments).
- Recording of concomitant medication.
- Assessment of AEs.
- Blood sampling for ADA testing.
- Blood sampling for PK assessments prior to the start of infusion and after the end of infusion.
- Blood sampling for assessment of cytokines and other relevant blood proteins (to be performed pre-dose, one hour after start of infusion and at the end of infusion).
- Blood sampling for assessment of immune status (to be performed pre-dose).
- Infusion of 60 mg CetuGEX™ priming dose.

**Day 1, Cycle 1 (Week 1)**

Day 1 of Cycle 1 will be the first treatment day for patients randomized to receive cetuximab. For those patients randomized to receive CetuGEX™ Day 1 of Cycle 1 should be performed within 24 hours after Day 0.

**Day 1 (of each treatment cycle)**

On Day 1 of each treatment cycle, the following assessments will be performed:

- Confirmation of inclusion/exclusion criteria (to be performed only for patients receiving cetuximab).
- Physical examination.
- Vital signs (blood pressure, heart rate and body temperature), body weight and BMI.
- Record ECOG performance status (to be performed in Cycle 1 only for patients receiving cetuximab and for all patients in every following cycle).
- 12-lead ECG (to be performed pre-dose, in Cycles 3 and 5 only; in Cycle 1 to be performed only for patients receiving cetuximab and only if not done within 7 days prior start of study medication administration during screening phase; to be performed).
- Evaluation of tumor size by CT or MRI (to be performed pre-dose, in Cycles 3 and 5 only; same equipment and type of imaging as used at Screening is required throughout the study). Assessment of the 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.
- Blood and urine sampling for safety laboratory (hematology, coagulation panel, blood chemistry and urinalysis) (to be performed pre-dose, in Cycle 2 and every following cycle; in Cycle 1 to be performed only for patients receiving cetuximab).
- Pregnancy test for female patients of childbearing potential (in Cycle 1 only; to be performed only in patients receiving cetuximab).
- Blood sampling for assessment of cytokines and other relevant blood proteins***** (to be performed only in a subset of approximately 30 patients per treatment arm; in Cycles 1 and 2 only: Cycle 1: pre-dose, at the start of the highest IMP infusion rate, 1 hour after start of the highest infusion rate and at the end of infusion; Cycle 2: pre-dose, 1 hour after start of infusion and at the end of infusion).
- Blood sampling for assessment of immune status***** (to be performed only in a subset of approximately 30 patients per treatment arm; pre-dose on Day 1 of Cycle 1 for patients receiving cetuximab).
- Blood sampling for ADA testing***** (to be performed only for patients receiving CetuGEX™; pre-dose on Day 1 of Cycle 2 and Cycle 4 only).
- Blood sampling for PK assessments***** (only for patients receiving CetuGEX™; to be performed prior to start of infusion and at the end of infusion in Cycles 1 to 4 only).
- Blood sampling for additional PK assessments***** (only for a subgroup of approximately 30 patients receiving CetuGEX™; to be performed 5 (± 5 min) and 7 (± 15 min) hours after start of infusion on Cycles 1 and 4 only).

- QoL questionnaires EORTC-QLQ-C30 and EORTC-QLQ-H&N35* (to be performed prior to any other assessments; to be performed in Cycles 3 and 5 only; in Cycle 1 to be performed only for patients receiving cetuximab).
- Study drug administration (CetuGEX™ according to infusion scheme as provided in Section 9.3 or cetuximab according to standard of care). Except for Day 1 of Cycle 1 a time window of ± 1 day will be allowed for the weekly infusions (calculated from the previous infusion).

- Administration of cisplatin (or carboplatin) and 5-FU (to be started not sooner than 1 hour after end of CetuGEX™/cetuximab infusion). The platinum-based chemotherapy should be given within 24 hours after the infusion of CetuGEX™/cetuximab. Administration of 5-FU should be started within 24 hours after the infusion of CetuGEX™/cetuximab. Cisplatin is mandatory in Cycle 1 and can be replaced with carboplatin in case of unacceptable toxicity in the subsequent cycles.
- Drug accountability.
- Recording of concomitant medication.
- Assessment of AEs.

**Days 2 to 4 (of each treatment cycle)**

Visits on Days 2 to 4 are only obligatory for patients who may not have a transportable pump for 5-FU administration on Days 2 to 4 and/or who are included in the subgroup of 30 CetuGEX™ patients for additional PK assessments.

On Day 2, Day 3 and Day 4 of each treatment cycle, the following assessments will be performed for patients visiting the site:

- Vital signs (blood pressure, heart rate and body temperature).
- Blood sampling for PK assessments*, for a subgroup of 30 CetuGEX™ patients only, and only during Cycles 1 and 4:
    - 24 ± 1 hours after start of infusion (Day 2)
    - 48 ± 2 hours after start of infusion (Day 3)
    - 72 ± 2 hours after start of infusion (Day 4).
- Administration of 5-FU (if not automatically performed by transportable pump).
- Drug accountability.
- Recording of concomitant medication.
- Assessment of AEs.

**Days 8 and 15 (of each treatment cycle)**

On Day 8 and Day 15 of each cycle of the combination treatment phase, the following assessments will be performed:

- Physical examination.
- Vital signs (blood pressure, heart rate and body temperature), body weight and BMI.
- Record ECOG performance status.
- Blood sampling for assessment of cytokines and other relevant blood proteins*, (to be performed only in a subset of approximately 30 patients per treatment arm; pre-dose, 1 hour after start of infusion and at the end of infusion in Cycle 1 only).
- Blood sampling for assessment of immune status* (to be performed only in a subset of approximately 30 patients per treatment arm; pre-dose on Day 8 of Cycle 2 only).
- Blood sampling for ADA testing* (to be performed only for patients receiving CetuGEX™; pre-dose on Day 8 of Cycle 1 only).
- Blood sampling for PK assessments* (only for patients receiving CetuGEX™; to be performed prior to start of infusion and at the end of infusion, in Cycles 1 to 3 only).
- Blood sampling for additional PK assessments* (only for a subgroup of approximately 30 patients receiving CetuGEX™; to be performed prior to start of infusion, on Day 8 of Cycle 4 only).
- Administration of CetuGEX™/cetuximab.
- Drug accountability.
- Recording of concomitant medication.
- Assessment of AEs.

It will be accepted that assessments of Days 8 and 15 will be performed one day before the infusion.

### 10.1.4 Single Agent Maintenance Phase

After completion of 6 cycles of combination chemotherapy cycles or after discontinuation of the chemotherapy for any other reason apart from progression, the patients will continue to receive CetuGEX™ alone or cetuximab alone, respectively. Single-agent maintenance therapy will be continued until progression of disease or limiting toxicity.

On **Day 1 of each week** of the single-agent maintenance phase, the following will be performed or assessed:

- Physical examination.

- Vital signs (blood pressure, heart rate and body temperature) and body weight and BMI.
- 12-lead ECG (every 6 weeks after randomization).
- Record ECOG performance status.
- Evaluation of tumor size by CT or MRI (to be performed pre-dose, every 6 weeks within the first 18 weeks after randomization, and every 8 weeks thereafter; same equipment and type of imaging as used at Screening is required throughout the study).
- Blood and urine sampling for safety laboratory (hematology, coagulation panel, blood chemistry and urinalysis; to be performed every 6 weeks after randomization).
- QoL questionnaires EORTC-QLQ-C30 and EORTC-QLQ-H&N35 (to be performed prior to any other assessments; to be performed 18 weeks after date of randomization. In case of premature discontinuation of combination treatment, also to be performed 6 weeks and 12 weeks after randomization, as applicable).
- Pregnancy test for female patients of childbearing potential (will be performed only on the first week of maintenance therapy pre-dose).
- Blood sampling for ADA testing (only for patients receiving CetuGEX™; only to be performed 1, 3 and 9 weeks after randomization, pre-dose, if chemotherapy was discontinued prematurely).
- Blood sampling for PK assessments (only for patients receiving CetuGEX™; only to be performed until the $10^{th}$ infusion of CetuGEX™, if chemotherapy was discontinued prematurely).
- Blood sampling for additional PK assessments (only for a subgroup of approximately 30 patients receiving CetuGEX™; only to be performed until the $11^{th}$ infusion of CetuGEX™ [pre-dose], if chemotherapy was discontinued prematurely).
- Administration of CetuGEX™/cetuximab (time window for infusion: ± 1 day calculated from the previous infusion).
- Drug accountability.
- Recording of concomitant medication.
- Assessment of AEs.

### 10.1.5 Follow-Up Phase

**Safety Visit (28 + 2 Days After Last Infusion)**

Four weeks (28 + 2 days) after the last administration of the study drug, a Safety Visit must be performed for all patients. During this visit, the following assessments will be carried out:

- Physical examination.
- Vital signs (blood pressure, heart rate and body temperature), body weight and BMI.
- 12-lead ECG
- Record ECOG performance status.
- Blood and urine sampling for safety laboratory (hematology, coagulation panel, blood chemistry and urinalysis).
- Blood sampling for assessment of immune status (only in a subset of approximately 30 patients per treatment arm).
- Blood sampling for ADA testing (only for patients receiving CetuGEX™).
- Blood sampling for PK assessments (only for patients receiving CetuGEX™).
- QoL questionnaires EORTC-QLQ-C30 and EORTC-QLQ-H&N35 (to be performed prior to any other assessments).
- Pregnancy test for female patients of childbearing potential.
- Recording of concomitant medication.
- Assessment of AEs.

The Safety Visit is identical to the Final Examination Visit for those patients who received treatment until progression of disease.

**Final Examination**

As soon as progression of disease is detected, a Final Examination Visit must be performed for all patients who prematurely discontinued study treatment for any other reason except progression of disease.

In case of complete study withdrawal before documented progressive disease, a Final Examination Visit should be performed at the time of premature discontinuation.

The following assessments will be performed:

- Vital signs (blood pressure, heart rate and body temperature).
- Record ECOG performance status.
- Recording of concomitant medication.
- Assessment of AEs.

For patients discontinuing study medication due to progressive disease, the 28-day Safety Visit will constitute the Final Examination.

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. Apart from post-PD anti-tumor therapies, no concomitant medications and no AEs will be recorded after the Final Examination.

## 10.2 Study Duration

The overall study duration is expected to be approximately 48 months (including 24 months of active enrollment, a treatment phase until the respective number of PFS events is reached of approximately 12 months after the date of randomization and ongoing follow-up for overall survival for 24 months after randomization of the last patient).

The sequence and maximum duration of the study periods and treatment for each patient will be as follows:

- Screening: to be performed within 28 days prior to randomization to assess general eligibility for this study.
- Combination treatment phase: maximum of 6 treatment cycles of combination treatment.
- Single-agent maintenance phase: until disease progression.
- Follow-up: at least 24 months after the date of randomization of the last patient.

All patients will be treated until disease progression, unacceptable toxicity or any other withdrawal criterion is met.

## 10.3 Assessments

### 10.3.1 Efficacy

#### 10.3.1.1 Assessment of Primary Endpoint

The primary endpoint of the study is the PFS, defined as the time from randomization until disease progression or death, whichever occurs first.

Disease will be evaluated by immune-related response criteria based on the RECIST 1.1 criteria[13] and adapted according to Wolchok et al[14] (modified irRC). Disease progression is defined as a 20% increase in tumor burden, taking as reference the smallest tumor burden recorded since the treatment started (details in Appendix C).

Date of disease progression is defined as the date of imaging showing disease progression or death, whichever occurs first.

Tumor assessments will be performed by the investigator and independent centralized reading during the combination treatment phase and single-agent maintenance phase based on CT or 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.

Tumor images to determine PFS will be evaluated based on the RECIST version 1.1 adapted according to Wolchok et al[14].

Patients with measurable disease at baseline may be included into study. Measurable disease is defined as the presence of at least one measurable lesion. A measurable tumor lesion is a lesion that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan or MRI scan. To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assess by CT scan. A detailed description of measurable and non-measurable lesions can be found in RECIST version 1.1 immune-related response criteria provided in Appendix C.

For the evaluation of the primary efficacy endpoint PFS, assessments performed by the investigator will be taken into account.

#### 10.3.1.2 Assessment of Secondary Efficacy Endpoints

Tumor assessments performed by the investigator and by independent centralized reading as described in detail above will also be used for evaluation of secondary efficacy endpoints.

**Progression-free Survival assessed by Centralized Read**

Tumor images to determine PFS as assessed by independent centralized reading will be evaluated as described in detail in Section 10.3.1.1.

**Objective Response Rate and Duration of Response**

Objective response rate is the portion of patients with a tumor size reduction of a predefined amount for a minimum time period and it is defined as the sum of partial responses and complete responses. Response duration is measured from the time of initial response until documented tumor progression.

The investigator and independent centralized reader will evaluate whether complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) has occurred, according to the criteria presented in Appendix C:

**Best Overall Response Rate**

The best overall response rate is the best response (CR, PR or SD) recorded per patient from the start of the treatment until disease progression/recurrence. Separate rates per CR, PR or SD as best response will be evaluated.

**Clinical Benefit Rate**

The clinical benefit rate is the portion of patients with an objective response or stable disease.

**Overall Survival**

The overall survival is defined as the duration of time from randomization to the time of death. The patients will be followed up by monthly phone calls until death or for a maximum duration of 24 months after randomization of the last patient for assessment of OS.

**Time to Treatment Failure**

Time to treatment failure is defined as the time from randomization to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death.

### 10.3.2 Quality of Life Measures

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). Patients will be required to complete the questionnaires prior to any other assessments on Day 0 (CetuGEX™ patients only) and Day 1 of Cycle 1 (cetuximab patients only), respectively, as well as on Day 1 of Cycles 3 and 5 (i.e., 6 weeks and 12 weeks after randomization), 18 weeks after randomization and 28 (+ 2) days after last treatment administration (Safety Visit).

### 10.3.3 Pharmacokinetics

#### 10.3.3.1 Pharmacokinetics Blood Samples Collection

Blood sampling for antibody trough levels and PK profiles assessments will be performed throughout the study for the patients randomized to the CetuGEX™ treatment group at several timepoints, as detailed in Appendix B.

For all patients randomized to the CetuGEX™ treatment group, blood sampling for PK trough levels will be performed at the following time points:

- Week 1, Cycle 1, Day 0: Before start and at the end of the 1st infusion.
- Week 1, Cycle 1, Day 1: Before start and at the end of the 1st infusion continuation.
- Week 2, Cycle 1, Day 8: Before start and at the end of the 2nd infusion.
- Week 3, Cycle 1, Day 15: Before start and at the end of the 3rd infusion.
- Week 4, Cycle 2, Day 1: Before start and at the end of the 4th infusion.
- Week 5, Cycle 2, Day 8: Before start and at the end of the 5th infusion.
- Week 6, Cycle 2, Day 15: Before start and at the end of the 6th infusion.
- Week 7, Cycle 3, Day 1: Before start and at the end of the 7th infusion.
- Week 8, Cycle 3, Day 8: Before start and at the end of the 8th infusion.

- Week 9, Cycle 3, Day 15: Before start and at the end of the 9th infusion.
- Week 10, Cycle 4, Day 1: Before start and at the end of the 10th infusion.
- Safety Visit: 28 + 2 days after last infusion.

Additionally, for a subgroup of approximately 30 patients receiving CetuGEX™, blood samples for assessment of PK profiles will be taken on Cycles 1and 4 at the following timepoints:

- Week 1, Cycle 1, Day 1: 5 hours ± 5 min and 7 hours ± 15 min hours after start of the 1st infusion.
- Week 1, Cycle 1, Days 2, 3 and 4: 24 ± 1, 48 ± 2 and 72 ± 2 hours after start of the 1st infusion on Day 1.
- Week 2, Cycle 1, Day 8: 7 days (168 ± 2 hours) after start of the 1st infusion on Day 1, before start of the 2nd infusion; identical to the pre-dose sampling for all patients).
- Week 10, Cycle 4, Day 1: 5 hours ± 5 min and 7 hours ± 15 min after start of the 10th infusion.
- Week 10, Cycle 4, Days 2, 3 and 4: 24 ± 1, 48 ± 2 and 72 ± 2 hours after start of the 10th infusion.
- Week 11, Cycle 4, Day 8: 7 days (168 ± 2 hours) after start of the 10th infusion, before start of the 11th infusion).

If a patient discontinues early the chemotherapy in the first-line treatment phase, blood samples for PK assessments will be collected on the first day of each week of the maintenance phase, but only until the 10th study drug infusion after randomization or, if the patient is participating in the subgroup analysis, in accordance with the additional PK blood sampling schedule until the start of the 11th study drug infusion (pre-dose).

#### 10.3.3.2 Pharmacokinetic Blood Sample Handling

Serum samples for pharmacokinetic analysis will be handled and stored at -20°C or below at the study site until shipment on dry ice to an external analytical laboratory. At the analytical laboratory, the samples will also be stored at - 20°C or below until analysis. Detailed instructions for handling of serum samples will be provided in the laboratory specific documentation. Pharmacokinetic sample assessment will be performed at a central laboratory.

In addition, the residual blood samples drawn for PK analysis may be stored and optionally be used at a later time point for the analysis of potential pharmacodynamics markers, as applicable. Potential pharmacodynamics markers to be assessed may include, but are not limited to, EGFR-pathway related markers.

### 10.3.4 Pharmacogenomics

Patients will consent to genotype testing of blood for a more detailed characterization of the patient population to enable a stratified randomization procedure with regard to

FcγRIIIa status. The stratified randomization is chosen to highlight the population that would benefit most from treatment with CetuGEX™.

At Screening, a blood sample for genotyping analyses will be taken. Samples will be shipped to the central laboratory where they will be shipped to the genomics laboratory for genotyping analysis of the patient's FcγRIIIa status.

Additionally, FcγRIIa status may be determined as further potential biomarker but not as a stratification factor.

Handling of blood samples will be performed according to the laboratory instructions and as outlined in Section 10.3.6.1.

### 10.3.5 Immunogenicity and Immunological Parameters

#### 10.3.5.1 Immunogenicity (Antibody Testing)

Blood samples for CetuGEX™ antibody testing (ADA) will be taken pre-dose at the start of treatment (Day 0), on Day 8 of Cycle 1, Day 1 of Cycles 2 and 4 and 28 + 2 days after last infusion (Safety Visit). Incidence of ADA will be tested in a central laboratory using validated assays.

Blood samples drawn for ADA assessments will be frozen for storage. Sampling, storage and shipment of samples will be performed according to the laboratory instructions and as outlined in Section 10.3.6.1.

#### 10.3.5.2 Cytokine Release and Immune Cells Status

Cytokine release and immune cell status will be assessed only in a subset of approximately 30 patients per treatment arm. Blood samples for the assessment of cytokines and other relevant blood proteins will be collected throughout the study according to the schedule presented as follows:

- Day 0: before first infusion, at 1 hour after start of the infusion and at the end of the first infusion (only for a subset of approximately 30 CetuGEX™ patients).
- Cycle 1, Day 1: before infusion, at the start of the highest infusion rate, at 1 hour after start of the highest infusion rate and at the end of infusion.
- Cycle 1, Days 8 and 15: before infusion, at 1 hour after start of the infusion and at the end of the infusion.
- Cycle 2, Day 1: before infusion, 1 hour after start of the infusion and at the end of the infusion.

Blood samples drawn for the assessment of cytokines and other relevant blood proteins will be frozen for storage. Sampling, storage and shipment of samples will be performed according to the laboratory instructions and as outlined in Section 10.3.6.1.

At selected sites blood samples will be taken from a subset of approximately 30 patients per treatment arm to perform a FACS analysis to determine the immune status of the patients using selected cluster of differentiation (CD) markers such as CD3, CD16,

CD19, CD56, CD4, CD8, and CD14. Blood samples for assessment of the immune cell status will be collected throughout the study according to the schedule presented as follows:

- Cycle 1, Day 0 (for patients receiving CetuGEX™)/Day 1 (for patients receiving cetuximab): before first infusion.
- Cycle 2, Day 8: before infusion.
- 28 + 2 days after last infusion (Safety Visit).

### 10.3.6 Safety

Safety assessments will include the evaluation of standard laboratory assessments, vital signs, electrocardiograms, physical examinations and occurrence of AEs and IRRs.

#### 10.3.6.1 Laboratory Safety Assessments

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 18.1).

**Standard Laboratory Assessments**

| | |
|---|---|
| Hematology | White blood cell (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils), hematocrit, hemoglobin, mean corpuscular volume, platelet count, red blood cell (RBC) count |
| Blood Chemistry | Albumin, total bilirubin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, sodium, potassium, chloride, calcium, magnesium, creatinine, creatinine clearance, lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), urea/blood urea nitrogen (BUN) |
| Coagulation Panel | Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen |
| Urinalysis | pH, blood, glucose, protein, ketones |
| EGFR | EGFR expression from pre-existent tumor tissue sample |
| p16 | p16 tumor suppressor gene status, indicative for high risk of HPV in the tumor (from pre-existing tumor tissue sample) |
| Pregnancy Test (serum or urine) | Females of childbearing potential only |

The safety laboratory tests as mentioned above will be performed at the study site (local laboratory). The assessment of EGFR expression and HPV and p16 status will be performed at the central laboratory. The pre-existing tissue sample will be sent to the central laboratory once the patient was randomized. The analysis of the status will be performed during the conduct of the study, but is no requirement for patient inclusion or randomization. Storage and shipment of tumor tissue samples will be performed according to the instructions of the laboratory.

Blood samples will be taken in accordance with local laboratory standard procedures and as detailed in the laboratory manual where applicable.

**Specimen Handling Requirements**

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of patient samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

**Evaluation of Laboratory Values**

All laboratory assessments regardless whether performed locally at the study site or at the central laboratory will be performed using established methods. Laboratory values will be recorded and assessed by the investigator as normal value, abnormal values or clinically significant abnormal values, based on the reference ranges and units of measurement provided by the corresponding laboratories or investigators. Changes as compared to baseline will be recorded. Any changes to clinically significant abnormal values should be reported as AEs as outlined in Section 11.

### 10.3.6.2 Clinical Examinations

Clinical examinations will be performed at different time points as outlined in the previous sections and in the schedule of visits (see Sections 10.1 and 18.1).

**Vital Signs**

Vital signs, including heart rate, diastolic and systolic blood pressure and body temperature, will be measured at every study visit prior to infusion after the patient has been at rest in a sitting position for at least 5 minutes.

### Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be recorded at each visit where study medication was administered, during combination treatment phase and single agent maintenance phase, at the Safety Visit and at the Final Examination. The performance status grades and corresponding descriptions are given in Appendix A.

### Electrocardiogram

A standard 12-lead ECG will be performed at scheduled time points after the patient has been supine for at least 5 minutes. The QT interval (defined as the time period from earliest onset of the QRS complex to the latest offset of the T wave in the same lead; the lead with the longest QT interval should be selected) has to be exactly measured. All ECG recordings will be identified with the patient number, date and time of the recording and data including 3 selected consecutive QT intervals will be entered into the patient's eCRF. Original ECG records will be kept in the patient's file. Copies will be filed in the Investigator's File.

In case of any clinically relevant abnormalities, these should be reported as AEs (see Section 11).

### ECHO/MUGA

An echocardiogram or a MUGA scan will be performed at screening. All the recordings will be identified with the patient number, date and time of the recording and data will be entered into the patient's eCRF. Original records will be kept in the patient's file. Copies will be filed in the Investigator's File.

### Physical Examination

A complete physical examination will be performed at screening, at each day of study drug administration, and at the Safety Visit, based on the following body systems: general appearance, head (eyes/ears/nose/throat), respiratory, cardiovascular, abdomen, urogenital, musculoskeletal, neurological, lymph nodes and skin.

Body weight, height and BMI will be measured as part of the demography assessments, and body weight will also be measured on further scheduled time points for safety assessments.

### 10.3.6.3 Adverse Events

Adverse events will be recorded at every visit and severity has to be assessed and documented by the investigator. The definitions and management of and special considerations for AEs are provided in Section 11.

As part of the AEs, IRRs and skin toxicities will be identified and recorded accordingly.

# 11 ADVERSE EVENTS

## 11.1 Definitions

### 11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events occurring in patients during study drug treatment free periods of the study (i.e., follow-up phase) are also considered AEs.

**Note**: Tumor progression is part of the primary endpoint and is not to be considered an SAE in this study.

### 11.1.2 Adverse Drug Reaction

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

The phrase “responses to an investigational product” means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an investigational product qualify as ADRs.

All AEs for which the judgment of relationship to IMP is “possible” or higher will be considered ADRs. If a relationship to IMP is not given, then the AE must be treated as if the relationship to IMP were “possible.”

### 11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For an IMP, the known information is contained in the Investigator’s Brochure (IB). For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected.)

### 11.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background or due to local requirements for administration of the study treatment does not need to be considered an SAE.*
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the IMP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a patient that has received an IMP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.*
- is an important medical event
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The occurrence of malignant tumors other than those resulting from underlying study diagnosis is also to be considered serious.*

### 11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

### 11.1.6 Treatment-Emergent Adverse Events

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

## 11.2 Management of Adverse Events

Adverse events will be collected from the time of signing the ICF through the Safety Follow-Up Visit which should be performed for all patients at 28 days (+ 2 days) after the last dose administered. In case patients have discontinued prematurely due to AE, this AE has to be followed-up for a maximum of 28 days after last IMP dose to a satisfactory resolution as described in Section 11.2.5. Drug related AEs must be followed until they are resolved. Related SAEs can be reported at any time post therapy.

### 11.2.1 Collection

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the patient will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

### 11.2.2 Evaluation

#### 11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be graded using the NCI CTCAE v4.0 (http://ctep.cancer.gov/reporting/ctc.html). For those AEs not listed in the CTCAE, the following grading system should be employed:

| | |
|---|---|
| Mild (CTCAE grade 1): | Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with patient's daily activities. |
| Moderate (CTCAE grade 2): | Marked signs/symptoms that interfere with patient's usual activities, but still acceptable. |

| | |
|---|---|
| Severe (CTCAE grade 3) | Incapacitating signs/symptoms, which cause considerable interference with the patient's daily activities, unacceptable. |
| Life-threatening (CTCAE grade 4) | Life-threatening or disabling adverse event. |
| Death (CTCAE grade 5) | Death-related adverse event. See CTCAE Guidelines for assigning grade 5 |

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

#### 11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

#### 11.2.2.3 Action(s) Taken

Allowed action(s) taken for IMPs and nIMPs may consist of:

| | |
|---|---|
| No action taken | An indication that a medication schedule was maintained. |
| Drug interrupted/infusion rate reduced | An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of IMPs or nIMPs. |
| Dose adjustment | An indication that adjustment of dose for either IMPs or nIMPs was performed as described in detail in Section 9.9. |
| Drug withdrawn | An indication that a medication schedule was modified through termination of a prescribed regimen of IMPs or nIMPs. |

#### 11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Death*
- Unknown

*Although "death" is usually an event outcome, events such as sudden death or unexplained death should also be reported as SAEs.

#### 11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are listed below.

| | |
|---|---|
| Not related | An AE with sufficient evidence to accept that there is no causal relationship to IMP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.) |
| Unlikely related | An AE, including laboratory test abnormality, with a temporal relationship to IMP administration that makes a causal relationship improbable, and in which other drugs, events or underlying disease provide plausible explanations. |
| Possibly related | An AE with a reasonable time sequence to administration of the IP, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear. |
| Related | An AE occurring in a plausible time relationship to IMP administration, and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (de-challenge) is clinically reasonable. |

### 11.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death)
- Action(s) taken
- Outcome
- Investigator opinion regarding the AE relationship to the IMP(s)

### 11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the patient might be withdrawn from the study at the discretion of the investigator. In such case, the reason must be documented in the eCRF. The decision about whether the patient may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a patient that are not tolerable, or for which continued administration of IMP is not reasonable in view of the potential benefit to patient, the investigator must decide whether to stop the study and/or treat the patient. Special procedures may be recommended for the specific IMP, such as the collection of a serum sample for blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

### 11.2.5 Follow-up

Any AE will be followed up to a maximum of 28 days after the last dose of study medication to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted.

An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not resolved" is an acceptable final outcome for non-serious AEs at the end of a patient's participation in the study. SAEs should be followed up until resolution, or - if resolution becomes unlikely - until stabilization, or until death. An outcome of "not resolved" for SAEs at data lock is not acceptable.

All findings relevant to the final outcome of an AE must be reported in the patient's medical record and recorded on the appropriate eCRF.

### 11.2.6 Notification

#### 11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to xxxxxxxxxxxxxxx within 24 hours of first becoming aware of the event either by phone, by email or by completing the SAE Report Form and faxing/emailing it to the fax number/email address designated in the study specific Safety Management Plan.

**European contact details for 24-hours immediate reporting:**

| |
|---|
| **xxxxxxxxxxxxxxx Global Pharmacovigilance** |
| Fax: +xxxxxxxxxxxxxx |
| Email: GlycotopeSafety@xxxxxxxxxxxxxxx.com |

**US contact details for 24-hours immediate reporting:**

| |
|---|
| **xxxxxxxxxxxxxxx Global Pharmacovigilance** |
| Fax: xxxxxxxxxxxxx |
| Email: GlycotopeSafety@xxxxxxxxxxxxxxx.com |

At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Patient's study number
- Patient's year of birth
- Patient's gender
- Date of first dose of IMP(s)
- Date of last dose of IMP(s), if applicable
- Adverse event term
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met

- Concomitant medication at onset of the event
- Relevant past history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IMP(s). ("Is there a reasonable possibility that the IMP caused the SAE? Yes or No?")

Within 24 hours of the initial telephone notification, the investigator must fax a written SAE Report Form that describes the SAE to the recipient(s) of the initial information, who will forward the information to the sponsor within one working day. The investigator must also immediately deliver any available supporting information requested on the SAE Report Form or by the sponsor.

Any missing or additional relevant information concerning the SAE should be provided to the recipient(s) of the initial information in a written, follow-up SAE Report Form. Ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided to the designated individual(s) as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his/her health authorities, Independent Ethics Committee (IEC) and Institutional Review Board (IRB), principal and coordinating investigators, other study investigators, and institutions. The detailed reporting duties and division of responsibilities between Glycotope GmbH and xxxxxxxxxxxxxxx will be provided in a separate document (see Safety Management Plan). Each investigator is obligated to learn about the reporting requirements for investigators in her/his country. The study monitor may be able to assist with this.

#### 11.2.6.2 Adverse Drug Reactions

All ADRs related to the IMP will be reported by xxxxxxxxxxxxxxx to the relevant authorities and institutions: serious unexpected ADRs will be reported immediately, serious expected ADRs will be reported annually within Development Safety Update Reports (DSURs) and non-serious ADRs will be reported after completion of the study. Suspected sADRs must be reported to the sponsor immediately, regardless of the time which has elapsed since the end of the period of observation.

#### 11.2.6.3 Non-serious Adverse Events

Non-serious AEs will be recorded in the eCRF and reported by xxxxxxxxxxxxxxxx to Glycotope according to instructions given in the project operation manual (POM) and/or the safety monitoring plan (SMP) of this study.

### 11.3 Special Considerations

#### 11.3.1 Other Adverse Events for Immediate Reporting

In addition to SAEs, events, such as overdose and severe IRRs will require immediate reporting.

For documentation of overdose, please refer to Section 11.3.3.

Documentation of AEs leading to any of the above mentioned significant intervention must be reported promptly to xxxxxxxxxxxxxxx within 24 hours of first becoming aware of the event either by phone, by email or by completing a specific AE report form and faxing/emailing it to the fax number/email address designated in the study specific Safety Management Plan.

### 11.3.2 Pregnancies

All women of childbearing potential and all male patients with a partner of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy (of the partner, as applicable) during study participation until 6 months after last administration of any study medication, particularly cisplatin or carboplatin. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted at randomization, prior to administration of IMP, at the beginning of single-agent maintenance phase of the study and at the Safety Visit on every woman of childbearing potential. A woman who is found to be pregnant at randomization will be excluded from the study and considered to be a screening failure.

Female patients who become pregnant during treatment period and 4 weeks after last dose of IMP in the study must be withdrawn from the study.

The investigator must report the pregnancy as if it were an SAE within 24 hours of learning of the pregnancy. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on a Pregnancy Data Collection Form provided by Glycotope or its designee.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities or maternal and newborn complications. Every infant has to be followed up for 2 months after delivery.

### 11.3.3 Overdose

The maximal dose of CetuGEX™ or cetuximab treatment should not be exceeded during the study.

Overdose that occurs during the study will be treated and documented as an AE, regardless of whether the overdose results in symptoms of an AE. Overdose should be reported in written form to the designated individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, patient identification, IMP, dose, action taken (e.g., administration of antidote or supportive measures or therapy), and any comments.

## 12 DATA SAFETY MONITORING BOARD

Xxxxxxxxxxxxxxx will establish an independent DSMB, whose task is to review periodically 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, 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 will be included to monitor a potential detrimental effect of the IMP. 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.

# 13 STATISTICS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) describing in detail the analyses to be conducted will be prepared as a separate document.

The main statistical analysis will be performed when 192 PFS events have been observed. Based on the statistical assumptions as described in Section 13.2 this is expected to occur after 36 months of study duration (24 months recruitment + 12 months follow up). The result of a prolonged follow-up for OS will be analyzed and reported in an amendment to the main analysis.

## 13.1 Study Endpoints

### 13.1.1 Primary Endpoint

Primary endpoint of the trial is PFS 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, assessed by the investigator according to adapted immune-related RECIST 1.1 (modified irRC).

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.

### 13.1.2 Secondary Endpoints

Secondary efficacy endpoints include:

- PFS as assessed by independent centralized reading according to modified irRC.
- Objective response rate (ORR, i.e., CR + PR) according to modified irRC at the end of combination treatment.
- Best overall response rates (CR, PR, SD) according to modified irRC including maintenance therapy treatment.
- Clinical benefit rate (CBR, i.e., CR + PR + SD) according to modified irRC.
- Overall survival (OS) defined as time from randomization until death of any cause.
- Time to treatment failure (TTF), as defined in Section 10.3.1.2.
- QoL scores assessed using EORTC-QLQ-C30 and EORTC-QLQ-H&N35H.

In addition, PFS and all secondary efficacy endpoints listed above will be analyzed by FcγRIIIa-allotype subgroups (i.e., FF, FV and VV), by p16 status, by EGFR status, and other potential parameters, unless the sample sizes in subgroups are too low.

### 13.1.3 Pharmacokinetic Endpoints

The PK samples for determining CetuGEX™ antibody concentrations will only be collected for the first-line treatment, according to the schedule presented in Appendix B. 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 more fully PK profile 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 and 5 hour ± 5 min, 7 hours ± 15 min (Day 1), 24 ± 1 hour (Day 2), 48 ± 2 hours (Day 3), 72 ± 2 hour (Day 4), and 7 days (168 ± 2 hours; Day 8) after the start of the infusion on Day 1. In addition, since the first infusion on Cycle 1 will be split between Day 0 and Day 1, PK samples will be available for pre- and post-infusions on Day 0.

### 13.1.4 Safety Endpoints

The safety endpoints are:

- Incidence of AEs and SAEs, including incidence of target/class-specific side effects (skin reactions, diarrhea).
- IRRs.
- Physical assessments.
- Laboratory assessments.
- Vital signs.
- ECG.

In addition, the incidence of AEs will be analyzed by FcγRIIIa-allotype subgroups (FF, FV and VV).

### 13.1.5 Exploratory Endpoints

The exploratory endpoints in this study are:

- Immunogenicity: incidence of ADAs.
- Immunological parameters: cytokine levels and immune cell status.

## 13.2 Sample Size Determination

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[15] 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 48 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.

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.

### 13.3 Analysis Populations

The analysis populations include the following:

- The intention-to-treat (ITT) population will consist of all randomized patients. The ITT population is 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 the statistical analysis plan and finally decided in a Data Review Meeting before database lock. This population will be utilized to evaluate the sensitivity of the primary efficacy analysis.
- The pharmacokinetic (PK) population will consist of all randomized patients including the subset of patients who had blood samples collected for PK noncompartmental profiling, 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.

## 13.4 Statistical Analyses

### 13.4.1 General Methods

For dichotomous and categorical variables, absolute and relative frequencies (counts and percents) will be calculated. For continuous variables, comprehensive data summaries will be presented with sample characteristics (n, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum) by treatment. Where data are collected over time, both the observed data and the change from baseline will be summarized at each visit.

### 13.4.2 Study Patients and Demographics

#### 13.4.2.1 Disposition and Withdrawals

The numbers of patients randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of patients in each analysis population will be reported. This analysis will be based on all patients.

#### 13.4.2.2 Demographics and Other Baseline Characteristics

Demographic variables will include age, race, weight, BMI, smoking status and alcohol consumption.

Other baseline characteristics will include:

- Tumor specific medical history (time since first diagnostic, tumor pre-treatment, tumor grading)
- FcγRIIIa status
- General medical history
- Prior and concomitant medications will be summarized by treatment group and by the number and percentage of patients taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD).

These analyses will be conducted for the safety population.

### 13.4.3 Efficacy Analyses

#### 13.4.3.1 Primary Analysis

Primary endpoint of the trial is PFS defined as time from randomization until disease progression (assessed by the investigator) or death of any cause. 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.

The primary efficacy analysis for PFS will be based on the ITT population. A log-rank test will be used to test the null hypothesis of equal treatment effects at an overall significance level of 0.05. 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. As a sensitivity analysis, a proportional hazards regression model will be applied and the effects of the stratification factors, the p16 status, and the EFGR status will be estimated:

- FcγRIIIa status (FF or FV or VV),
- p16 status (+/-),
- EGFR status (+/-),
- Oral cavity and oropharynx vs. other locations,
- Locally recurrent vs. metastatic disease.
- EGFR treatment naïve vs. EGFR treatment as part of multimodal treatment.

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.

The analysis will be repeated for the PP population as a sensitivity analysis.

#### 13.4.3.2 Secondary Analyses

A Chi-squared test will be performed to evaluate the effects of treatment on response rates as defined in Section 13.1.2. A logistic regression model will be fit to estimate odds ratios for the association of stratification factors, the p16 status, and the EGFR status with response categories. Corresponding 95%-confidence intervals will be calculated for the treatment differences in response rates.

Overall survival and TTF will be analyzed analogously to PFS on an ITT basis. Additional models will be applied to evaluate the impact of second line treatments on OS. Details will be given in the SAP.

If subgroup sample sizes allow, analyses of the primary and secondary efficacy endpoints will be repeated for the FcγRIIIa-allotype subgroups (i.e., FF, FV, VV), the p16 status subgroups as well as the EGFR status subgroups, omitting the FcγRIIIa factor, the p16 status and the EGFR status factor, respectively.

#### 13.4.3.3 Pharmacokinetics

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 10$^{th}$ infusion). The samples from the PK profile group will be used for non-compartmental analyses. All samples will be pooled for a population PK analysis estimating clearance and volume of distribution. Both results from PK methods of analysis will be reported as they have different strengths and weaknesses.

The population PK analysis will be described in a separate population PK plan that follows recommendations from regulatory guidance from FDA (Guidance for Industry – Population Pharmacokinetics) and EMA (Guideline on reporting the results of population pharmacokinetic analyses CHMP/EWP/185990/95, June 2007). These regulatory

guidance will also be followed for conduct of the population PK analysis with validation by boot-strapping techniques and reporting results. Population PK analysis will be conducted using Pharsight Phoenix NLME® software or other established population PK software such as NONMEM®.

These analyses will be conducted for the PK population.

### 13.4.4 Safety and Tolerability Analyses

The safety analysis will be performed for the safety population.

#### 13.4.4.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of incidence rates (frequencies and percentages) of individual TEAEs by MedDRA System Organ Class and Preferred Term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum intensity and TEAEs by strongest relationship to study treatment.

Treatment emergent adverse events (TEAEs) are defined as any AE which started or deteriorated at or after start of treatment. Incidences for TEAE will be calculated on Preferred Term level, on System Organ Class level and globally by treatment group. On each analysis level, a patient will be counted only once. Frequencies for TEAE will also be given for causality and severity graded according to NCI-CTC (AE criteria Version 4.0).

In addition, toxicity as evaluated via incidence of AEs will be analyzed by FcγRIIIa allotype subgroups (FF, FV and VV).

The incidences of ADA will be summarized in frequency tables per treatment arm.

#### 13.4.4.2 Clinical Laboratory Evaluations

For hematology and biochemistry variables, descriptive summaries of observed values and changes from baseline will be presented by treatment arm.

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, 5 categories will be used that take into account the investigator’s assessment of clinical relevance: "clin. rel., above", "non-clin. rel., above", "within", "non clin. rel., below", "clin. rel., below".

The assessments of laboratory variables concerning reference ranges and clinical relevance will be tabulated by visit for each clinical laboratory parameter by treatment arm (frequency tables). Additionally, for each laboratory parameter, shifts in assessments from baseline to the last on-study value 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.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by treatment arm (frequency tables). Additionally, for each of these urine

parameter shifts in assessments from baseline the last on-study value will be presented for each treatment arm (shift tables).

#### 13.4.4.3 Vital Signs

Descriptive summaries of observed values and changes from baseline will be calculated for vital signs. These summaries will be presented by visit and treatment arm.

#### 13.4.4.4 Electrocardiograms and Echocardiograms

Descriptive summaries of observed values and changes from baseline will be calculated for ECG variables. QT will be corrected according to Bazett. Frequency and shift tables will be presented for the classified values of $QT_c$ as given by the International Conference on Harmonisation (ICH)-E14, as well as for the overall clinical assessment.

For ECHO/MUGA assessments, descriptive values of observed values at baseline ("Normal"/"Abnormal [not] clinically significant") will be presented by treatment arm.

#### 13.4.4.5 Physical Examination Findings

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

### 13.4.5 Interim Analysis

No formal interim analysis will be performed. Descriptive summaries of PFS and OS events, including point estimates and 95% confidence intervals of the hazard ratios, will be provided to the DSMB at all meetings starting from the second meeting (approximately 9 months after start of enrollment) in order to monitor potential detrimental effects of the investigational compound.

## 14 STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

### 14.1 Sponsor and Investigator Responsibilities

### 14.1.1 Sponsor Responsibilities

The Sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a patient from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.6), and/or to discontinue the study (Section 14.5.2).

Glycotope GmbH agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

### 14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.2), the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the July 2002 ICH Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 2008 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, IMPs, and their specific duties within the context of the study. Investigators are responsible for providing Glycotope GmbH with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by Glycotope GmbH and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

## 14.2 Site Initiation

Study personnel may not screen or enroll patients into the study until after receiving notification from Glycotope GmbH or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The conduct of the study has been approved by the corresponding competent authority.
2. The study site has received the appropriate IEC/IRB approval for the protocol and the appropriate ICF.
3. All GCP documents have been submitted to and approved by Glycotope or its designee.
4. The study site has a Clinical Trial Agreement in place.
5. Study site personnel, including the investigator, have participated in a study initiation meeting.

## 14.3 Study Documents

All documentation and material provided by Glycotope GmbH for this study are to be retained in a secure location and treated as confidential material.

### 14.3.1 Site Documents

Site specific documents according to regulatory and GCP requirements must be received from the investigator and reviewed and approved by Glycotope GmbH or its designee before the study site can initiate the study and before Glycotope GmbH will authorize shipment of IMP to the study site. Copies of the investigator's documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the IB, eCRF completion guidelines, copies of regulatory references, copies of IEC/IRB correspondence, and IMP accountability records should also be retained as part of the investigator's site documents. It is the investigator's responsibility to ensure that copies of all required documents are organized, current, and available for inspection.

### 14.3.2 Case Report Forms

By signing the Investigator's Agreement (Section 18.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who sign an ICF.

Case Report Forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by Glycotope or its designee.

The eCRFs may be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

### 14.3.3 Source Documents

All information recorded in the EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Before the study starts, a list identifying any data to be recorded directly on the eCRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to Glycotope GmbH or its designee. The results of the FcγRIIIa status assessment will be provided to the study site and should be retained with each patient's source data.

## 14.4 Data Quality Control

Glycotope GmbH and its designees will perform quality control checks on this clinical study.

### 14.4.1 Monitoring Procedures

Glycotope GmbH and/or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Glycotope GmbH personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review documents and procedures as outlined in the Monitoring Plan.

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of Glycotope, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.2), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Glycotope GmbH or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

### 14.4.2 Data Management

Glycotope GmbH or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and xxxxxxxxxxxxxxxxxx standard operating procedures (SOPs). A comprehensive data management plan (DMP) will be developed including a data management overview, database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

### 14.4.3 Quality Assurance/Audit

This study will be subject to audit by Glycotope GmbH or designee. The audits will be undertaken to check compliance with GCP guidelines.

Glycotope GmbH or designee may conduct additional audits on a selection of study sites, requiring access to patient notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IEC/IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Glycotope GmbH immediately.

## 14.5 Study Termination

The study may be terminated at Sponsor's discretion at any time and for any reason.

### 14.5.1 Regular Study Termination

The end of this study is defined as the date when:

- The number of PFS events required for analysis are reached,
- all patients have discontinued medication, and
- a relevant number of deaths have occurred to obtain information on overall survival.

Within 90 days of the end of the clinical study, Glycotope GmbH or designee will notify the IEC/IRBs and regulatory authorities on the regular termination of the study as required according to national laws and regulations.

### 14.5.2 Premature Study Termination

The study may be terminated prematurely for any reason and at any time by Glycotope GmbH, IEC/IRBs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Reasons for premature study termination may be: new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk ratio, the sponsor decides to stop the study because of failure to meet expected goals, or the development of the IMP is discontinued.

Within 15 days of premature termination of a clinical study, Glycotope GmbH or designee will notify the IEC/IRBs and regulatory authorities on the premature termination as required according to national laws and regulations. Glycotope GmbH or designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all investigators have to inform their patients and take care of appropriate follow-up and further treatment of the patients to ensure protection of the patients' interests. Study sites may be asked to have all patients currently participating in the study complete all of the assessments for the Final Examination Visit.

## 14.6 Study Site Closure

At the end of the study, all study sites will be closed. Glycotope GmbH may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate patient enrolment

### 14.6.1 Record Retention

After completing the study, Glycotope GmbH will receive the original eCRFs or at least a legible copy and retain the documents at least 10 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the patient identification codes, patient files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with Glycotope.

At the end of such period, the investigator shall notify Glycotope GmbH in writing of her/his intent to destroy all such material. Glycotope GmbH shall have 30 days to respond to the investigator's notice, and shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

### 14.6.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until Glycotope GmbH has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the patient.

### 14.7 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Glycotope GmbH. The protocol amendment must be signed by the investigator and approved by the IEC/IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

### 14.8 Use of Information and Publication

All information concerning CetuGEX™, Glycotope GmbH operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Glycotope GmbH or designee to the investigator and not previously published, is considered confidential and remains the sole property of Glycotope GmbH. Case report forms also remain the property of Glycotope GmbH. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of Glycotope GmbH.

The information developed in this study will be used by Glycotope GmbH in connection with the continued development CetuGEX™ and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Glycotope GmbH. Publication or other public presentation of CetuGEX™ data resulting from this study requires prior review and written approval of Glycotope GmbH. Abstracts, manuscripts, and presentation materials should be provided to Glycotope GmbH for review and approval at least 90 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Glycotope GmbH has reviewed and consented on such a presentation or manuscript for publication.

## 15 FINAL CLINICAL STUDY REPORT

Glycotope GmbH will retain ownership of the data.

The final clinical study report (CSR) will be written within one year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR will be submitted to the regulatory authorities according to local requirements.

# 16 ETHICAL AND LEGAL CONSIDERATIONS

## 16.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the July 2002 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 2008 Version of the Declaration of Helsinki, the applicable regulations of the countries in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

See Appendix D for regulation and guidelines.

## 16.2 Patient Information and Informed Consent

According to the Declaration of Helsinki and ICH GCP, patients must provide their written informed consent prior to enrolment in a clinical study and before any protocol-specified procedures are performed. Patients must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each patient should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC/IRB. Patients must be given ample opportunity to inquire about details of the study.

Patient information and the ICF must be in a language fully comprehensible to the prospective patient. The written information must be provided to the patient to give him/her sufficient time to understand the information and to prepare questions before being asked for his/her consent. The investigator must confirm that the text was understood by the patient. The patient will then sign and date the IEC/IRB-approved consent form indicating that he/she has given his/her consent to participate in the study. The signature confirms the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study patient number. Each patient's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Glycotope GmbH and/or xxxxxxx xxxxxxxx personnel. Collection of informed consent must be documented on the eCRF.

Furthermore, the patient will be informed that if he/she wishes to drop-out or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Patients may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Patients will be asked to agree to a final assessment in the event of an early termination of the study.

Patients will be informed that data from their case may be stored in a computer without inclusion of their name and such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IEC/IRBs. The terms of the local data protection legislation will be applied as appropriate.

## 16.3 Approval by Independent Ethics Committee/Institutional Review Board

For Investigational New Drug (IND) studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IEC/IRB and competent authorities must review and approve this protocol before study initiation. Written notification of approval is to be submitted by xxxxxxxxxxxxxx to Glycotope GmbH before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature.

Until written approval by the IEC/IRB has been received by the investigator, no patient may undergo any study-related procedure.

Protocol amendments must also be reviewed and approved by the IEC/IRB and competent authority. Written approval from the IEC/IRB, or a designee, must be received by Glycotope GmbH and by the investigator before implementation of the amendment.

## 16.4 Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and Glycotope GmbH or designee.

# 17 REFERENCES

[1] Umana P, Jean-Mairet J, Moudry R, Amstutz H, Bailey JE. Engineered glycoforms of an antineuroblastoma IgG1 with optimized antibody-dependent cellular cytotoxic activity. Nat Biotechnol. 1999;17:176 – 180.

[2] Suzuki E, Niwa R, Saji S, et al. A nonfucosylated anti-HER2 antibody augments antibody-dependent cellular cytotoxicity in breast cancer patients. Clin Cancer Res.2007;13:1875-1882.

[3] Shields RL, Lai J, Keck R, et al. Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. J Biol Chem.2002;277:26733-26740.

[4] Shinkawa T, Nakamura K, Yamane N, et al. The absence of fucose but not the presence of galactose or bisecting N-acetylglucosamine of human IgG1 complex-type oligosaccharides shows the critical role of enhancing antibody-dependent cellular cytotoxicity. J Biol Chem. 2003;278: 3466-3473.

[5] Bibeau F, Lopez-Crapez E, Di Fiore, F, et al. Impact of FcgammaRIIa-FcgammaRIIIa polymorphisms and KRAS mutations on the clinical outcome of patients with metastatic colorectal cancer treated with cetuximab plus irinotecan. J Clin Oncol. 2009; 27:1122-1129.

[6] Musolino A, Naldi N, Bortesi B, et al. Journal of Clinical Oncology 2008; 26:1778-1780.

[7] Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol.2003; 21:3940-3947.

[8] Zhang W, Gordon M, Schultheis AM, et al. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. J Clin Oncol.2007; 25:3712-3718.

[9] Vermorken JB. Medical treatment in head and neck cancer. Ann Oncol 16 (Suppl. 2). 2005, ii: 258-264

[10] Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2006; 24 (17): 2644-2652

[11] EMA, SmPC for Erbitux® (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000558/human_med_000769.jsp&mid=WC0b01ac058001d124)

[12] Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7: 1748-1756

[13] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247

[14] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009; 15 (23): 7412-7420.

[15] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008; 359:1116-1127

# 18 ATTACHMENTS

## 18.1 Schedule of Events

| | **Screening (within 28 days prior first infusion)** | **Random-ization (1-3 d before first infusion)** | **Day 0*** | **Combination treatment phase (max. 6 cycles of chemotherapy)** | | | | | | **Single-agent maintenance therapy** | **Safety Visit[1] (28 + 2 days after last dose)** | **FE Visit[2]** | **Follow -up[3]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | D1 | D2 | D3 | D4 | D8 | D15 | **D1 of each week** ± 1 day | | | |
| | | | | W1 | | | | W2 | W3 | | | | |
| Written informed consent | X | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | X[4] | X[4,5] | | | | | | | | | |
| Check availability of pre-existing tumor tissue sample | X | | | | | | | | | | | | |
| Assign identification number (IWRS) | X | | | | | | | | | | | | |
| Assign randomization number (IWRS) | | X[6] | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| SCCHN diagnosis and history | X | | | | | | | | | | | | |
| Medical history apart SCCHN | X | | | | | | | | | | | | |
| Physical examination | X[36] | | X[20] | X | | | | X | X | X | X | | |
| ECOG performance status | X | | X[4] | X[7] | | | | X | X | X | X | X | |
| Vital signs [38] | X | | X[4] | X[4] | X[34] | X[34] | X[34] | X | X | X | X | X | |
| Height, weight, and BMI[8] | X | | X[4] | X[4] | | | | X | X | X | X | | |
| 12-lead electrocardiogram | X | | X[9] | X[5,10] | | | | | | X[10] | X | | |
| ECHO/MUGA | X | | | | | | | | | | | | |
| Evaluation of tumor size by CT or MRI | X [41] | | | X[10, 41] | | | | | | X[11, 41] | | | |
| Clinical laboratory tests [38] (hematology, coagulation panel, chemistry, urinalysis) | X[33] | | X[4] | X[4,7] | | | | | | X[12] | X | | |
| EGFR expression | | X[13] | | | | | | | | | | | |
| p16 tumor suppressor gene status | | X[13] | | | | | | | | | | | |
| HPV status | | X[32] | | | | | | | | | | | |
| Cytokine release[14, 39] | | | X[15,20] | X[16] | | | | X[17] | X[17] | | | | |

| | **Screening (within 28 days prior first infusion)** | **Random-ization (1-3 d before first infusion)** | **Day 0*** | **Combination treatment phase (max. 6 cycles of chemotherapy)** | | | | | | **Single-agent maintenance therapy** | **Safety Visit[1] (28 + 2 days after last dose)** | **FE Visit[2]** | **Follow -up[3]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | D1 | D2 | D3 | D4 | D8 | D15 | **D1 of each week** ± 1 day | | | |
| | | | | W1 | | | | W2 | W3 | | | | |
| Immune status[14, 39] | | | X[4,20] | X[18] | | | | X[19] | | | X | | |
| Anti-Drug-Antibody testing (ADA)[20, 39] | | | X[4] | X[21] | | | | X[22] | | X[35] | X | | |
| Genotyping (Fcγ receptors status)[23] | X | | | | | | | | | | | | |
| Pregnancy test for female subjects | | | X[4] | X[5] | | | | | | X[24] | X | | |
| PK blood sample collection[20, 39] | | | X[25] | X[25,26] | X[26] | X[26] | X[26] | X[27] | X[28] | X[26,29] | X | | |
| Quality of Life questionnaires [39] | | | X[4] | X[5,10] | | | | | | X[30] | X | | |
| Administer study drug (CetuGEX™ or cetuximab) [40] | | | X[20] | X[37] | | | | X[37] | X[37] | X[37] | | | |
| Administer cisplatin/carboplatin | | | | X[31] | | | | | | | | | |
| Administer 5-FU (continuous administration) | | | | X | X[34] | X[34] | X[34] | | | | | | |
| Drug accountability | | | | X | X[34] | X[34] | X[34] | X | X | X | | | |
| Concomitant medications | X | | X[4] | X | X[34] | X[34] | X[34] | X | X | X | X | X | |
| Adverse events | | | X[4] | X | X[34] | X[34] | X[34] | X | X | X | X | X | |
| Record of post-PD tumor therapies | | | | | | | | | | | | | X |

Abbreviations: BMI = body mass index, CT = computed tomography, ECHO = echocardiogram, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, FE = Final Examination, HPV = human papilloma virus, IWRS = interactive web response system, MRI = magnetic resonance imaging, MUGA = Multiple Gated Acquisition, PK = pharmacokinetics, SCCHN = squamous cell carcinoma of the head and neck, 5-FU = 5-fluorouracil, W = week.

* Day 0 only applies for patients randomized to receive CetuGEX™.

1 The Safety Follow-Up Visit constitutes the Final Examination Visit for the patients treated with study medication until progression of disease.

2 As soon as progression of disease is detected, FE assessments will be performed for all patients who prematurely discontinued study treatment. For patients withdrawing prematurely from the complete study, the Final Examination will be performed at the date of withdrawal.

3 Will be performed quarterly by phone calls for at least 24 months after randomization of last patient.

4 To be performed pre-dose, as applicable.

5 To be performed only for patients receiving cetuximab, only on Day 1 of Cycle 1.

6 The investigator may contact the IWRS for randomization within 1 to 3 days prior to first infusion.

7 To be performed in Cycle 2 and every following cycle; To be performed in Cycle 1 only for patients receiving cetuximab.
8 Height will be measured only at screening.
9 Only to be performed, if not done within 7 days prior randomization.
10 To be performed every 6 weeks after randomization (i.e., Day 1 of Cycles 3 and 5, and every 6 weeks thereafter).
11 To be performed every 6 weeks within the first 18 weeks after randomization, and every 8 weeks thereafter.
12 To be performed every 6 weeks after randomization.
13 Pre-existing tumor-tissue samples will be sent to laboratory once patient was randomized; remaining tumor-tissue needs to be stored for further analysis
14 To be performed only in a subset of approximately 30 patients per treatment arm.
15 To be performed pre-dose, 1h after start of infusion and at the end of the first infusion.
16 To be performed pre-dose, at the start of the highest infusion rate, 1 h after start of the highest infusion rate and at the end of infusion on Day 1 of Cycle 1; pre-dose, 1 h after start of infusion and at the end of infusion on Day 1 of Cycle 2.
17 To be performed pre-dose, 1 h after start of infusion and at the end of infusion on Cycle 1, only.
18 To be performed pre-dose, only on Day 1 of Cycle 1 for patients receiving cetuximab.
19 To be performed pre-dose, only on Day 8 of Cycle 2.
20 To be performed only for patients receiving CetuGEX™.
21 To be performed pre-dose, on Day 1 of Cycles 2 and 4 only.
22 To be performed pre-dose, on Day 8 of Cycle 1 only.
23 Only in case the patient will enter the study, this blood sample might be used at a later time point for further analyses like FCγRII status.
24 To be performed pre-dose, only on the first week of maintenance therapy.
25 Blood sampling for PK prior to the start of infusion and at the end of infusion, on Day 1 of Cycles 1 to 4, only.
26 For a subgroup of approximately 30 patients only: Additional blood sampling for PK as detailed in Appendix B.
27 Blood sampling for PK prior to start of infusion and after the end of infusion: in Cycles 1 to 3 for all patients; in Cycle 4 only for a subgroup of approximately 30 patients, prior to start of infusion; all PK samplings as detailed in Appendix B.
28 Blood sampling for PK prior to start of infusion and at the end of infusion, only in Cycle 1 to 3, for all patients.
29 Blood sampling for PK prior to start of infusion and after the end of infusion until $10^{th}$ infusion after randomization, if combination therapy was discontinued prematurely.
30 To be performed 18 weeks after randomization. In case combination therapy was discontinued prematurely, also 6 and 12 weeks after randomization, as applicable.
31 For Cycle 1, cisplatin is mandatory. Change to carboplatin in subsequent cycles might be accepted in case of toxicity of cisplatin.
32 HPV status will be assessed at a central laboratory, either at randomization or at a later time point. A tumor-tissue sample provided will be used for evaluation.
33 Please note that creatinine clearance needs to be assessed at screening unless previous results not older than 6 weeks are available.
34 Site visits on days 2 to 4 are only obligatory for patients either included in the PK subgroup or if they have no transportable pump for 5-FU administrations. Assessment of vital signs and records of drug accountability, adverse events, and concomitant medication will only be performed for patients visiting the site.
35 To be performed pre-dose, 1, 3 and 9 weeks after randomization, if combination therapy was discontinued prematurely.
36 Including underlying disease condition.

37 Except for Day 1 of Cycle 1 a time window of ± 1 day will be allowed for the weekly infusions (calculated from the previous infusion).
38 If chemotherapy administration is delayed for any reasons, assessments should be repeated in relation to the chemotherapy administration.
39 Assessments to be done in relation to administration of CetuGEX™/cetuximab (also in case of delay in chemotherapy administration).
40 If the administration of CetuGEX™/cetuximab is skipped for any reason, all assessments scheduled for this study visit day are to be performed as planned.
41 Screening: head and neck region, chest, and abdomen. Subsequent assessments: 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.

## 18.2 Investigator's Agreement

PROTOCOL NUMBER: GEXMab52201

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 (The "RESGEX" Study)

FINAL PROTOCOL: Final Version 4.0, 06 February 2015

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Glycotope GmbH and xxxxxxx xxxxxxxx during the study. I ensure that this study will be conducted in accordance with the revised Declaration of Helsinki 2008, ICH-GCP and the local laws and regulations relevant to the use of new therapeutic agents.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

## APPENDICES

A. ECOG Performance Status

B. Time Schedule for PK Blood Sampling

C. Response Evaluation Criteria in Solid Tumors

D. Regulations and Good Clinical Practice Guidelines

E. SmPC for Cetuximab (Erbitux®)

F. SmPC for Cisplatin

G. SmPC for 5-FU

H. SmPC for Carboplatin

## A. ECOG Performance Status

| ECOG Performance Status* | |
|---|---|
| Grade | Description |
| 0 | Asymptomatic (Fully active, able to carry on all pre-disease performance without restriction). |
| 1 | Symptomatic but completely ambulatory (Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | Symptomatic, in bed <50% of the time (Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours). |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedbound. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |

*As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

## B. Time Schedule for Pharmacokinetics Blood Sampling

| | Treatment Cycle 1 (Infusions 1-3) | | | | | | | | | | | | | Treatment Cycle 2 / Treatment Cycle 3 (Infusions 4-9) | | | | | | Treatment Cycle 4 (Infusions 10) | | | | | | | SV / FE | Total Number of Samples |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit*** | Day 0 | | Day 1 (Inf. 1) | | | | Day 2 to Day 4 | | | Day 8 (Inf. 2) | | Day 15 (Inf. 3) | | Day 1 (Inf. 4/7) | | Day 8 (Inf. 5/8) | | Day 15 (Inf. 6/9) | | Day 1 (Inf. 10) | | | Day 2 to Day 4 | | | Day 8 | | |
| | W1 | | | | | | | | | W2 | | W3 | | W4/ W7 | | W5/ W8 | | W6/ W9 | | W10 | | | W11 | | | W12 | | |
| **Timing** | Prior infusion | At end of inf. | Prior infusion | At end of inf. | After start of inf. | | After start of inf. | | | Prior infusion (168 ± 2 h after start of 1st infusion on Day 1) | At end of inf. | Prior infusion | At end of inf. | Prior infusion | At end of inf. | Prior infusion | At end of inf. | Prior infusion | At end of inf. | Prior infusion | At end of inf. | After start of inf. | | After start of inf. | | | Prior inf. (168 ± 2 h after start of 10th infusion) | 28 days after last inf. | |
| | | 0 h | | 0 h | 5 h ± 5 min | 7 h ± 15 min | 24 ± 1 h | 48 ± 2 h | 72 ± 2 h | | 0 h | | 0 h | | 0 h | | 0 h | | 0 h | | 0 h | 5 h ± 5 min | 7 h ± 15 min | 24 ± 1 h | 48 ± 2 h | 72 ± 2 h | | | |
| **All Patients (CetuGEX™ arm)** | X | X | X | X | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | X | 23 |
| **Selected Subset** | | | | | X | X | X | X | X | | | | | | | | | | | | | X | X | X | X | X | X | | 11 |

If the administration of CetuGEX™/cetuximab is skipped for any reason, the pre-dose blood sample scheduled for this study visit day is to be taken as planned.

* In case of premature discontinuation of chemotherapy cycles, please refer to the corresponding CetuGEX™ infusion numbers for scheduling PK assessments.

W = Week

## C. Response Evaluation Criteria in Solid Tumors

The criteria below are based on RECIST 1.1 criteria as described by Eisenhauer et al. (2009) and adapted according to immune-related response criteria (irRC) as defined by Wolchok et al. (2009). The adapted immune-related RECIST 1.1 (modified irRC) criteria are used in order to permit physicians to continue treatment in spite of the appearance of small new lesions and/or transient increases in tumor burden, as these may be manifestations of an anti-tumoral inflammatory response in a therapeutic setting which involves immunological mechanism of action.

### Measurable Lesions:

The tumor lesion must be accurately measured in at least one dimension (longest diameter in the plane of measurement will be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 20 mm by chest x-ray

Measurable malignant lymph node:

To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assessed by CT/MRI scan (CT/MRI 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. Nodes with a short axis >10 and <15 mm will be considered pathologically enlarged but non-measurable (see below).

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft-tissue components will be considered measurable if the soft-tissue component can be evaluated by cross-sectional imaging (i.e., CT scan) and meets the general definition of measurability.

A lesion located in a previously irradiated area, or an area previously subjected to any locoregional therapy, will be considered measurable only if there has been a documented increase in lesion size subsequent to prior treatment but before study entry.

### Non-Measurable Lesions

Non-measurable lesions are all other lesions, including small lesions (longest diameter smaller than 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Legions considered truly non-measurable are: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Simple cysts will not be considered malignant lesions, and will be neither measurable nor non-measurable. Cystic lesions believed to be metastases may be considered measurable if they meet the general definition of measurability, but non-cystic lesions are preferred as target lesions.

**New Lesions**

The definition of measurable and non-measurable lesions also applies to new lesions to be included in the assessments for adapted immune-related RECIST 1.1.

**Methods of Measurement**

All measurements must be recorded in metric notation, using a ruler or calipers. All baseline evaluations must 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 must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluations 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 will only be considered measurable when they are superficial and at least 10 mm as assessed using calipers (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. However, CT scan is preferred.

CT scans and MRI are the best currently available and reproducible methods to measure lesions selected for response assessment.

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 one assessment to the next.

Endoscopy and laparoscopy: the use of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

**Baseline Documentation of Target and Non-Target Lesions**

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special attention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As previously mentioned, pathological nodes defined as measurable must meet the criterion of a short axis of at least 15 mm by CT/MRI scan to be identified as target lesions. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis less than 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. The baseline sum diameters will be used as reference to further characterize the objective tumor response.

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 but the presence or absence of each should be noted throughout follow-up.

**Response Criteria According to Adapted Immune-Related RECIST 1.1**

In this study, disease progression using adapted immune-related RECIST 1.1 as determined by the investigator will serve to determine discontinuation from study treatment. New lesions will be measured and incorporated into the tumor assessment. Tumor diameter will be treated as a continuous variable and new lesion diameter will be added to the diameter of existing target diameter sum.

The response assessment in this study is based on total measurable tumor burden adapted from Wolchok et al. (2009). Selected target lesions and measurable new lesions occurring after start of study treatment are incorporated into the tumor burden. Up to 2 measurable new lesions per organ are added together with the sum of diameters of the target lesions to provide the total tumor burden.

<u>Evaluation of target lesions</u>

1. Complete Response (CR): Disappearance of all non-nodal target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
2. Partial Response (PR): At least a 30% decrease in the tumor burden (sum of the longest lesion diameter (LD) of target lesions (including the short axes of any target lymph nodes plus measurable new lesions), taking as reference the baseline sum diameters.
3. Progressive Disease (PD): At least a 20% increase in the tumor burden (including the short axes of any target lymph nodes plus measurable new lesions), taking as reference the smallest tumor burden recorded since the treatment started.

4. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest tumor burden since the treatment started.

Evaluation of non-target lesions

1. Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
2. Non-CR/Non-Progressive Disease (-PD): Persistence of one or more non-target lesions.
3. PD: Unequivocal progression of existing non-target lesions. To achieve "unequivocal PD", there must be an overall level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target lesion, the treating physician would feel it important to change therapy.

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

**Evaluation of Best Overall Response According to Adapted Immune-Related RECIST 1.1**

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

| **Measurable response** | **Non-measurable response** | | **Overall Response** |
|---|---|---|---|
| **Target and new, measurable lesions (tumor burden), %** | **Non-target lesions** | **New, non-measurable lesions** | **Using irRECIST** |
| ↓100 | CR | Absent | irCR |
| ↓100 | Stable | Any | irPR |
| ↓100 | Unequivocal progression | Any | irPD |
| ↓≥30* | Absent/Stable | Any | irPR |
| ↓≥30* | Unequivocal progression | Any | irPD |
| ↓<30 to <20↑ | Absent/Stable | Any | irSD |
| ↓<30 to <20↑ | Unequivocal progression | Any | irPD |
| ≥20 | Any | Any | irPD |

*Decrease assessed relative to baseline, including measurable lesions only (≥10mm longest diameter).

**Duration of Response**

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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 until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

## D. Regulations and Good Clinical Practice Guidelines

### 1. Regulations

Refer to the following United States Code of Federal Regulations (CFR) and European Directives:

- FDA Regulations 21 CFR, Parts 50.2 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personal
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators
- European Directive 2001/20/EC and related guidance documents
- Relevant local laws and regulations

### 2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

http://www.ich.org/LOB/media/MEDIA482.pdf

## E. SmPC for Cetuximab (Erbitux®)

(An English version and a version translated to local language of the SmPC will be attached as separate documents.)

## F. SmPC for Cisplatin

(An English version and a version translated to local language of the SmPC will be attached as separate documents.)

## G. SmPC for 5-FU

(An English version and a version translated to local language of the SmPC will be attached as separate documents.)

## H. SmPC for Carboplatin

(An English version and a version translated to local language of the SmPC will be attached as separate documents.)