

# CLINICAL STUDY PROTOCOL

## **RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND PHASE 2 STUDY OF PATRITUMAB (U3-1287) IN COMBINATION WITH CETUXIMAB PLUS PLATINUM-BASED THERAPY IN FIRST LINE SETTING IN SUBJECTS WITH RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**

**PROTOCOL U31287-A-U203**

**IND NUMBER 102,396**

**EUDRACT: 2015-002222-40**

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SPONSOR	Daiichi Sankyo, Inc. 399 Thornall Street Edison, NJ 08837, United States
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## INVESTIGATOR AGREEMENT

### RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND PHASE 2 STUDY OF PATRITUMAB (U3-1287) IN COMBINATION WITH CETUXIMAB PLUS PLATINUM-BASED THERAPY IN FIRST LINE SETTING IN SUBJECTS WITH RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

#### Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo representative listed below.

\_\_\_\_\_ MD  
Print Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Title

14/06/2016  
Date (DD MMM YYYY)

#### Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

\_\_\_\_\_  
Print Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Title

\_\_\_\_\_  
Date (DD MMM YYYY)

## PROTOCOL SYNOPSIS

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IND Number:	102,396
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Protocol Number:	U31287-A-U203
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Investigational Product:	Patritumab (U3-1287)
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Active Ingredient(s)/INN:	Fully human monoclonal immunoglobulin G Subclass 1 (IgG1) antibody directed against human epidermal growth factor receptor 3 (HER3)
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Study Title:	Randomized, Placebo-Controlled, Double-Blind Phase 2 Study of Patritumab (U3-1287) in Combination with Cetuximab plus Platinum-Based Therapy in First Line Setting in Subjects with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck
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Study Phase:	Phase 2
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Indication Under Investigation:	Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)
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Study Objectives:	<p><b>Primary Objective</b></p> <ul style="list-style-type: none"><li>• To evaluate progression-free survival (PFS) in the heregulin (HRG) high expression population from subjects treated with patritumab + cetuximab + platinum-based therapy compared to placebo + cetuximab + platinum-based therapy.</li></ul> <p><b>Secondary Objectives</b></p> <ul style="list-style-type: none"><li>• Evaluate overall survival (OS)</li><li>• Evaluate overall response rate (ORR)</li><li>• Refine the cutoff between heregulin high and low expression based on clinical data from this study</li><li>• Assess the population PK of patritumab in subjects with SCCHN</li><li>• Assess the PK parameters of serum cetuximab and platinum concentrations when cetuximab and cisplatin or carboplatin (platinum-based therapy) are coadministered with patritumab in a sub group (n = 30) of subjects</li><li>• Evaluate the incidence of human antihuman antibody (HAHA) formation (anti-patritumab antibodies)</li><li>• Evaluate the safety and tolerability of the combination of</li></ul>
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patritumab + cetuximab + platinum-based therapy in first-line treatment of subjects with SCCHN

**Exploratory Objectives**

- Duration of response, time to response, time to disease progression, duration of stable disease from subjects treated with patritumab + cetuximab + platinum-based therapy compared to those treated with placebo + cetuximab + platinum-based therapy
- Explore potential exposure-response and possibly other biomarker relationships
- Evaluate disease-specific patient reported outcomes using the Functional Assessment of Cancer Therapy-Head and Neck questionnaire, the 10-item FACT – Head and Neck Symptom Index, and the EuroQoL 5 Dimensions-5 Levels.

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**Study Design:** This is a multicenter, randomized, placebo-controlled, double blind Phase 2 study to evaluate the PFS and safety in recurrent/metastatic first-line SCCHN in subjects treated with patritumab plus cetuximab plus platinum-based therapy compared with subjects randomized to the control arm consisting of placebo plus cetuximab plus platinum-based therapy.

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**Study Duration:** For the purpose of collecting survival data, the duration of the study will be until all subjects have died or a minimum of 13 months after the last subject is randomized whichever comes first, approximately 22 months for PFS and 25 months for OS. Subjects receiving clinical benefit from treatment will be offered the opportunity to continue therapy with patritumab and cetuximab (platinum-based therapy administered for no more than 6 cycles) in the extension phase of this protocol.

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**Study Sites and Location:** Approximately 35 sites in Europe.

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**Planned Sample Size:** Approximately 105 subjects will be randomized to the patritumab and the control arms in a 2:1 stratified fashion (approximately 70 HRG-high and approximately 35 HRG-low subjects). When one arm is filled with the required sample size, the enrollment in that arm will cease and the other arm will be filled.

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**Subject Eligibility Criteria:** **Key Inclusion Criteria**

1. Adult subjects  $\geq 18$  years old

2. Histologically confirmed recurrent disease or metastatic SCCHN tumor and/or from its lymph nodal metastases originating from the oral cavity, oropharynx, hypopharynx, and larynx
  3. Heregulin expression level is required
    - Samples must be taken from subjects who have recurrent or metastatic disease. These samples can be from either rec/met archived or fresh biopsy samples
    - No cancer treatment between time of biopsy and submission of sample
    - Surgical or core needle biopsy is acceptable
    - Fine-needle aspiration or cytology is not acceptable for biopsies
  4. Human papilloma virus (HPV) status or p16 (surrogate for HPV) is required. These results must come from tumor tissue. These results may be obtained from either a local lab or samples sent to the central lab
    - HPV or p16 status can be from any tumor biopsy material from initial diagnosis
  5. Measurable disease per Response Evaluation Criteria in Solid Tumor (RECIST) Version 1.1
  6. Eastern Cooperative Oncology Group performance status 0 or 1
  7. Hematological function, as follows:
    - Absolute neutrophil count  $\geq 1.5 \times 10^9/L$
    - Platelet count  $\geq 100 \times 10^9/L$
    - Hemoglobin  $\geq 10$  g/dL
  8. Renal function, as follows:
    - Estimated serum creatinine clearance (mL/min) or glomerular filtration rate (GFR)  $\geq 60$  mL/min for cisplatin and  $\geq 30$  mL/min for carboplatin
  9. Hepatic function, as follows:
    - Aspartate aminotransferase  $\leq 2.5$  x upper limit of normal (ULN) (if liver metastases are present,  $< 5$  x ULN)
    - Alanine aminotransferase  $\leq 2.5$  x ULN (if
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- liver metastases are present,  $< 5 \times \text{ULN}$ )
  - Alkaline phosphatase  $\leq 2.0 \times \text{ULN}$  (if bone or liver metastases are present,  $< 5 \times \text{ULN}$ )
  - Bilirubin  $\leq 1.5 \times \text{ULN}$
10. Prothrombin time or partial thromboplastin time  $\leq 1.5 \times \text{ULN}$
  11. Women of childbearing potential must have a negative serum pregnancy test performed within 14 days prior to enrollment (where demanded by local regulations, test may be required within 72 hours prior to enrollment)
  12. Adult subjects of child-bearing potential must agree to use double-barrier contraceptive measures. Two of the following precautions must be used: bilateral vasectomy, bilateral tubal ligation, intrauterine device (IUD), combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine hormone-releasing system (IUS), condom with spermicide, abstinence. These contraception measures must be used for the entire duration of the study and for 6 months after the last study dose is received
  13. Subjects must be willing and able to comply with schedule visits, treatment plan, laboratory tests, and other study procedures
  14. Provided written informed consent(s)

**Key Exclusion Criteria**

1. Left ventricular ejection fraction  $< 50\%$
  2. Prior epidermal growth factor receptor targeted regimen
  3. No HRG expression result
  4. No HPV or p16 status
  5. Prior anti-HER3 therapy
  6. Prior chemotherapy for recurrent/metastatic disease
  7. Anti-cancer therapy between biopsy and submission of sample
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8. Presence of squamous cell tumors of the nasopharynx
  9. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated with no evidence of disease for  $\geq 2$  years
  10. Known history of brain metastases or currently active brain metastases
  11. Uncontrolled hypertension (systolic  $> 160$  mm Hg or diastolic  $> 100$  mm Hg)
  12. Clinically significant electrocardiogram (ECG) changes
  13. Myocardial infarction within 1 year before enrollment, symptomatic congestive heart failure (New York Heart Association  $>$ Class II), unstable angina, or unstable cardiac arrhythmia requiring medication
  14. Platinum-containing drug therapy with radiotherapy less than 6 months before study drug treatment
  15. Therapeutic or palliative radiation therapy or major surgery within 4 weeks before study drug treatment. Radiation treatment to all sites of measureable disease unless progression is documented after radiation
  16. Participated in clinical drug trials within 4 weeks before study drug treatment. Current participation in other investigational procedures
  17. Uncontrolled infection requiring intravenous (IV) antibiotics, antivirals, or antifungals, known HIV infection, or active hepatitis B or C infection or undergoing medical treatment for infection
  18. Uncontrolled type 1 or 2 diabetes mellitus
  19. Known hypersensitivity or allergic reaction against any of the components of the trial treatment
  20. Pregnant, breastfeeding, or unwilling/unable to use acceptable contraception
  21. Residual toxicities  $\geq$  Grade 1 from previous therapies that the Investigator determines would exclude participation
  22. Psychological, social, familial, or geographical factors that would interfere with study participation or follow-up
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23. Committed to an institution by virtue of an order issued either by judicial or administrative authorities
  24. Employee or immediate relative of an employee of the sponsor, CRO, the study center, or their affiliates or partners
  25. Receiving yellow fever vaccine or live attenuated vaccines (for subjects receiving carboplatin)
  26. Presence of hemorrhagic tumors (for subjects receiving carboplatin)
  27. Prophylactic use of phenytoin or fosphenytoin (for subjects receiving cisplatin or carboplatin)
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Dosage Form, Dose and  
Route of Administration:

Patritumab

Placebo lyophilisate will be diluted in an identical manner in 8 mL water.

The order of IV administration will be:

1. Patritumab or placebo
  - Patritumab/placebo initial loading dose [REDACTED] over 60 minutes ( $\pm$  10 minutes) followed in cycle 2 and beyond with a maintenance dose of [REDACTED] over 60 minutes ( $\pm$  10 minutes) every three weeks
    - Infusion time can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion
2. Cetuximab
  - Cetuximab initial dose at 400 mg/m<sup>2</sup> IV as a 2-hour infusion on Week 1, followed by 250 mg/m<sup>2</sup> over 60 minutes weekly, plus

One hour after the end of the cetuximab administration infuse with either:

3. Cisplatin OR carboplatin selected at the discretion of the Investigator.
    - Cisplatin at 100 mg/m<sup>2</sup> IV infused over 1 hour, every three weeks up to a maximum of 6 cycles
      - Pretreatment hydration with 2 liters of fluid prior to a cisplatin infusion is recommended and should adhere to institutional standards.
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Adequate hydration and urinary output must be maintained during the following 24 hours. Other pretreatments such as anti-emetic prophylaxis and post-treatments such as hydration are up to the discretion of the Investigator.

OR

- Carboplatin, at AUC 5 IV bolus over 30 to 60 minutes, every 3 weeks for a maximum of 6 cycles. The carboplatin dose will be calculated using the Calvert formula:
  - AUC 5 is the target
  - Carboplatin Dose (mg) = 5 x ([glomerular filtration rate] GFR + 25)
  - Estimated serum creatinine clearance (mL/min) calculated using the modified Cockcroft-Gault equation ([Appendix 17.1](#)) can also be used as an estimate for GFR
  - The carboplatin dose is required to be re-calculated for every dosing based on the current GFR (or creatinine clearance as an estimate of GFR as per the protocol)
  - Pre- and post-treatments are up to the discretion of the investigator

Note: It is important to use the infusion times given above for cisplatin and carboplatin; however, different infusion durations may be used if local practice dictates otherwise, except during Cycle 1, Day 1 for those subjects participating in the Intense PK sampling.

Commercial supplies of cetuximab, cisplatin, and carboplatin (if used) will be used.

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Study Endpoints:

**Primary Endpoint**

The primary efficacy endpoint is PFS, defined as the time from the date of randomization to the earlier of the dates of the first objective documentation of radiographic disease progression (per RECIST v1.1 as assessed by investigator) or death due to any cause.

**Secondary Endpoints**

- OS

- Date of randomization to death due to any cause
- Subjects alive at time of data cut off for OS analysis will be censored at the last contact date at which subject is known to be alive
- ORR (CR and PR)
  - Proportion of subjects with the best ORR of CR or PR regardless of whether it is confirmed or unconfirmed
- Pharmacokinetic parameters:  $AUC_{0-t}$  and  $C_{max}$  at end of infusion (EOI) for serum patritumab, cetuximab, and platinum concentrations in a subgroup (approximately 30 subjects).
  - Population PK methods will be used to assess the sparse data for serum patritumab concentrations
- Safety
  - Treatment-emergent adverse events
  - $\geq$  Grade 3 National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
  - Clinical lab evaluations
  - Myocardial function status (assessed by echocardiograms or multigated acquisition scan )
  - ECGs
  - Vital signs
  - Physical exams
  - Human anti-humanized antibody formation

#### **Exploratory Endpoints**

- Duration of response, time to response, time to disease progression, duration of stable disease
- Explore potential exposure-response and possibly other biomarker relationships
- Evaluate patient-reported outcomes

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Statistical Analyses:

The primary efficacy endpoint is PFS. Primary analysis is the comparison of PFS between the patritumab arm and control

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arm in the HRG high stratum of the full analysis set (FAS). The hypotheses testing to compare PFS between the patritumab arm versus the control arm will be performed in two steps. In step 1, PFS will be tested in the HRG high stratum of the FAS at the one-sided 0.10 significance level. If this test in step 1 does not reject the null hypothesis, then in step 2A, the PFS will be tested in the FAS at the one sided 0.05 significance level. If the test in step 1 is rejected, then in step 2B, the two sided 80% confidence interval (CI) for hazard ratio (HR) of PFS in HRG low stratum of the FAS will be estimated. The results from both steps (PFS comparison in the HRG high stratum, and PFS comparison in the FAS or PFS estimate in the HRG low stratum) will be used to optimize future study designs.

The comparison of PFS between the patritumab arm and the control arm will be performed using a log-rank test stratified by the stratification factors at randomization. Kaplan-Meier methods will be used to calculate median PFS and CIs and generate Kaplan-Meier curves for PFS by treatment arm. Estimates of HR between 2 arms along with their two-sided 80% and 95% CIs will be calculated using stratified Cox's proportional hazards regression model.

Secondary efficacy variables include OS and ORR (CR and PR). Overall survival is defined from the date of randomization to death due to any cause and will be analyzed in the same manner as PFS. Subjects who are alive at the time of data cut off for overall survival analysis will be censored at the last contact date at which the subject is known to be alive. ORR is defined as the proportion of subjects with the best overall response of CR or PR regardless of whether it is confirmed or unconfirmed. The differences in the ORR and OS between 2 arms in both the HRG high and low population will be presented along with two sided 80% and 95% CIs based on the Wilson's score method with continuity correction.

Safety data will be analyzed descriptively.

For the PK subgroup, serum patritumab, cetuximab, and platinum concentrations and PK parameters will be summarized using descriptive statistics and plotted as appropriate. To explore possible drug-drug interactions between patritumab plus cetuximab or cisplatin/carboplatin, the PK of serum cetuximab and platinum concentrations will be compared with and without patritumab. For all subjects, sparse samples for serum patritumab concentrations will be assessed using population PK methods. The relationship

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between exposure and response will be explored using  
population PK modeling.

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## LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
5-FU	5-Fluorouracil
AE	Adverse Event
ALT	Alanine aminotransferase
AKT	phosphatidylinositol 3-kinase /protein kinase B
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC <sub>0-21d</sub>	Area under concentration–time curve to Day 21
CBC	Complete blood count
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence intervals
C <sub>max</sub>	Maximum observed circulating concentration
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOI	End of infusion
EQ-5D-5L	EuroQoL-5 Dimensions -5 Levels
EQ VAS	EuroQoL Visual Analogue Scale
ERK	Extracellular-signal-regulated kinases
FACT-H&N	Functional Assessment of Cancer Therapy—Head and Neck
FAS	Full analysis set
FDA	Food and Drug Administration
FHNSI	FACT—Head and Neck Symptom Index

<b>ABBREVIATION</b>	<b>DEFINITION</b>
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HAHA	Human antihuman antibody
HER	Human epidermal growth factor receptor
HER3	Human epidermal growth factor receptor 3
HER4	Human epidermal growth factor receptor 4
HNS	Head and neck subscale
HPV	Human papilloma virus
HR	Hazard ratio
HRG	Heregulin (product neuregulin-1 gene [nRG1])
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IgG1	Immunoglobulin G subclass 1
ILD	Interstitial lung disease
IRB	Institutional review board
IV	Intravenous
IxRS	Interactive Web/Voice Response System
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition (scan)
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PGx	Pharmacogenomics
PK	Pharmacokinetic or pharmacokinetics
PR	Partial response

<b>ABBREVIATION</b>	<b>DEFINITION</b>
PRO	Patient reported outcome
QTc (QTcB; QTcF)	Heart rate-corrected QT interval (by Bazett's; by Fridericia's)
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAVER	Serious adverse event report
SCCHN	Squamous cell carcinoma of the head and neck
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal



## **1. INTRODUCTION AND BACKGROUND INFORMATION**

### **1.1. Data Summary**

#### **1.1.1. Investigational Product(s)**

Patritumab (U3-1287)

##### **1.1.1.1. Name**

Patritumab

##### **1.1.1.2. Description**

Patritumab is a high-affinity, fully human monoclonal immunoglobulin G subclass 1 (IgG1) antibody directed against human epidermal growth factor receptor 3 (HER3).

##### **1.1.1.3. Intended Use Under Investigation**

This study will examine patritumab's effect on heregulin (HRG) expressing head and neck tumors in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).

##### **1.1.1.4. Nonclinical Studies**

Flow cytometry analysis of Chinese hamster ovary (CHO) cells engineered to express individual HER family members demonstrated that patritumab specifically binds the extracellular domain of HER3 and did not bind to epidermal growth factor receptor (EGFR), HER2, or HER4.

The binding affinity of patritumab to endogenous HER3 expressed on human tumor cells was 1 nmol/L to 4 nmol/L as determined in melanoma, breast cancer, and pancreatic cancer cells. These affinities are comparable to marketed anticancer antibodies such as trastuzumab and should allow for efficient targeting of HER3 on tumor cells.

In Western blot analysis of head and neck cancer cell lines, patritumab clearly reduced HER3- and phosphatidylinositol 3-kinase/protein kinase B (AKT)-phosphorylation in 11 and 10 out of 11 cell lines, respectively. Cetuximab reduced extracellular-signal-regulated kinases (ERK)-phosphorylation in 8 out of 11 cell lines. Combinatorial effects of patritumab and cetuximab were seen in 8 out of 11 cell lines and in 3 out of 3 cetuximab-resistant head and neck cancer cell lines patritumab exerted inhibitory effects.

In FaDu head and neck cancer cells, patritumab treatment resulted in inhibition of basal HER3 and AKT activation, whereas cetuximab treatment resulted in inhibition of basal ERK activation and the combination of both mAbs resulted in inhibition of HER3-, AKT- and ERK-activation.

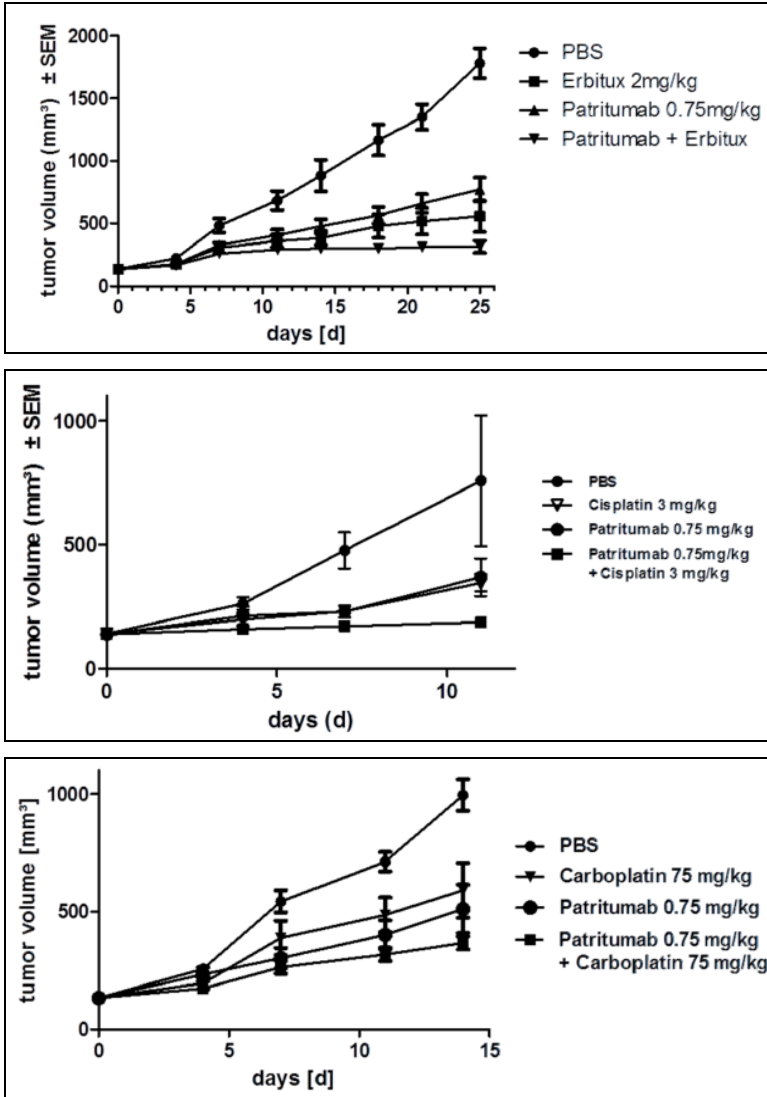
Treatment of FaDu and Cal-27 head and neck cancer cells with patritumab resulted in a reduction of proliferation ranging from 9% to 23% whereas treatment with cetuximab resulted in 35% to 54% inhibition of proliferation. In both cell lines, the combination of

patritumab and cetuximab caused a substantial stronger inhibition of proliferation (68% to 83%) than either single agent treatment alone.<sup>1,2</sup>

Mice with subcutaneous FaDu head and neck tumors demonstrated greater reduced tumor volumes when treated with patritumab 0.75 mg/kg in combination with either cetuximab, cisplatin, or carboplatin intraperitoneally compared to treatment with either drug alone (Figure 1.1).

The mean steady-state pre-infusion concentration ( $C_{min}$ ) at the 9 mg/kg dose level or above in humans was at least 5-fold greater than the threshold concentration determined from PK and pharmacodynamic modeling in nonclinical tumor xenograft studies and resulted in 90% maximal phosphorylated-HER3 inhibition and maximal nonclinical efficacy. Therefore, the patritumab PK profile supports intravenous (IV) administration of patritumab at or above 9 mg/kg every 2 to 3 weeks. Furthermore, as PK analysis indicated that in subjects treated with 9, 14, or 20 mg/kg every 2 weeks, steady-state was reached after approximately 3 doses, it is likely that a dose de-escalation to 6 mg/kg after initial loading dose of 18 mg/kg, followed by 9 mg/kg maintenance would still be in the range of the threshold concentration determined from PK and pharmacodynamic modeling in nonclinical tumor xenograft studies.

**Figure 1.1: Growth Inhibition of FaDu Head and Neck Tumors with Patritumab Alone or in Combination with Cetuximab, Cisplatin, or Carboplatin**



Please refer to the current Investigator's Brochure for patritumab for nonclinical data supporting its use in clinical studies.

#### 1.1.1.5. Clinical Experience

A multicenter Phase 1b study, U3-1287-A-U106, was designed to evaluate patritumab in combination with cetuximab plus platinum-based therapy as first-line therapy for subjects with recurrent or metastatic SCCHN. The main objectives were to define the safety, tolerability, and recommended phase 2 dose of patritumab. The recommended phase 2 dose was determined to be a loading dose of 18 mg/kg by continuous IV infusion over 60 minutes ( $\pm$  10 minutes) followed by maintenance dose of 9 mg/kg once every three weeks. There were no dose limiting toxicities in the subjects evaluated for safety and recommended Phase 2 dose. This dose of patritumab in combination with cetuximab and a platinum agent is the same as the established dose of patritumab in combination with

other therapies, including erlotinib in non-small cell lung cancer (NSCLC) and trastuzumab and paclitaxel in HER2-positive breast cancer.

Previously reported PK results for patritumab (using a new manufacturing process) at a dose of 18 mg/kg were similar to another Phase 1 study where the mean  $AUC_{0-21d}$  and  $C_{max}$  were observed as 3056.5  $\mu\text{g}\cdot\text{day/mL}$  and 526.0  $\mu\text{g/mL}$ , respectively.<sup>1</sup>

As of 01 September 2014, 6 clinical studies have been completed. From completed studies the following pharmacology, efficacy, and safety results are reported below. More detailed information from these studies can be found in Section 6 of Investigator brochure.

### **Clinical Pharmacology**

Key clinical pharmacology results from completed studies are presented below and can be found in the Investigator Brochure.

- The current pharmacokinetic (PK) data for patritumab (Process 2) support the dosing regimen of a patritumab 18-mg/kg loading dose and 9 mg/kg administered every 3 weeks as the maintenance dose
- Population PK analyses to date suggest no apparent effect of hepatic or renal impairment on patritumab PK
- To date, there has been low incidence of HAHA ( $\leq 1\%$ ) and no report of acute hypersensitivity reaction to patritumab<sup>1</sup>

### **Efficacy**

Key efficacy results from completed studies can be found in the Investigator Brochure.

### **Safety**

Key safety results from completed studies can be found in the Investigator Brochure. Diarrhea and vomiting have been identified as adverse drug reactions associated with patritumab. These events are mostly Grade 1 or 2.

## **1.2. Study Rationale**

HER3 is a type 1 transmembrane glycoprotein expressed in many normal tissues and in a variety of solid tumors including NSCLC, breast cancer, colon cancer and ovarian cancer. HER3 is up-regulated in many solid tumors including head and neck cancer and is generally associated with poor prognosis in cancer patients.<sup>3</sup> Elevated membranous HER3 expression was shown to be strongly associated with poor prognosis in patients with SCCHN and therefore is a potential candidate molecule for targeted therapy.<sup>3</sup>

There is growing evidence that the presence of HRG, a soluble secreted growth factor, determines disease progression and patient survival. Heregulin is a natural ligand for HER3 whose binding to the extracellular domain accelerates heterodimer formation and, as a consequence, HER3 activation and downstream signaling. High expression frequencies of HRG have been demonstrated in head and neck tumor cell lines and clinical samples. In a panel of 15 *in vivo* tumor models of different tissue origin, HRG protein expression was found to be predictive of single-agent patritumab activity.<sup>4</sup>

Patritumab (U3-1287) is an internalizing anti-HER3 monoclonal antibody that competes with HRG for receptor binding and thus is capable of inhibiting HRG-mediated HER3 activation in vitro and in vivo. In 10/11 head and neck tumor cell lines patritumab inhibited basal HER3 and/or AKT activation in vitro. Synergistic effects of patritumab with cetuximab on signaling were seen in 7/10 (70%) patritumab-responsive head and neck cancer cell lines.<sup>5</sup>

Given that HRG-induced stimulation appears to play a critical role in the progression of HER3-expressing head and neck tumors, an antibody that blocks HER3-dependent oncogenic signaling, such as patritumab, may inhibit tumor cell survival, proliferation, and metastasis and may overcome resistance against anti-HER therapeutic agents. The proposed trial design in SCCHN with patritumab plus cetuximab plus platinum chemotherapy is a randomized study to test whether heregulin high-expressing tumors demonstrate better response versus the whole population in subjects with recurrent or metastatic squamous cell carcinoma of the head and neck.

Given the results from the Shames et al 2013<sup>3</sup> study demonstrating a significant HRG expression increase in the recurrent setting compared to primary disease in matched patient specimens, it is mandatory to obtain tissue at the diagnosis of recurrent/metastatic SCCHN.

Patients with human papilloma virus (HPV) positive status will be included. Molecular and epidemiological studies strongly suggest HPV-positive oropharyngeal cancers comprise a distinct molecular, clinical, and pathologic disease entity that is likely associated with HPV infection and for which SCCHN patients who are HPV positive have a markedly improved prognosis. In addition, it has been shown that other SCCHN subtypes have been found to be p16 (surrogate for HPV) positive such as nasopharyngeal, hypopharyngeal, laryngeal, and in the oral cavity.<sup>6</sup> Therefore, HPV status or p16 will be evaluated in all tumor tissue in this study.

### **1.2.1. Epidemiology**

Worldwide, more than half a million head and neck cancer cases and more than 370,000 deaths due to head and neck cancer are estimated to occur each year. The half million cases are comprised of approximately 300,000 oral cavity cancers, 229,000 pharyngeal cancers, and 157,000 laryngeal cancers.<sup>7</sup> In 2002, the crude incidence rates of carcinoma of the head and neck in Europe were 36/100,000/year in the male population and 7/100,000/year for females. Corresponding mortality rates were 18 and 3/100,000/year, respectively. On the European scale, head and neck cancer accounts for 139,000 new cases per year. Over 90% of head and neck malignancies are squamous cell carcinomas.<sup>8</sup>

### **1.2.2. Rationale for not Using Fluorouracil**

The combination of cetuximab and cisplatin plus fluorouracil (5-FU) is approved for first-line treatment of SCCHN in countries worldwide.<sup>9</sup> With respect to efficacy, therapeutic regimens are used for SCCHN with or without 5-FU. Few studies have demonstrated that 5-FU has provided progression free survival (PFS) or overall survival (OS) advantage compared to combinations without 5-FU.<sup>10</sup> With respect to safety, 5-FU

used in combination with other drugs in SCCHN and other indications have been associated with increased toxicities.<sup>11,12,13</sup>

In a Phase 3 study<sup>11</sup> in advanced head and neck cancer, it was found that the 5-FU plus cisplatin group had more toxicities overall than subjects in the cisplatin plus paclitaxel group, especially in leukopenia, granulocytopenia, thrombocytopenia, anemia, infection, genitourinary, vomiting, stomatitis, metabolic disorders, and fatigue. In a Phase 3 randomized study in SCCHN,<sup>12</sup> a comparison was made between cisplatin plus 5-FU versus 5-FU alone and cisplatin alone. It was found that, in general, toxicities were higher in the 5-FU alone and in the cisplatin plus 5-FU combination arm, compared to the cisplatin alone group. The increased toxicities in the 5-FU alone and 5-FU plus cisplatin arms included diarrhea, mucositis, ototoxicity, phlebitis, alopecia, and leukocytosis. Tribius et al conducted a study in locally advanced unresectable stage IV SCCHN comparing courses of cisplatin and cisplatin plus 5-FU and found that the regimen containing cisplatin alone had 46% grade 3 toxicities and the regimen containing cisplatin and 5-FU had 70% grade 3 toxicities.<sup>13</sup> In summary of the above mentioned studies, the safety profile of regimens using 5-FU has generally shown a high percentage of toxicities which include anemia, neutropenia, mucositis, diarrhea and thrombocytopenia.

Administration of 5-FU is also inconvenient because it requires a continuous infusion pump, with infusions of 12-24 hours for 4-5 consecutive days. In addition, the quality of life of head and neck cancer patients without infusion pumps is significantly better compared to those using infusion pumps.<sup>14</sup>

The safety data of studies in SCCHN with and without 5-FU demonstrated that 5-FU is associated with increased toxicities as well as reduced quality of life. Given the very modest efficacy benefits associated with 5-FU, the benefit-risk ratio of 5-FU-containing cetuximab plus platinum regimens is not clearly superior to that of similar regimens without 5 FU.

### **1.3. Risks and Benefits for Study Subjects**

Patritumab is an investigational anti-HER3 antibody with demonstrated preclinical and early clinical activity as a single agent and in combination with other chemotherapies. The toxicities of approved HER family antibody inhibitors may not be predictive of toxicity for patritumab due to differing antibody and target specificity. The most significant adverse reactions identified with patritumab use are diarrhea, vomiting, rash, and dry skin. However, administration of some therapeutic antibodies has been associated with infusion or allergic reactions. Subjects receiving patritumab should be monitored for these reactions.

### **1.4. Population, Route, Dosage, Dosage Regimen, Treatment Period**

Adult subjects with metastatic SCCHN originating from the oral cavity, oropharynx, hypopharynx, and larynx, with documented disease recurrence following previous treatment regimen for non-metastatic disease will be studied. See Section 4 for a detailed description of the study population. See Section 3.1.2 for information regarding route, dosage, and dosage regimen, and Section 3.1.5 for information on the duration of the treatment period.

## **1.5. Compliance Statement, Ethics and Regulatory Compliance**

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (2013), the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products/ICH/135/95), and applicable regulatory requirement(s).

- European Commission Directive (2001/20/EC Apr 2001) and/or
- European Commission Directive (2005/28/EC Apr 2005) and/or
- Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or
- Other applicable local regulations

### **1.5.1. Subject Confidentiality**

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the electronic Case Report Forms (eCRF) or other documents submitted to the Sponsor and/or agent, subjects should be identified by a unique subject identifier as designated by the sponsor. Documents that are not distributed (eg, signed Informed Consent Forms [ICF]) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

### **1.5.2. Informed Consent Procedure**

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. The written ICF should be prepared in the local language(s) of the potential subject population and documented in the subject's medical records, as required by 21 CFR Part 312.62.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IEC or IRB prior to being provided to potential subjects.

The ICF should be signed and personally dated by the subject, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the case report form (CRF).

### **1.5.3. Regulatory Compliance**

The study protocol, subject information and consent form, the Investigator brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IEC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

The Investigator must submit and, where necessary, obtain approval from the IEC or IRB for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IEC or IRB of deviations from the protocol or serious adverse events (SAEs) occurring at the site and other adverse event (AE) reports received from Daiichi Sankyo and/or Contract Research Organization (CRO), in accordance with local procedures.

Daiichi Sankyo's Regulatory Affairs group will ensure that approval by the appropriate regulatory bodies is obtained prior to study initiation and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.



## **2. STUDY OBJECTIVES AND HYPOTHESES**

### **2.1. Study Objectives**

#### **2.1.1. Primary Objectives**

- To evaluate PFS in the HRG high expression population from subjects treated with patritumab + cetuximab + platinum-based therapy compared to placebo + cetuximab + platinum-based therapy

#### **2.1.2. Secondary Objectives**

- Evaluate OS
- Evaluate objective response rate (ORR)
- Refine the cutoff between HRG high and low expression based on clinical data from this study
- Assess the population PK of patritumab in subjects with SCCHN
- Assess the PK parameters of serum cetuximab and platinum concentrations when cetuximab and cisplatin or carboplatin (platinum-based therapy) are coadministered with patritumab in a subgroup (n = 30) of subjects
- Evaluate the incidence of HAHA formation (anti-patritumab antibodies)
- Evaluate the safety and tolerability of the combination of patritumab + cetuximab + platinum-based therapy in first-line treatment of subjects with SCCHN

#### **2.1.3. Exploratory Objectives**

- Duration of response, time to response, time to disease progression, duration of stable disease (SD) from subjects treated with patritumab + cetuximab + platinum-based therapy compared to those treated on placebo + cetuximab + platinum-based therapy
- Explore potential exposure-response and possibly other biomarker relationships
- Evaluate disease specific patient reported outcomes (PROs) using the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) which assesses:
  - Physical well-being
  - Functional well-being
  - Social/Family well-being
  - Emotional well-being

- Head and neck cancer symptoms
- Evaluate head and neck cancer symptoms using the FACT-Head and Neck Symptom Index (FHNSI), a 10-item instrument comprising items from the FACT-H&N
- Evaluate PROs using the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire, which assesses five dimensions:
  - Mobility
  - Self-care
  - Usual activities
  - Pain/discomfort
  - Anxiety/depression (See [Appendix 17.2](#)).

## **2.2. Study Hypothesis**

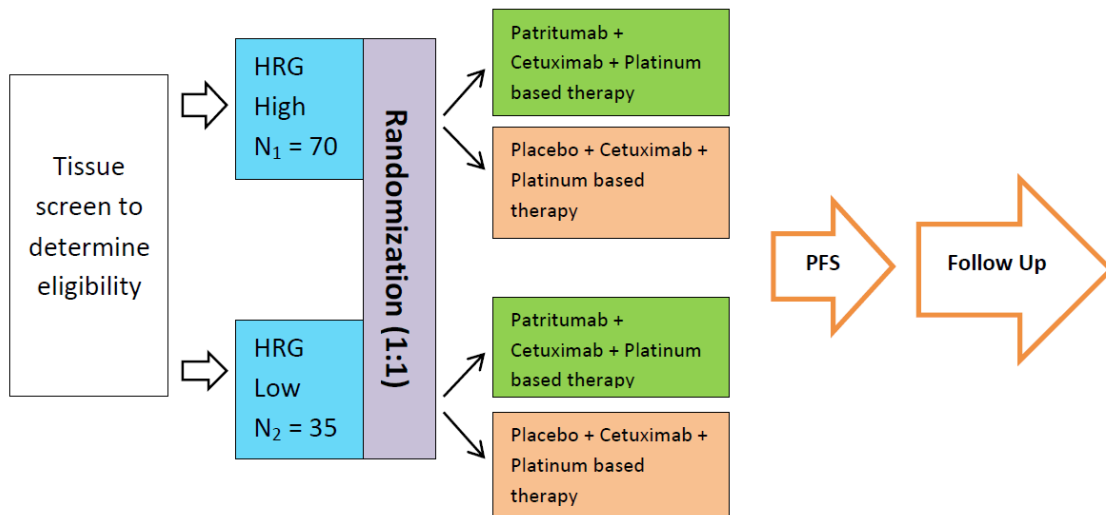
- The combination of patritumab + cetuximab + platinum-based therapy will improve PFS in the first-line treatment of SCCHN in the HRG high expression population compared to subjects in the placebo + cetuximab + platinum-based arm

### 3. STUDY DESIGN

#### 3.1. Overall Plan

Approximately 105 subjects will be randomized to the patritumab and the control arms in 2:1 stratification fashion between HRG high versus low strata (approximately 70 HRG-high and approximately 35 HRG-low subjects). When one HRG stratum is filled with the required sample size, the enrollment in that HRG stratum will cease. The randomized subjects will also be further stratified 1:1 by HPV status (positive vs negative). The cut-off for HRG high versus low before randomization will be set using the median HRG value of commercial tissue samples. See Figure 3.1 for a schematic of the study design.

**Figure 3.1: Phase 2 Study Design**



The enrolled subjects will be stratified by HRG (high, low) and HPV (positive, negative)

##### 3.1.1. Study Type

This is a multicenter, randomized, placebo-controlled, double blind Phase 2 study designed to evaluate the PFS and safety in recurrent/metastatic first-line SCCHN in subjects treated with patritumab plus cetuximab plus either cisplatin or carboplatin or randomized to the control arm consisting of a placebo plus cetuximab plus either cisplatin or carboplatin.

Adult subjects with metastatic SCCHN originating from the oral cavity, oropharynx, hypopharynx, and larynx with documented disease recurrence following previous treatment for non-metastatic disease will be studied.

### 3.1.2. Treatment Groups

There will be two treatment arms (See [Figure 3.1](#)) stratified by HRG status (high and low).

1. Patritumab + cetuximab + platinum-based therapy with HRG high and HRG low subjects
2. Placebo + cetuximab + platinum-based therapy with HRG high and HRG low subjects

#### 3.1.2.1. Treatment Administration

[Figure 3.2](#) illustrates the order and timing of the treatments involved.

- Patritumab initial loading dose is 18 mg/kg IV (or placebo) over 60 minutes ( $\pm 10$  minutes) followed in cycle 2 and beyond with a maintenance dose of 9 mg/kg IV over 60 minutes ( $\pm 10$  minutes) every three weeks
  - Infusion time can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion
- Cetuximab initial dose at 400 mg/m<sup>2</sup> IV as a 2-hour infusion followed by 250 mg/m<sup>2</sup> over 60 minutes weekly

One hour after the end of the cetuximab administration (on the weeks when cetuximab and platinum therapy are coadministered) infuse with either:

- Cisplatin at 100 mg/m<sup>2</sup> IV infused over 1 hour, every three weeks up to a maximum of 6 cycles
  - Pretreatment hydration with 2 liters of fluid prior to a cisplatin infusion is recommended and should adhere to institutional standards. Adequate hydration and urinary output must be maintained during the following 24 hours. Other pretreatments such as anti-emetic prophylaxis and post-treatments such as hydration are up to the discretion of the Investigator
  - This can be given in a separate infusion during patritumab and cetuximab infusion

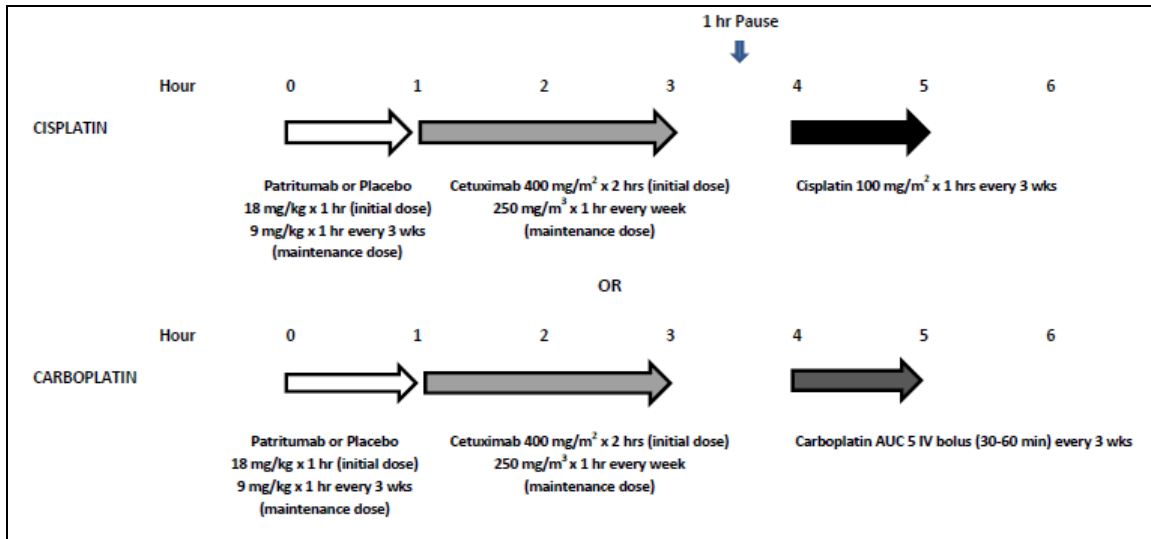
OR

- Carboplatin, IV bolus over 30-60 minutes, every 3 weeks for a maximum of 6 cycles. The carboplatin dose will be calculated using the Calvert formula:
  - AUC 5 is the target
  - Carboplatin Dose (mg) = 5 x (glomerular filtration rate [GFR] + 25)
  - Estimated serum creatinine clearance (mL/min) calculated using the modified Cockcroft-Gault equation ([Appendix 17.1](#)) can also be used as an estimate for GFR

- The carboplatin dose is required to be re-calculated for every dosing based on the current GFR (or creatinine clearance as an estimate of GFR as per the protocol).
- Pre- and post-treatments are up to the discretion of the investigator

Note: It is important to use the infusion times given above for cisplatin and carboplatin; however, different infusion durations may be used if local practice dictates otherwise, except during Cycle 1, Day 1 for those subjects participating in the Intense PK sampling.

**Figure 3.2: Order and Timing of Treatments**



### 3.1.3. Study Endpoints

#### 3.1.3.1. Primary

- PFS in the HRG high expression population from subjects treated with patritumab + cetuximab + platinum-based therapy compared to placebo + cetuximab + platinum-based therapy

#### 3.1.3.2. Secondary

- OS
- ORR
- PK parameters of serum cetuximab and platinum concentrations when cetuximab and cisplatin or carboplatin are coadministered with patritumab in a subgroup (n=30) of subjects
- Population PK of patritumab
- Incidence of HAHA formation (anti-patritumab antibodies)
- Safety and tolerability of the combination of patritumab + cetuximab + platinum-based therapy in first-line treatment of subjects with SCCHN

### **3.1.3.3. Exploratory**

- Duration of response
- Time to response
- Time to disease progression
- Duration of SD in both HRG groups
- Explore potential exposure-response and possibly other biomarker relationships
- Evaluation of PROs

### **3.1.4. Duration of the Study**

For the purpose of collecting survival data, the duration of the study will be until all subjects have died or a minimum of 13 months after the last subject is randomized whichever comes first, approximately 22 months for PFS and 25 months for OS.

### **3.1.5. Duration of Subject Participation**

The screening period is up to 14 days. Each cycle of treatment will be 21 days. There is no limit to how many cycles for patritumab and cetuximab treatment. Treatment will continue without interruption in subjects with complete response (CR), partial response (PR), or stable disease (SD). However, platinum treatment (cisplatin or carboplatin) will be given up to a maximum of 6 cycles. Subject participation is expected to be approximately 20 months.

Subjects who benefit from therapy may continue in the extension phase (Section 6.5) to receive treatment until progressive disease (PD), toxicity, withdrawal of consent, or starting another treatment for cancer therapy.

## **3.2. Selection of Doses**

The dosing regimen of patritumab to be administered in this study was selected on the basis of efficacy and tolerability established in prior Phase 1 and Phase 2 studies. Doses of each of the study treatments are specified in Section 3.1.2.

### **3.2.1. Experimental Treatments**

Please see Section 3.1.2.

### **3.2.2. Control Treatments**

See Section 3.1.2.

## **4. STUDY POPULATION**

### **4.1. Enrollment**

Each subject will be provided with information about the study, will have all questions answered to their satisfaction, and will sign and date an ICF. There will be individual ICFs for the main study, pharmacogenetics, and tissue sampling. Additional information about informed consent procedures is provided in Section 1.5.2.

A subject is considered enrolled in the study upon the Investigator or designee obtaining written informed consent from the subject (Section 1.5.2), and upon determination that all inclusion and exclusion criteria have been satisfied.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited subject information (initials, age, and sex), date, and outcome of screening process (eg, enrollment in the study, reason for ineligibility, refused to participate) will be maintained.

The Investigator or designee will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

#### **4.1.1. Inclusion Criteria**

Subjects must satisfy all of the following criteria to be included in the study:

1. Adult subjects  $\geq 18$  years old
2. Histologically confirmed recurrent disease or metastatic SCCHN tumor and/or from its lymph nodal metastases originating from the oral cavity, oropharynx, hypopharynx, and larynx
3. Heregulin expression level is required
  - Samples must be taken from subjects who have recurrent or metastatic disease (rec/met). These samples can be from either rec/met archived or fresh biopsy samples (either primary tumor or metastases)
  - No cancer treatment between time of biopsy and submission of sample
  - Surgical or core needle biopsy is acceptable
  - Fine-needle aspiration or cytology is not acceptable for biopsies
4. HPV status or p16 (surrogate for HPV) is required. These results must come from tumor tissue. These results may be obtained from either a local lab or samples sent to the central lab
  - HPV or p16 status can be from any tumor biopsy material from initial diagnosis
5. Measurable disease per Response Evaluation Criteria in Solid Tumor (RECIST) Version 1.1

6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
7. Hematological function, as follows:
  - Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$
  - Platelet count  $\geq 100 \times 10^9/L$
  - Hemoglobin  $\geq 10$  g/dL
8. Renal function, as follows:
  - Estimated serum creatinine clearance (mL/min) or GFR  $\geq 60$  mL/min for cisplatin and  $\geq 30$  mL/min for carboplatin
9. Hepatic function, as follows:
  - Aspartate aminotransferase (AST)  $\leq 2.5$  x upper limit of normal (ULN) (if liver metastases are present,  $< 5$  x ULN)
  - Alanine aminotransferase (ALT)  $\leq 2.5$  x ULN (if liver metastases are present,  $< 5$  x ULN)
  - Alkaline phosphatase  $\leq 2.0$  x ULN (if bone or liver metastases are present,  $< 5$  x ULN)
  - Bilirubin  $\leq 1.5$  x ULN
10. Prothrombin time or partial thromboplastin time  $\leq 1.5$  x ULN
11. Women of childbearing potential must have a negative serum pregnancy test performed within 14 days prior to enrollment (where demanded by local regulations, test may be required within 72 hours prior to enrollment)
12. Adult subjects of child-bearing potential must agree to use double-barrier contraceptive measures. Two of the following precautions must be used: bilateral vasectomy, bilateral tubal ligation, intrauterine device (IUD), combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine hormone-releasing system (IUS), condom with spermicide, abstinence. These contraception measures must be used for the entire duration of the study and for 6 months after the last study dose is received<sup>15</sup>
13. Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
14. Provided written informed consent(s)



#### 4.1.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Left ventricular ejection fraction (LVEF) <50%
2. Prior EGFR targeted regimen
3. No HRG expression result
4. No HPV or p16 status
5. Prior anti-HER3 therapy
6. Prior chemotherapy for recurrent/metastatic disease
7. Anti-cancer therapy between biopsy and submission of sample
8. Presence of squamous cell tumors of the nasopharynx
9. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated with no evidence of disease for  $\geq 2$  years
10. Known history of brain metastases or active brain metastases
11. Uncontrolled hypertension (systolic > 160 mm Hg or diastolic > 100 mm Hg)
12. Clinically significant electrocardiograph (ECG) findings
13. Myocardial infarction within 1 year before enrollment, symptomatic congestive heart failure (New York Heart Association >Class II), unstable angina, or unstable cardiac arrhythmia requiring medication
14. Platinum-containing drug therapy with radiotherapy less than 6 months before study drug treatment
15. Therapeutic or palliative radiation therapy or major surgery within 4 weeks before study drug treatment. Radiation treatment to all sites of measureable disease unless progression is documented after radiation
16. Participated in clinical drug trials within 4 weeks before study drug treatment. Current participation in other investigational procedures
17. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals, known HIV infection, or active hepatitis B or C infection or undergoing medical treatment for infection
18. Uncontrolled type 1 or 2 diabetes mellitus
19. Known hypersensitivity or allergic reaction against any of the components of the trial treatment
20. Pregnant, breastfeeding, or unwilling/unable to use acceptable contraception
21. Residual toxicities  $\geq$  Grade 1 from previous therapies that the Investigator determines would exclude participation

22. Psychological, social, familial, or geographical factors that would interfere with study participation or follow-up
23. Committed to an institution by virtue of an order issued either by judicial or administrative authorities
24. Employee or immediate relative of an employee of the sponsor, CRO, the study center, or their affiliates or partners
25. Receiving yellow fever vaccine or live attenuated vaccines (for subjects receiving carboplatin)
26. Presence of hemorrhagic tumors (for subjects receiving carboplatin)
27. Prophylactic use of phenytoin or fosphenytoin (for subjects receiving cisplatin or carboplatin)

#### **4.1.3. Removal of Subjects From Therapy**

Any subject may withdraw from the study treatment or from the study at any time without specifying a reason. If a subject withdraws from the study treatment or study, the reason for withdrawal will be recorded on the eCRF. The Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

#### **4.1.4. Reasons for Discontinuation of Study Treatment**

Reasons for discontinuation of a subject from the study include: PD as per RECIST 1.1 or clinician's assessment, AE, death, withdrawal of consent by subject, significant protocol violation, or sponsor decision to terminate the study.

In the event of a decision to discontinue study drug treatment the investigator will contact the subject directly to explain the circumstances requiring study treatment to be stopped. The subject will be instructed to attend the safety follow-up visit required by the study protocol, and the treating physician will discuss alternative treatment options with the subject.

The reason for discontinuation will be recorded.

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

- Adverse Event
- Lost to Follow-up
- Withdrawal of Consent by Subject
- Physician Decision
- Death
- Pregnancy
- Progressive Disease

- Study Terminated by Sponsor
- Other

All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures, unless they withdraw their consent (Section 4.1.5).

Elevations in AST/ALT and/or total bilirubin that meet the criteria described in Table 4.1 require permanent discontinuation of the subject from patritumab/placebo and cetuximab.

**Table 4.1: Criteria for Permanently Discontinuing Study Drug for Elevations of Aminotransferase and/or Bilirubin**

<b>Discontinuation Criteria</b>	<b>Confirmation Period</b>
Serum AST or ALT > 3 x ULN and total bilirubin of > 2 x ULN	Repeat testing 3-7 days later to confirm laboratory results
AST or ALT > 5 x ULN	Repeat testing 3-7 days later to confirm laboratory results

#### **4.1.5. Withdrawal Procedures**

If a subject withdraws from the study, the Investigator or designee will complete and report the observations in the eCRF as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

The End of Study Treatment visit will be conducted within 21 days after administration of the last dose of study treatment (ie, the last dose of any study drug administered). At 40 days after the last dose a telephone call will be placed to the subject to record AEs.

For subjects with positive anti-patritumab neutralizing antibody in the serum sample drawn at the End of Study Treatment visit, additional serum samples should be obtained every 3 months for antibody measurement until the antibody level returns to baseline (or becomes negative) or up to 1 year from the last dose of study drug or if the subject starts another therapy for their cancer, whichever occurs first. A PK sample for patritumab will be collected at the time of HAHA collection for interpretation of HAHA results.

#### **4.1.6. Reasons for Discontinuation of Study Participation**

Subjects may terminate participation with study procedures if any of the following occurs:

- Subject withdraws consent to participate in study procedures
- Subject dies
- Study is terminated by sponsor
- Subject is lost to follow-up

Note: All subjects will be followed for survival status even after consent for study procedures is withdrawn. Subjects discontinued from the study because of withdrawal of consent will be followed for survival by collecting public records (eg, death certificates) unless prohibited by local laws.

**4.1.7. Subject Replacement**

Subjects will not be replaced in this study.

**4.1.8. Subject Re-screening Procedures**

Re-screening is permitted for any subject who failed to meet reversible or transient eligibility criteria upon initial screening. The subject identification number must remain the same at the time of re-screening. The initial reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for a subject who is re-screened.

## **5. TREATMENTS ADMINISTERED**

### **5.1. Investigational Products**

The Investigator must ensure that the blinded investigational product (ie, patritumab) will be used only in accordance with the protocol, as specified in Section 3.1.2. Placebo will be provided in a matching vial.

The vial labels will contain a description of the contents, batch number, and where appropriate, storage conditions and any additional statements as required by local regulations.

Daiichi Sankyo will provide carboplatin for this study. Wherever possible, commercial supplies of cetuximab and cisplatin will be supplied by the clinical site.

Daiichi Sankyo will only supply cetuximab and cisplatin to those sites that are not able to supply themselves.

#### **5.1.1. Method of Assigning Subjects to Treatments and Blinding**

Approximately 105 subjects who have an HRG expression value and HPV status (+/-) will be assigned randomly in a blinded manner by the Interactive Web/Voice Response System (IxRS) to the patritumab or the control arms in a 2:1 stratification (approximately 70 HRG-high and approximately 35 HRG-low subjects).

Please refer to Section 3.1 and Figure 3.1 for details.

#### **5.1.2. Method of Assessing Treatment Compliance**

All study drugs will be administered at the study site, under the supervision of the Investigator or designee in accordance with the protocol, to subjects participating in the clinical study. Administration of study drugs, including time of administration and dose administered, must be recorded in the eCRF.

#### **5.1.3. Labeling and Packaging**

The vial label will contain a description of the contents, batch number, and where appropriate, storage conditions and any additional statements as required by local regulations.

#### **5.1.4. Preparation**

Patritumab will be provided as a sterile lyophilisate with 240 mg/vial to be reconstituted with 8 mL water for injection to obtain a concentration of 30 mg/mL patritumab solution. Placebo lyophilisate will be diluted in an identical manner.

Subjects will be dosed based on the previous visit's weight. If the subject's weight at any visit has changed by  $\pm 10\%$  from the previous visit weight, the dose will be recalculated.

Patritumab or placebo will be prepared for each subject from allocated vials. Multiple individually numbered vials will be allocated to the subject via the IxRS and confirmed

on a subject/visit vial allocation report. Allocation of vials is not possible outside the IxRS. Concerns may be discussed with the CRO or Sponsor.

Refer to the Pharmacy Manual for detailed information regarding the preparation and administration of patritumab or placebo. Cetuximab, cisplatin, and carboplatin will be prepared according to the package insert.

#### **5.1.5. Storage**

Acknowledgement of drug shipments is managed through the IxRS to ensure materials are received in good condition before use. Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions.

Patritumab or matching placebo powder must be stored in a refrigerator set between 2°C and 8°C, and protected from light. Exposure to temperatures outside the recommended range or vigorous shaking of reconstituted drug product solution should be avoided. Temperature excursions outside the recommended range should be reported to the CRO and Sponsor. Once thawed, the product solution should not be refrozen.

Storage conditions for cetuximab, cisplatin, and carboplatin will follow respective labeling.

Records of the actual storage conditions during the period of the study must be maintained (eg, records of the date and time and the initials of the person checking, the “working day” temperatures of the refrigerator used for storage of trial supplies, continuous temperature recordings or regularly maintained temperature alarm systems used in conjunction with temperature recording).

#### **5.1.6. Drug Accountability**

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, and drug expiration date. The original shipment document will be retained at the site.

A Drug Accountability Record (separate from the eCRF) will be provided for patritumab/placebo, cetuximab, cisplatin, and/or carboplatin if applicable. The record must be kept current and should contain the dates and quantities of drugs received, the subject’s details (ie, identification number and/or initials or supply number, as applicable), for whom the drug was dispensed, the date and quantity of drug dispensed, as well as the initials of the dispenser.

At the end of the study, or as directed, the unused patritumab/placebo and carboplatin, if applicable, in addition to cetuximab and cisplatin supplies, if provided by the sponsor, will be returned to a designee as instructed by the Sponsor. The drug supplies will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned and reconciled any discrepancies. The return of the drug supplies must be documented and the documentation included in the shipment. At the end of the study, a final Investigational Product reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may only be sent for destruction by the pharmacy, per sites’ standard operating procedures (SOPs) if the sites have been given permission from the sponsor in writing following SOP review.

If permission has not been given to destroy unused drug supplies locally they must be returned as instructed.

All investigational product inventory forms must be made available for inspection by a Sponsor's authorized representative or designee and regulatory agency inspectors. The Investigator or designee is responsible for the accountability of all used and unused study supplies at the site.

#### **5.1.7. Guidelines For Dose Modifications**

For those subjects who continue treatment, the Investigator will evaluate which hematological and/or non-hematological toxicities are attributed to which drug(s), and adjust the dose of one or more of the drugs as recommended below.

If a subject experiences an unacceptable toxicity to cisplatin, the Investigator will be able to withhold drug, reduce dose, or switch to carboplatin. If the Investigator chooses to start treatment with carboplatin, then carboplatin will be administered throughout the study. If a subject also experiences an unacceptable toxicity to carboplatin, then carboplatin treatment will be withheld or dose reduced.

Subjects with unacceptable toxic effects of one of the study drugs will receive only the tolerated drugs until disease progression.

- If patritumab/placebo needs to be discontinued, the subject will be withdrawn from the study
- In subjects whose cisplatin or carboplatin therapy is discontinued, reduced, or delayed, the patritumab and cetuximab will be continued and subjects will continue to undergo tumor assessments at 6 week intervals until disease progression or unacceptable toxicity
- In subjects whose cetuximab dose is discontinued, reduced, or delayed, the patritumab will be continued. Cisplatin or carboplatin will be administered for a maximum of 6 cycles
- In subjects whose cetuximab and cisplatin or carboplatin are either discontinued or delayed, patritumab will be continued as monotherapy

In addition to the recommendations provided below, please refer to the respective current prescribing information for detailed recommendations on managing suspected toxicities, for guidance on withholding, dose reductions, and discontinuation. If toxicities occur, it is up to the discretion of the Investigator to dose reduce or withhold one or more medications until recovery or resolution of the AE to Grade 0 or 1.

In individual cases, if a subject discontinues study drugs for an extended time period, the subject may restart study drugs at the discretion of the investigator after discussion with the Sponsor and CRO's medical monitors.

Investigators may contact the Sponsor's medical monitor to discuss any question regarding dose modification or discontinuation of study drugs.

### 5.1.7.1. Dose Modification of Patritumab

Patritumab is contraindicated for subjects with known hypersensitivity to either the drug substance or inactive ingredients in the drug product. In previous patritumab studies, the most common toxicities that occurred were rash, diarrhea, vomiting, nausea, fatigue, dyspnea, and skin and subcutaneous tissue disorders. Table 5.1 and Table 5.2 pertain to patritumab dose modifications.

If the initial loading dose of 18 mg/kg is not tolerated, infusion time can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion. Patritumab/placebo is to be withheld from a subject experiencing a CTCAE Grade 3 AE, and resumed at the next regularly scheduled patritumab dosing (maintenance dose of 9 mg/kg) only after resolution of the AE to Grade 0 or 1 (or baseline grade if higher than Grade 1).

If a rash or mucositis occurs following the initial dose of patritumab 18 mg/kg, then hold the patritumab until the AE resolves to Grade 0 or 1 (or baseline grade if higher than Grade 1). If the rash or mucositis has not resolved, then hold cetuximab 250 mg/m<sup>2</sup> until the AE resolves to Grade 0 or 1 (or baseline grade if higher than Grade 1). If a rash or mucositis occurs on the maintenance dose of patritumab at 9 mg/kg, hold patritumab until the AE resolves to Grade 0 or 1 (or baseline grade if higher than Grade 1) and then decrease patritumab dosing to 6 mg/kg. If the AE does not resolve, hold the next dose of cetuximab until resolution to Grade 0 or 1 (or baseline grade if higher than Grade 1).

Left ventricular ejection fraction will be monitored throughout the study (see Section 9.11.1) for possible effects of patritumab treatment on cardiac function. Dose modification or suspension of patritumab treatment will be based on decreased LVEF, as outlined in Table 5.1.

For cases of ILD, refer to Section 9.3.2.

Both patritumab/placebo are to be withheld from a subject experiencing a Grade 4 AE.

**Table 5.1: Patritumab Maintenance Dose Modification for Toxicities**

Toxicity	Withhold Criteria	Resumption Criteria	Dose Reduction Criteria	Discontinuation Criteria
All AEs <sup>a</sup>	Grade 3 or higher	Grade 0 or 1 (or baseline grade if higher than Grade 1) <sup>b</sup>	Reduce patritumab maintenance dose from 9 mg/kg to 6 mg/kg (for mucositis follow dose modification as defined above)	Failure to recover within 3 weeks



Toxicity	Withhold Criteria	Resumption Criteria	Dose Reduction Criteria	Discontinuation Criteria
Ejection fraction	Grade greater than or equal to 3, (LVEF of less than 40% or LVEF decrease of more than 20% from the baseline)	LVEF of at least 50% (or baseline) based on a repeat echocardiogram or MUGA scan performed in 3 weeks	Reduce patritumab maintenance dose from 9 mg/kg to 6 mg/kg	LVEF that does not recover within 3 weeks: Decreased $\geq$ Grade 3 <40% >20% decrease from baseline

a For elevations of aminotransferase (AST/ALT) and/or bilirubin, please see Section 4.1.4.

b Patritumab/placebo dosing may be resumed upon consultation with the Sponsor's medical monitor if the event has resolved to Grade 2.

MUGA = multigated acquisition (scan); LVEF = left ventricular ejection fraction.

Dose delays/reductions for toxicities related to patritumab are summarized in Table 5.2.

**Table 5.2: Dose Delays/Reductions for Toxicities Related to Patritumab**

Grade	Action
1	Continue current dose level
2	Continue current dose level
3	Discontinue patritumab/placebo for up to 3 weeks until the event has recovered to Grade 1 or baseline. <sup>a</sup> Administer patritumab at a dose that is decreased by one dose level for subsequent cycles. A maximum of 1 dose reduction from the 9 mg/kg IV maintenance dose to 6 mg/kg IV maintenance dose will be permitted. No dose reductions below patritumab 6 mg/kg will be allowed.
4	Discontinue patritumab/placebo for up to 3 weeks until the event recovers to Grade 1 or baseline. <sup>a</sup> Discuss the event with the sponsor's Medical Monitor or designee before restarting patritumab/placebo. If the investigator and the sponsor's Medical Monitor/designee agree, the weekly maintenance dose will also be decreased from 9 mg/kg IV to 6 mg/kg IV.

<sup>a</sup> If the subject fails to recover to Grade 1 or baseline and dose must be delayed >3 weeks, the subject will be withdrawn from all study treatment, but should continue to undergo all follow-up evaluations

To receive patritumab, a subject's ANC must be  $\geq 1.5 \times 10^9/L$  ( $\geq 1500/mm^3$ ) and platelet count must be  $\geq 100 \times 10^9/L$  ( $\geq 100,000/mm^3$ ). Patritumab may be withheld for up to 3 weeks to allow cell counts to recover to these values. Dose administration may be delayed no more than 3 weeks to allow for recovery. If the dose is delayed more than 3 weeks, the subject will be withdrawn from study treatment, unless discussed and agreed with the sponsor.

All subjects should be carefully monitored for possible infusion reactions during the administration of patritumab/placebo. If, during infusion, a subject experiences mild to moderate symptoms suggestive of infusion reaction (such as fever and chills, with or without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension), slow down the infusion up to 120 minutes (see Section 3.1.2.1 for administration of patritumab/placebo). All subsequent infusions should be administered at the same slow rate (up to 120 minutes).

Interrupt patritumab/placebo infusion in all subjects experiencing severe infusion reactions (eg, dyspnea, clinically significant hypotension) and administer interventional medical therapy, which may include: epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Subjects should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Subjects experiencing severe infusion reactions will be permanently discontinued.

In the event of a dose reduction, the dose change(s) must be captured in the eCRF. If questions or considerations regarding dose modification arise or a specific dose modification is needed, the medical monitor or designee should be consulted. The contact information for the Daiichi Sankyo medical monitor is located in Section 15.2.1.1.

#### **5.1.7.2. Dose Modification of Cetuximab**

Prior to first and all subsequent infusions of cetuximab, subjects must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab (please see package insert for further information). Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Some of these reactions may be anaphylactic or anaphylactoid in nature, accompanied by bronchospasms or urticaria, or represent a cytokine release syndrome. Symptoms may occur during the first infusion and for up to several hours afterwards, or with subsequent infusions. They can occur despite the use of premedication. It is recommended to warn subjects of the possibility of such a late onset and instruct them to contact their physician if symptoms or signs of an infusion-related reaction occur.

If during the first infusion, infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. If an infusion-related reaction develops later during the infusion or at a subsequent infusion, further management will depend on its severity:

- Grade 1: continue slow infusion under close supervision
- Grade 2: continue slow infusion and immediately administer treatment for symptoms
- Grade 3 and 4: stop infusion immediately, treat symptoms vigorously, and contraindicate further use of cetuximab

Mild or moderate infusion-related reactions are very common, comprising symptoms such as fever, chills, dizziness, or dyspnea that occur in a close temporal relationship, mainly to the first cetuximab infusion. If the subject experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Additionally, cetuximab must be immediately discontinued in case of:

- Grade 3 or 4 infusion-related reaction related to cetuximab

- Occurrence of a second infusion-related reaction, following administration of cetuximab at a slower infusion rate.
- A fourth occurrence of Grade 3 skin reactions, despite appropriate dose reductions
- Occurrence of Grade 4 skin reactions

A close monitoring of subjects, particularly during the first administration, is required. Special attention is recommended for subjects with reduced performance status and pre-existing cardiopulmonary disease.

When cetuximab is administered with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia, and sepsis compared to platinum-based chemotherapy alone.

If a subject develops an intercurrent illness (eg, infection) that, in the opinion of the Investigator and/or the Sponsor, mandates interruption of therapy, this intercurrent illness must resolve within a time frame such that no more than 2 consecutive cetuximab infusions are withheld.

When cetuximab is administered in combination with chemotherapeutic agents such as cisplatin or carboplatin, refer to their respective product information. Chemotherapy must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Cetuximab therapy will not be delayed for cisplatin-related toxicity. Therefore, if the next infusion of cisplatin is delayed, the subject will continue to receive weekly infusions of cetuximab. In case of cetuximab-related toxicity, cisplatin will not be delayed and the planned schedule for administration should be maintained. If the cetuximab therapy is terminated for cetuximab-related toxicity, cisplatin will be continued. If there is cetuximab-related toxicity that does not resolve to Grade 0 or 1 (or baseline grade if higher than Grade 1), cetuximab will be discontinued at the discretion of the investigator.

Dose modifications for cetuximab are described in Table 5.3 and [Table 5.4](#).

**Table 5.3: Cetuximab Dose Modifications**

<b>Toxicity</b>	<b>Dose Reduction</b>	<b>Discontinuation</b>
Infusion reaction	Reduce infusion rate by 50% for CTCAE Grade 1 or 2 and non-serious CTCAE Grade 3 infusion reaction	Immediately interrupt and permanently discontinue cetuximab infusion for serious infusion reactions

CTCAE = Common Terminology Criteria for Adverse Events.

**Table 5.4: Cetuximab Dose Modification Guidelines for Acneiform Rash**

Severe Acneiform Rash (Grade 3-4)	Cetuximab	Outcome	Cetuximab Dose Modification
1 <sup>st</sup> occurrence	Delay infusion 1-2 weeks*	Improvement	Continue at 250 mg/m <sup>2</sup>
		No improvement	Discontinue cetuximab
2 <sup>nd</sup> occurrence	Delay infusion 1-2 weeks*	Improvement	Reduce dose to 200 mg/m <sup>2</sup>
		No improvement	Discontinue cetuximab
3 <sup>rd</sup> occurrence	Delay infusion 1-2 weeks*	Improvement	Reduce dose to 150 mg/m <sup>2</sup>
		No improvement	Discontinue cetuximab
4 <sup>th</sup> occurrence	Discontinue		

\* If infusion is delayed >2 weeks, discontinue cetuximab treatment.

### 5.1.7.3. Dose Modification of Cisplatin

Repeating administration of cisplatin must be delayed until normal values are achieved (wait one cycle for recovery) for the following parameters:

- Serum creatinine < 1.5 mg/dL
- Urea < 25 mg/dL
- White blood cells > 4.0 x 10<sup>9</sup>/L
- Blood platelets > 100 x 10<sup>9</sup>/L
- Non-hematological cisplatin-related toxicities to resolve to ≤ Grade 1
- However, skin reactions, paronychia, fatigue, ototoxicity, or neurotoxicity should resolve to ≤ Grade 2

Please see package insert for further information.

#### *Nephrotoxicity*

Cisplatin causes severe cumulative nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by prehydration with 2 liters of an appropriate IV solution, and similar post cisplatin hydration (recommended 2,500 mL/m<sup>2</sup>/24 hours) or according to institutional standards. If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (eg, mannitol).

#### *Neuropathies*

Neuropathies may manifest by paresthesia, areflexia, and a proprioceptive loss of sensation of vibrations. A neurologic examination must be carried out at regular intervals.

#### *Ototoxicity*

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m<sup>2</sup>, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz).

*Allergic phenomena*

As with other platinum-based products, hypersensitivity reactions appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion as an appropriate symptomatic treatment.

Anaphylactic-like reactions to cisplatin have been observed. These reactions can be controlled by administration of antihistamines, adrenaline, and/or glucocorticoids.

*Hepatic function and hematological status*

The hematological status and the hepatic function must be monitored at regular intervals.

*Injection site reactions*

Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

Special care is required for subjects with acute bacterial or viral infections.

Table 5.5 lists toxicities and related dose modifications and discontinuations.

**Table 5.5: Cisplatin Dose Modifications and Discontinuations\* for Toxicities**

<b>Toxicity</b>	<b>Dose Modification/Discontinuation</b>
Hematological	A repeat course should not be given until circulating blood elements are at an acceptable level (ie, platelets $\geq 100 \times 10^9/L$ , white blood cells $\geq 4 \times 10^9/L$ )
Febrile neutropenia/infection	The first episode of febrile neutropenia or infection will result in reduction by 20% of cisplatin dose. If there is a second episode, despite dose reduction, the subject must receive prophylactic antibiotics during subsequent cycles. If there is a third episode, the subject will be withdrawn from study.
Neutropenia	Grade 2 or 3: cisplatin treatment delay until < Grade 1. Grade 4: cisplatin treatment delay until < Grade 1; dose reduction of all further doses of cisplatin by 20%.
Nephrotoxicity	A repeat course of cisplatin should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the urea is below 25 mg/100 mL
Thrombocytopenia	Grade 1: cisplatin treatment delay until platelets $\geq 100,000/mm^3$ . $\geq$ Grade 2: cisplatin treatment delay until platelets $>100,000/mm^3$ , dose reduction of all further doses of cisplatin by 20%

Toxicity	Dose Modification/Discontinuation
Organ Toxicity	Grade 2: Delay chemotherapy until $\leq$ Grade 1. $\geq$ Grade 3 or more: Delay chemotherapy until $\leq$ Grade 1; dose reduction of all further doses of cisplatin by 20%. Do not delay or reduce cisplatin dose if there are asymptomatic increases in transaminases, cetuximab-induced skin reactions, and subclinical side effects (e.g. nausea, vomiting, alopecia, altered taste).
Ototoxicity	Criteria for hearing testing
Neuropathy	In case of sensory neuropathy $\geq$ Grade 2, change cisplatin to carboplatin

Note: Please refer to the cisplatin package insert for additional information on potential toxicities and their management. When cisplatin is administered in combination with other agents such as cetuximab, refer to their respective product information. \*If events do not recover within 3 weeks, discontinue cisplatin treatment.

#### 5.1.7.4. Dose Modification of Carboplatin

##### *Myelosuppression*

Carboplatin myelosuppression is closely related to its renal clearance. Subjects with abnormal kidney function or receiving concomitant therapy with other drugs with nephrotoxic potential are likely to experience severe and prolonged myelotoxicity. Renal function parameters should therefore be carefully assessed.

##### *Hematological toxicity*

Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. Anemia is frequent and cumulative. Frequent monitoring of peripheral blood counts is recommended during and following therapy. Carboplatin should not be repeated until after leukocytes, platelets, and neutrophils have returned to normal ([Table 5.6](#)).

##### *Hepatic and/or renal insufficiency*

Renal or hepatic function impairment may be encountered with carboplatin. Dose reduction or discontinuation of carboplatin is required in the presence of moderate to severe alterations in renal or hepatic function.

##### *Allergic reactions*

Infrequent allergic reactions such as erythematous rash, fever with no apparent cause, or pruritus, anaphylaxis, angioedema, and anaphylactoid reactions (including bronchospasm, urticarial, and facial oedema) may occur. These occur more often during perfusion. Discontinuation of the perfusion should be carried out immediately and appropriate symptomatic treatment must be given such as with antihistamines, adrenalines, and/or glucocorticoids.

##### *Neurotoxicity*

Neurotoxicity such as paresthesia, decreased deep tendon reflexes, and ototoxicity are more likely in subjects older than 65 years old. Monitoring and neurological examinations should be carried out at regular intervals.

**Table 5.6: Carboplatin Dose Modification for Toxicities**

Toxicity	Dose Reduction <sup>a</sup>		
Myelosuppression*	Platelets	Neutrophils	Adjusted Dose (from prior course)
	> 100,000	> 1,500	No adjustment
	50-100,000	500-1,500	No Adjustment
	< 50,000	< 500	25% dose reduction
Nephrotoxicity*	Baseline creatinine clearance		Recommended Dose on Day 1
	41-59 mL/min		AUC 3.75 (25% dose reduction)
	30-40 mL/min		AUC 3.0 (40% dose reduction)

<sup>a</sup> Initial dose is AUC 5 calculated by Calvert formula. AUC = area under the curve.

Note: Please refer to the carboplatin package insert for additional information on potential toxicities and their management. When carboplatin is administered in combination with other agents such as cetuximab, refer to their respective product information.

\*If events do not recover within 3 weeks, discontinue carboplatin treatment.

### 5.1.8. Retention Samples

Not Applicable.

### 5.1.9. Emergency Unblinding

In the case of a rare emergency where, in the opinion of the Investigator, discontinuation of study drug is not sufficient and study treatment must be unblinded to evaluate a further course of medical treatment, the following procedures will apply:

The investigator is encouraged to contact the CRO medical monitor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of the study treatment will not be dependent upon the investigator receiving approval from the CRO medical monitor (ie, the Investigator will be able to obtain the code break information independent of the CRO medical monitor).

The method for determining a subject's treatment assignment once a subject is randomized in the study is through the IxRS. The investigator and one designated sub-investigator will have access to perform emergency unblinding in the IxRS. The treatment assignment of the selected subject randomized at their site will be revealed to the investigator performing the IxRS call upon completion of the emergency unblinding call.

The investigator must contact CRO medical monitor by telephone with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code.

In the event of emergency unblinding, the subject will be informed about their treatment assignment. Information about the treatment assignment must be restricted to designated study site staff/personnel who are providing immediate care to the subject. Any documentation of the treatment assignment must be maintained separately (ie, a secured

file). The information must not be included in the subject's source files to ensure the treatment assignment will remain blinded to the CRO monitor and other study personnel who are not involved with the subject's immediate care.

When an emergency unblinding has occurred, an automatic notification (via e-mail) will be sent to the investigator and selected Daiichi Sankyo study personnel from the IxRS vendor. The notification will not contain any unblinding information. This will trigger the follow up process to document the unblinding by completing the Emergency Unblinding by Investigator Form (to be provided to the CRO medical monitor by study personnel upon receipt of IxRS notification) and submission to Daiichi Sankyo Clinical Safety and Pharmacovigilance; please refer to the form for completion instructions.

Once the study treatment has been unblinded for a specific subject, the study treatment should be discontinued for the subject, and the subject should leave the study treatment phase. The end of treatment and follow-up assessments for the subjects will be performed as defined in the protocol.

## **5.2. Concomitant Medications**

Subjects cannot receive any nonstudy anticancer therapy, hormonal therapy, or radiotherapy during the treatment period.

Use of hematopoietic growth factors, if required, are permitted in Cycle 1. In subsequent cycles, hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator.

Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.

Please refer to package inserts for cetuximab, cisplatin, and carboplatin for additional information on use of concomitant medications.

All concomitant medication taken by subjects during the study must be recorded in the eCRF.

### **5.2.1. Patritumab**

Patritumab is contraindicated for subjects with known hypersensitivity to either the drug substance or inactive ingredients in the drug product. There are no known contraindications. Drug-drug interaction studies have not yet been conducted.

### **5.2.2. Cetuximab**

In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia, and sepsis compared to platinum-based chemotherapy alone.



### **5.2.3. Cisplatin**

#### **Nephrotoxic substances**

Concomitant administration of nephrotoxic (eg, cephalosporins, aminoglycosides, amphotericin B or contrast media) or ototoxic (eg, aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin on the kidneys.

#### **Ototoxic substances**

Concomitant administration of ototoxic (eg, aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function. Except for subjects receiving doses of cisplatin exceeding 60 mg/m<sup>2</sup>, whose urine secretion is < 1000 mL per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.

#### **Weakened live vaccines**

Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease. In view of the risk of generalized illness, it is advisable to use an inactive vaccine if available. Live/attenuated or inactivated influenza vaccine is allowed.

#### **Antihistamines, Phenothiazines and others:**

Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozone, phenothiazines, thioxanthenes or trimethobenzamines may mask ototoxicity symptoms (such as dizziness and tinnitus).

#### **Anticonvulsive substances**

Serum concentrations of anticonvulsive medicines may remain at subtherapeutic levels during treatment with cisplatin.

#### **Anti-epileptics**

In subjects receiving cisplatin and anticonvulsant agents, the serum level of the anticonvulsant agent might be reduced. This is probably due to reduced absorption and/or increased metabolism. In these subjects, the plasma levels of anticonvulsants should be monitored, and the dose adjusted accordingly. Prophylactic use of phenytoin or fosphenytoin is prohibited.

### **5.2.4. Carboplatin**

Concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin, and diuretics, may increase or exacerbate toxicity due to carboplatin induced changes in renal clearance.

Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses in order to minimize the additive myelosuppressive effects.

Prophylactic use of phenytoin or fosphenytoin is prohibited.

Receiving yellow fever vaccine or live attenuated vaccines is prohibited.

## 6. STUDY PROCEDURES

A study visit schedule is provided in [Table 17.2](#). Study treatments should be administered as specified in [Section 3.1.2](#).

### 6.1. Screening

#### 6.1.1. Tissue Screening

Samples must be taken from subjects who have recurrent or metastatic disease (rec/met). These samples must be from either rec/met archived or fresh biopsy material. Samples can derive from either primary recurrent tumor or from its lymph nodal metastases originating from the oral cavity, oropharynx, hypopharynx, and larynx. No additional treatment is allowed between biopsy and study entry.

Tissue samples must be formalin fixed, paraffin embedded, slides cut of 5 microns, unstained and unbaked. Please refer to the laboratory manual for additional information on management of tissue samples.

The following procedures will be conducted:

- Obtain written consent from the subject to collect tissue or perform a biopsy
  - If a tumor biopsy is performed, record only SAEs directly related to the procedure.
- Samples will be analyzed for and must meet eligibility criteria:
  - HRG expression
  - HPV status or p16 is required. These results may be obtained from either a local lab or samples sent to the central lab

#### 6.1.2. Screening (Up to 14 Days Before the First Dose of Study Treatment Unless Otherwise Noted)

Screening procedures can be done at the same time as tissue screening (Section 6.1.1) at the discretion of the Investigator.

The following activities and/or assessments will be performed at/during screening (within 14 days before the first dose of study treatment [unless otherwise noted]):

- Obtain signed informed consent
- Obtain signed informed consent for pharmacogenomics (optional)
- Evaluation of inclusion and exclusion criteria
- Confirm results of the HRG expression level and HPV or p16 status.
- Record demographic and medical history information
  - Including smoking history

- Record AEs and concomitant medications
- Perform a physical examination, including vital sign measurements, blood pressure, heart rate, temperature, weight, and height. Height will be measured only at Screening
- Assess functional status using the ECOG Performance Status Scale (Section 10.1)
- Perform an echocardiogram or multigated acquisition (MUGA) scan (the same test must be used for a subject throughout the study) (Section 9.11.1)
- Perform a 12-lead ECG
- Collect blood sample for complete blood count (CBC) (Section 9.7)
- Collect blood sample for coagulation-only at Screening (Section 9.7)
- Collect blood sample for serum chemistry (Section 9.7)
- Obtain urine sample for urinalysis (Section 9.7)
- Perform a serum or urine pregnancy test for female subjects of childbearing potential (must be confirmed negative before dosing). Additional pregnancy testing may be done at the discretion of the Investigator and/or if required by local regulations for women of child-bearing potential (Section 9.7)
- Perform radiographic tumor assessments after eligibility is determined. Existing radiographic scans can be used for the baseline evaluation if the scans were performed within 4 weeks prior to randomization. Computed tomography (CT) and/or magnetic resonance imaging (MRI) (spiral CT or MRI with  $\leq 5$  mm cuts) should be used for tumor assessment unless another modality of radiographic disease assessment is necessary for the lesions per RECIST guidelines Version 1.1, (see Appendix 17.3)

### 6.1.3. Randomization

For subjects who are eligible to participate in the study, complete the following:

- Randomize subject in the IxRS
- Study treatment should begin within 3 business days after randomization

## 6.2. Treatment Period

A hospital overnight stay associated with study procedures or treatment is allowed and will not be reported as an SAE (see Section 9.4.2).

Additional pregnancy testing may be done during the treatment period at the discretion of the Investigator and/or if required by local regulations for women of child-bearing potential.

### 6.2.1. Cycle 1: Week 1, Day 1

#### Pre-dose

- Perform a physical examination
  - Weight measured within 3 days prior to Day 1 may be used to calculate the drug dose
- Vital sign measurements (blood pressure, heart rate, temperature)
- Assess functional status using the ECOG Performance Status Scale (Section 10.1).
- Record AEs
- Record concomitant medications
- Have subject complete the PRO assessments before any study-related procedures are performed
- Collect blood sample for CBC (Section 9.7)-within 3 days prior to visit
- Collect blood sample for serum chemistry (Section 9.7)-within 3 days prior to visit
- Collect blood sample for HAHA-within 3 days prior to visit (Section 8.4 and Table 8.1)
- Collect blood sample for sparse PK (Table 8.1)
- Collect blood sample for pharmacogenetics (PGx) (optional)
- Collect blood samples for additional biomarkers

#### Study Treatment

Information for dosing and administration is found in Section 3.1.2 . Study drugs should be administered consecutively in the order below:

- Administer patritumab IV as specified in Section 3.1.2
- Administer cetuximab IV as specified in Section 3.1.2
- Administer cisplatin (or carboplatin) IV one hour after cetuximab, as specified in Section 3.1.2.

#### End of Patritumab, Cetuximab, and Cisplatin or Carboplatin Infusions

- Perform vital sign measurement
- Record concomitant medications and AEs throughout administration of study drugs
- Sparse PK: collect a blood sample for PK at end of patritumab infusion (EOI) at 1 hr  $\pm$  10 min for all subjects (Table 8.1)
- Intense PK substudy

- Collect blood sample for PK at 3 hrs  $\pm$  10 min after start of patritumab infusion (approximately EOI for cetuximab) (Table 8.2)
- Collect blood sample for PK at 4 hrs  $\pm$  10 min after start of patritumab infusion (or 4.25 hrs  $\pm$  10 min, approximately EOI for carboplatin for those subjects receiving carboplatin) (Table 8.2)
- Collect blood sample for PK at 5 hrs  $\pm$  10 min after start of patritumab infusion) (approximately EOI for cisplatin for those subjects receiving cisplatin) (Table 8.2)
- Collect blood sample for PK at 6 hrs  $\pm$  10 min after start of patritumab infusion (Table 8.2)
- Collect blood sample for PK at 7 hrs  $\pm$  10 min after start of patritumab infusion (Table 8.2)

**6.2.2. Cycle 1: Week 1, Day 2**

- Intense PK substudy: collect blood sample for PK at 24 hrs  $\pm$  1hr after start of patritumab infusion (Table 8.2)

**6.2.3. Cycle 1: Week 1, Day 3**

- Intense PK substudy: collect blood sample for PK at 48 hrs  $\pm$  1hr after start of patritumab infusion (Table 8.2)

**6.2.4. Cycle 1: Week 2, Day 8**

- Physical examination
- Vital signs
- ECOG Performance Status
- Record concomitant medications and AEs
- Blood samples for CBC (hematology with differential and platelet count), (Section 9.7)-may be collected within 3 days prior to visit
- Serum chemistries-may be collected within 3 days prior to the visit
- Intense PK substudy: collect blood sample for PK at 168 hrs  $\pm$  24 hrs (Table 8.2)-within 3 days prior to visit
- Administer cetuximab IV (infused weekly) as specified in Section 3.1.2 (given on Day 8 and Day 15 of all cycles)

**6.2.5. Cycle 1: Week 3, Day 15**

- Physical examination
- Vital signs
- ECOG Performance Status

- Record concomitant medications and AEs
- Blood samples for CBC (hematology with differential and platelet count) (Section 9.7)-may be collected within 3 days prior to visit
- Serum chemistries-may be collected within 3 days prior to visit
- Intense PK substudy: collect blood sample for PK at 336 hrs  $\pm$  1 day (Table 8.2)
- Administer cetuximab IV (infused weekly) as specified in Section 3.1.2 (given on Day 8 and Day 15 of all cycles)

#### 6.2.6. Cycle 2 and 3

##### 6.2.6.1. Cycle 2, Day 1

- Collect blood samples for additional biomarkers

##### 6.2.6.2. Cycles 2 and 3, Day 1

#### Before Start of Patritumab Infusion

- Physical examination \*
- Vital signs \*
- Weight\*
- ECOG Performance Status
- At Cycle 3 only, perform an echocardiogram or MUGA scan (the same test must be used for a subject throughout the study)
- Record concomitant medications and AEs \*
- Have subject complete the PRO assessments before any study-related procedures are performed
- Collect blood sample for CBC with differential and platelet count\*
- Collect blood sample for serum chemistries \*
- For Cycle 2 Sparse PK: collect blood sample for HAHA/patritumab PK (Table 8.1).
- For subjects participating in the Intense PK substudy, the preinfusion patritumab PK sample is also the PK at 504 hrs  $\pm$  1 day (Table 8.2)
- At Cycle 3 Sparse PK: collect blood sample for PK at preinfusion and the patritumab EOI at 1 hr  $\pm$  10 min for all subjects (Table 8.2)
- Serum sample for HAHA

*Note: \* Can be collected on Days 8 and 15 at the discretion of the Investigator.*

### Study Treatment Administration

- Administer patritumab IV (infused once every 3 weeks) as specified in Section 3.1.2
- Administer cetuximab IV (infused weekly) as specified in Section 3.1.2
- Administer cisplatin or carboplatin IV (infused every 3 weeks, for a maximum of 6 cycles) as specified in Section 3.1.2

#### 6.2.7. Cycle 4 and all Subsequent Cycles, Day 1

##### 6.2.7.1. Day 1

- Physical examination\*
- Vital signs\*
- Weight\*
- ECOG Performance Status (Section 10.1)
- At visits for every third subsequent cycle (eg, Cycles 6, 9, 12 ...) conduct an echocardiogram or MUGA scan (the same test must be used for a subject throughout the study)
- Record concomitant medications and AEs\*
- Have subject complete the PRO assessments before any study-related procedures are performed
- Collect blood sample preinfusion for CBC with differential and platelet count\*
- Collect blood sample preinfusion for serum chemistries\*

*Note: \* Can be collected on Days 8 and 15 in Cycle 4 and all subsequent cycles at the discretion of the Investigator.*

### Study Treatment Administration

- Administer patritumab IV (infused once every 3 weeks) as specified in Section 3.1.2
- Administer cetuximab IV (infused weekly) as specified in Section 3.1.2
- Administer cisplatin or carboplatin IV (infused every 3 weeks, for a maximum of 6 cycles) as specified in Section 3.1.2

#### End of Cycle 6 and Every 4 Cycles

- Collect blood samples for additional biomarkers

#### 6.2.8. Every 6 Weeks

- Frequency of tumor assessments will be every 6 weeks to Week 24 ( $\pm 3$  days); every 12 Weeks ( $\pm 7$  days) thereafter

### **6.2.9. End of Study Treatment Visit (21 days after last dose)**

At the end of study treatment, the following procedures will be performed.

- Physical examination
- Vital signs
- Weight
- ECOG Performance Status (Section 10.1)
- Perform an echocardiogram or MUGA scan
- Perform a 12-lead ECG
- Record concomitant medications and AEs
- Have subject complete the PRO assessments before any study-related procedures are performed
- Collect blood sample for CBC with differential and platelet count
- Collect blood sample for serum chemistries
- Collect urine sample for urinalysis (Section 9.7)
- Sparse PK: collect a blood sample for PK (Table 8.1)
- Collect blood sample for HAHA
- Perform a serum or urine pregnancy test for female subjects of childbearing potential
- Tumor measurement assessments unless it was performed within the previous 6 weeks or the previous assessment demonstrated disease progression
- Collect blood samples for additional biomarkers

If there is a significant clinical or laboratory abnormality in need of monitoring beyond the end-of-study treatment visit, subjects will be followed until resolution of the abnormality, until it is considered stable, or the subject begins another cancer treatment.

For subjects with positive HAHA at the end-of-study treatment visit, additional serum samples for HAHA and PK should be collected every 3 months until HAHA titers return to baseline or until the start of another cancer therapy. Samples will be collected up to 1 year from the last dose of study drug or collected up to the time that a subject starts another cancer therapy, whichever occurs first.

### **6.2.10. 40 Days After Last Dose**

At 40 days after the last dose of any study drug administered, a telephone call will be placed to the subject to record AEs (See Section 4.1.5).

- Collect blood samples for additional biomarkers



### **6.2.11. Discontinuation From Study Treatment**

Subjects discontinued from study treatment without documented (by imaging) PD, withdrawal of consent, death or loss to follow-up should continue tumor evaluation at 6-week intervals up to the first 24 weeks after randomization, then every 12 weeks ( $\pm 7$  days) until disease progression, start of new anticancer therapy, death, withdrawal of consent, loss to follow-up, or study closure.

### **6.2.12. Subjects Deriving Clinical Benefit**

Subjects receiving clinical benefit (SD or better) from study treatment at the time of closure of the main study may be offered the opportunity to continue study treatment in an open label extension phase (see Section 6.5).

## **6.3. Follow-up Survival**

After discontinuation from study treatment, follow-up information for survival will be obtained per telephone approximately every 3 months for a minimum of 13 months.

## **6.4. Protocol Deviations**

The investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose of investigational treatment, and had at least one administration of investigational product, data should be collected for safety purposes.

The Investigator should notify the IEC or IRB of deviations from the protocol in accordance with local procedures.

## **6.5. Extension Phase**

Subjects receiving clinical benefit (SD or better) from study treatment at the time of closure of the main study may be offered the opportunity to continue study treatment. After database lock individual sites will be informed of subject treatment. Subjects will be provided open-label treatment in an extension phase of this study.

For subjects continuing in the extension phase, the following study procedures will be performed: physical examination, weight, vital signs, hematology, blood chemistry, HAHA levels (and PK) if HAHA is positive at the end of study treatment, blood samples for biomarkers, and AEs (see Extension Phase Schedule of Events, [Table 17.3](#)).

## 7. EFFICACY ASSESSMENTS

Tumor response assessments, including subjects who discontinued from treatment, will be performed every 6 weeks ( $\pm$  3 days) for the first 24 weeks independent of treatment cycle until disease progression, death, start of new anticancer therapy, withdrawal of subject consent, lost to follow-up, or study closure, whichever occurs first. After 24 weeks, tumor assessments will be performed every 12 weeks ( $\pm$  7 days).

### 7.1. Primary Efficacy Variable

The primary efficacy variable is PFS. This is defined as the time from the date of randomization to the earlier of the dates of the first objective documentation of radiographic disease progression (per RECIST v1.1 as assessed by investigator-see [Appendix 17.3](#)) or death due to any cause. Progressive Disease is defined as  $\geq$  20% increase in the sum of diameters of target lesions; taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “clinical progression.” Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease. If a radiographic tumor assessment has not been performed within 4 weeks of the time of clinical progression, then another radiographic assessment should be performed without waiting for the next regularly scheduled scan.

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

### 7.2. Secondary Efficacy Variable(s)

- Overall survival and objective response rate

### 7.3. Exploratory Efficacy Variable(s)

- Duration of response, time to response, time to disease progression, duration of SD

## 8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

### 8.1. Pharmacokinetic (PK) Variable(s)

All subjects will have a PK sample for serum patritumab collected at Cycles 1- 3 and at End of Study Treatment Visit as shown in Table 8.1. This will be a sparse PK assessment (limited sampling).

**Table 8.1: Sparse PK Assessments (Patritumab Only) for All Subjects**

Cycle 1		Cycle 2		Cycle 3		End of Treatment
Pre-inf (collected with HAHA sample)	EOI	Pre-inf (collected with HAHA sample)		Pre-inf (collected with HAHA sample)	EOI	Collected with HAHA sample

Pre-inf = Preinfusion, EOI = end of infusion, HAHA = human antihuman antibody. EOI samples should be collected  $\pm$  10 min of the end of patritumab infusion.

For a subset of 30 subjects, a blood sample for PK analyses of patritumab, cetuximab, and platinum concentrations will be obtained at the time points, relative to the start of patritumab infusion at Cycle 1, shown in Table 8.2. This will be an intense PK assessment.

**Table 8.2: Sub Study: Intensive PK Assessments Relative to the Start of Patritumab Infusion at Cycle 1 [n = 30]**

Study Treatment	Pre-inf	Day 1						Day 2	Day 3	Day 8	Day 15	Day 21
		1 h (EOI) $\pm$ 10 min	3 h $\pm$ 10 min	4 h $\pm$ 10 min	5 h $\pm$ 10 min	6 h $\pm$ 10 min	7 h $\pm$ 10 min	24 h $\pm$ 1 h	48 h $\pm$ 1 h	168 h $\pm$ 24 h	336 h $\pm$ 24 h	504 h $\pm$ 24 h
Patritumab	X	X	X	X	X	X	X	X	X	X	X	X
Cetuximab	X		EOI	X	X	X	X	X	X	X		
Cisplatin	X				EOI	X	X	X	X			
or												
Carboplatin	X			4.5 h EOI	X	X	X	X	X			

Pre-inf = Preinfusion, EOI = End of infusion, h = hours, min = minutes.

Note: One blood sample to produce 3 mL of serum sample will be collected at each time point. The resulting serum will be divided into 3 aliquots of 1 mL for analysis of each analyte depending on the dose regimen. Further details will be provided in the lab manual.

Patritumab will be infused over 1 hour followed by cetuximab infused over 2 hours (end of infusion at  $\sim$ 3 h) and then a 1 h pause ( $\sim$ 4 h). Then cisplatin will be infused over 1 hour (end of infusion  $\sim$ 5 h) or carboplatin infused over 30-60 minutes (end of infusion  $\sim$ 4.5 h). Subjects will remain in the clinic for hydration following cisplatin/carboplatin

infusions for approximately 2 hours following infusions to complete hydration (ie, ~7 h in total). Only one blood sample will be collected at each scheduled time point and the resulting serum will be aliquoted for each analyte. Blood collection should approximately correspond to EOI of each drug as listed, at the nominal times defined relative to the start of patritumab infusion.

Serum concentrations of patritumab, cetuximab, and platinum will be measured, as appropriate, using validated assays. Specific instructions for collection and shipping of PK samples will be provided in the Laboratory Manual.

## **8.2. Pharmacodynamic Variable(s)**

Not applicable.

## **8.3. Predictive Biomarker and Exploratory Variable(s)**

A predictive biomarker will be analyzed with the intent of identifying those subjects who might derive clinical benefit from treatment with patritumab. Heregulin is the candidate biomarker prospectively selected as the single predictive biomarker. Heregulin messenger RNA will be measured in tumor samples using a quantitative reverse transcription polymerase chain reaction assay.

Subjects with HPV positive status will be included. Molecular and epidemiological studies strongly suggest HPV-positive oropharyngeal cancers comprise a distinct molecular, clinical, and pathologic disease entity that is likely associated with HPV infection and for which SCCHN patients who are HPV positive have a markedly improved prognosis. In addition, it has been shown that other SCCHN subtypes have been found to be p16 positive such as nasopharyngeal, hypopharyngeal, laryngeal, and in the oral cavity.<sup>5</sup> Therefore, HPV status or p16 will be evaluated in all tumor tissue in this study.

Further exploratory tissue, soluble, or genomic biomarkers in subject tissue and blood samples (possibly including circulating cell-free DNA and exosomes) may be analyzed based on emerging scientific knowledge to better understand the target disease and also the effects of study treatment.

For instructions on management of blood and tissue samples please refer to the laboratory manual.

## **8.4. Human Antihuman Antibodies**

The formation of antibodies to patritumab will be characterized by a screening test for HAHA and, if positive, a confirmatory test to determine antibody titers. If antibody titers indicate HAHA to patritumab are present, then the sample will be assayed to determine whether antibodies are neutralizing.

Blood samples will be collected within 3 days prior to Day 1 of Cycle 1 (baseline), Cycle 2 (preinfusion), Cycle 3 (preinfusion), and at End of Study Treatment visit. For subjects with positive HAHA at the End of Study Treatment visit, additional serum HAHA and PK samples should be collected every 3 months up to 1 year from the last dose of study

drug or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first. Detection of HAHA formation in serum samples will be performed using validated assays.

For instructions on management of HAHA samples please refer to the laboratory manual.

## **8.5. Pharmacogenomics**

Blood samples will be collected for pharmacogenetic sample banking from subjects who have provided a separate informed consent for this part of the study as an exploratory objective (Section 2.1.3). Participation in this part of the study is optional for all subjects. For those subjects who choose to participate, samples will be banked for possible future pharmacogenetic and germ-line DNA analysis. These samples may be analyzed only for genes suspected to contribute to the safety and efficacy of the study medications.

Samples will be retained until the DNA has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample (in accordance with laboratory procedures). During the period of storage, the DNA sample will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time.

For instructions on management of pharmacogenomics, please refer to the laboratory manual.

## **9. SAFETY ASSESSMENTS**

### **9.1. Adverse Events**

All clinical AEs occurring after the subject signs the Informed Consent Form for general study participation and up to 40 days after the last dose of any study drug administered, whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event CRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history.

All AEs, SAEs, and events of special interest are to be reported according to the procedures in Section 9.5.

Any laboratory findings should be appraised by the investigator as to clinical significance. An isolated abnormal laboratory result (ie, not related to a reported diagnosis) should be reported as an AE if it is symptomatic, leads to study drug reduction or discontinuation, requires corrective treatment, or is defined as an AE of Special Interest in Section 9.3.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Always report the diagnosis as an AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.4 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently, should not be reported as an AE/SAE. However, when a subject dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE on the Serious Adverse Event Report (SAVER) form (see Section 9.5) and recorded on the patient outcome eCRF. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

## **9.2. Safety Endpoints**

Not applicable

## **9.3. Events of Special Interest**

### **9.3.1. Combined Elevations of Aminotransferases and Bilirubin**

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the criteria of a potential Hy's Law case (ALT or AST  $\geq 3 \times$  ULN with simultaneous total bilirubin level  $> 2 \times$  ULN) should always be reported to the Sponsor using a SAVER form with the investigator's assessment of seriousness, causality, and a detailed narrative.<sup>16</sup> In addition, an eCRF for liver toxicity should be completed (See Section 9.5).

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will be followed until the abnormality resolves or is considered stable.

### **9.3.2. Interstitial Lung Disease**

In a subject who develops an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, study treatment should be interrupted pending diagnostic evaluation. If interstitial lung disease (ILD) is diagnosed by the Investigator, the subject should be treated immediately and permanently discontinued from study treatment. Information relevant to safety reporting of ILD will be captured on the eCRF.

## **9.4. Definitions**

### **9.4.1. Adverse Event**

An AE is any untoward medical occurrence in a patient, or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.<sup>17</sup>

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

### **9.4.2. Serious Adverse Event**

Any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect, or
- Is an important medical event

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.<sup>17</sup>

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias, or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE
- Pre-planned (prior to signing the Informed Consent Form) procedures or treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs

#### **9.4.3. AE Severity**

The following definitions should be used to assess intensity of AEs according to the latest NCI CTCAE:

- Grade 1 Mild: Awareness of sign or symptom, but easily tolerated, ie, does not interfere with subject’s usual function
- Grade 2 Moderate: Discomfort enough to cause interference with usual activity
- Grade 3 Severe: Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject’s usual functions
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

The NCI CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI CTCAE guidelines should be followed closely.

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event, while the event itself, however, may be of relatively minor medical significance (such as



severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event. For example, the NCI CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated, or disabling) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

#### **9.4.4. Causality Assessment**

The investigator should assess causal relationship between an AE and each of the study drugs on the basis of his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications)
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications)

#### **9.4.5. Action Taken Regarding the Study Product**

- 1 = Dose Not Changed: No change in study drug dosage was made
- 2 = Drug Withdrawn: The study product was permanently stopped
- 3 = Dose Reduced: The dosage of study product was reduced
- 4 = Drug Interrupted: The study product was temporarily stopped

#### **9.4.6. Adverse Event Outcome**

- 1 = Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable
  - Include sequelae/residual effects

- 3 = Not Recovered/Not Resolved
  - The AE itself is still present and observable
- 4 = Fatal
- 5 = Unknown

#### **9.4.7. Other Action Taken for Event**

- 1 = None
  - No treatment was required
- 2 = Medication required
  - Prescription and/or over-the-counter medication was required to treat the AE
- 3 = Other

### **9.5. Safety Reporting – Procedure for Investigators**

All AEs, SAEs, and events of special interest will be reported in the eCRF. In addition, the Investigator should report the following types of events on a SAVER form within 24 hours of becoming aware of them:

- SAEs (see Section 9.4.2)
- Hepatic events, both serious and nonserious, presenting with combination abnormalities meeting criteria for a potential “Hy’s law” case (ie, ALT or AST  $\geq 3 \times$  ULN, with simultaneous total bilirubin  $> 2 \times$  ULN; see Section 9.3.1)

All events (serious and nonserious) must be reported with the Investigator’s assessment of the event’s seriousness, severity, and causal relationship to study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and should include the results if available. Source documents will be retained in site’s files and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

Please call the local SAE Hotline number (Section 15.2.1.5) or your study monitor for any questions on SAE reporting.

### **9.5.1. Notifying Regulatory Authorities, Investigators, and IRBs/IECs**

Daiichi Sankyo and/or CRO will inform Investigators, IRBs/IECs, and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions occurring in other study centers or other Daiichi Sankyo studies of the investigational product, as appropriate per local reporting requirements.

## **9.6. Exposure In Utero During Clinical Studies**

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 40 days of discontinuing the investigational product. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the Exposure In Utero Reporting form. Please contact your study monitor to receive the Exposure In Utero Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

## **9.7. Clinical Laboratory Evaluations**

Safety laboratory assessments will include hematology, serum chemistry, coagulation, and urinalysis.

- Coagulation (only at Screening): prothrombin time, international normalized ratio, and partial thromboplastin time
- Hematology: CBC including hemoglobin, hematocrit, white blood cell count with 5 part differential (including ANC), red blood cell, and platelet count
- Serum chemistry: bicarbonate, calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, uric acid, total protein, urea, AST, ALT, lactic dehydrogenase, alkaline phosphatase, total and direct bilirubin, sodium, potassium, and chloride
- Routine urinalysis: dipstick and microscopy (if indicated), including protein, specific gravity, glucose, and blood
- Serum or urine  $\beta$ -HCG pregnancy test

At Screening, either GFR or the estimated serum creatinine clearance (mL/min) as an estimate of GFR will be calculated. The estimated serum creatinine clearance rate (CrCl; mL/min) will be calculated using the modified Cockcroft-Gault equation ([Appendix 17.1](#)). The estimated GFR will also be calculated before each cisplatin or carboplatin administration. This will be performed only until completion of chemotherapy.

All laboratory values must be assessed by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the investigator or NCI

CTCAE Grade  $\geq 3$  should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, a SAVER form should be submitted and other relevant procedures must be followed (see Section 9.4.2). Abnormal laboratory values (NCI CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

## **9.8. Vital Signs**

Vital sign measurements include blood pressure, heart rate, temperature, height, and weight.

## **9.9. Electrocardiograms**

A 12-lead ECG will be performed within 14 days prior to Screening, at the End-of-Study Treatment visit, and during the study at the discretion of the Investigator.

## **9.10. Physical Findings**

Physical examinations will evaluate the following body systems/organs: respiratory, cardiovascular, gastrointestinal, musculoskeletal, genitourinary/reproductive (optional), psychiatric (optional), hematological, neurological, immunological, head, eyes, ears, nose and throat, and other. Abnormal physical examination findings that are new or changed will be reported as AEs; otherwise, physical examination observations will not be recorded.

## **9.11. Other Safety Assessments**

### **9.11.1. Echocardiograms or MUGA (LVEF Assessment)**

To monitor for possible effects of treatment on cardiac function, LVEF will be assessed at Screening, Cycle 3, and then every third subsequent cycle, the End of Treatment Visit, and as otherwise clinically indicated using either echocardiography or MUGA scanning (if MUGA is considered local standard of care). The same test must be used for a subject throughout the study. Clinically significant changes from baseline in LVEF will be reported as AEs.

### **9.11.2. Human Antihuman Antibodies**

The presence of anti patritumab neutralizing antibody in serum will be assessed. Blood samples will be taken on Day 1 of Cycle 1 (preinfusion), Cycle 2 (preinfusion), Cycle 3 (preinfusion), and at End-of-Study Treatment visit. A PK sample will be collected at the same time of HAHA collection for interpretation of HAHA results, which will be provided to the study sites. For subjects with positive anti patritumab neutralizing antibody on the serum sample drawn at the end of study treatment visit, additional serum samples should be obtained for antibodies, until the antibody level returns to baseline (or becomes negative) or up to 1 year from the last dose of study drug or if the subject starts another therapy for cancer, whichever occurs first.

## 10. OTHER ASSESSMENTS

### 10.1. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be determined at Screening, and then at each scheduled visit throughout the study. See Table 10.1 below.

**Table 10.1: Eastern Cooperative Oncology Group Performance Status Scale Grade Description<sup>18</sup>**

0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	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% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-55.

### 10.2. Patient-Reported Outcomes

Patient-reported outcomes will be used to evaluate study treatment in subjects treated with patritumab + cetuximab + platinum-based therapy compared to placebo + cetuximab + platinum-based therapy (see [Appendix 17.2](#)).

#### 10.2.1. Functional Assessment of Cancer Therapy—Head and Neck (FACT-H&N) Instrument

The FACT-H&N is a multidimensional, self-report quality of life instrument specifically designed for use with head and neck cancer patients.<sup>19,20,21</sup> It consists of 28 core items, the FACT-G, which assess patient function in four domains: Physical, Social/Family, Emotional, Functional well-being, and relationship with doctor which is further supplemented by 12 head and neck-specific items to assess head and neck related symptoms, and form the FACT-Head and Neck Subscale (HNS). Each item is rated on a 0 to 4 Likert type scale, and then combined to produce subscale scores for each domain, as well as a global QoL score. Higher scores represent better quality of life.

Ten items of the FACT-H&N also form a symptom related index, FHNSI-10, which can be analyzed separately.<sup>22</sup>

### **10.2.2. EuroQoL-5 Dimensions-5 Levels Instrument**

The EQ-5D-5L is a preference based measure of health status that is now widely used in clinical trials, observational studies, and other health surveys.<sup>23,24</sup>

The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EuroQoL Visual Analogue scale (EQ VAS). The descriptive system comprises the following 5 domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each domain has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box with the most appropriate statement in each of the 5 domains. This decision results in a 1-digit number expressing the level selected for that domain. The digits for 5 domains can be combined in a 5-digit number or profile describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. Patient preferences or utilities can be assigned to the health profiles from country-specific patient value sets for the calculation of quality adjusted life years which are applied in economic evaluation (cost-utility analysis).

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. This information is used as a quantitative measure of health as judged by the individual respondents. The instructions for the EQ VAS asks respondents to 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below.'

## **11. STATISTICAL METHODS**

### **11.1. Analysis Sets**

In addition to the analysis sets described below, the PK analysis set, and the PRO analysis set will be defined in the SAP.

#### **11.1.1. Full Analysis Set**

The full analysis set (FAS) will be based on the intention-to-treat principle and will comprise all subjects randomized into the study. This set will contain HRG high stratum and HRG low stratum. Subjects will be analyzed as randomized.

#### **11.1.2. Per-Protocol Analysis Set**

The per-protocol analysis set will include all subjects in the FAS who have completed at least 1 cycle of treatment, and who were sufficiently compliant with the protocol and without major protocol violation. Full criteria for defining sufficient compliance will be finalized and documented prior to database unblinding.

#### **11.1.3. Safety Analysis Set**

The safety analysis set includes all subjects who received any amount of study medication. Subjects will be analyzed according to actual treatment received. All safety analyses will be performed on the safety analysis set. Key safety data will also be summarized for HRG-high stratum. Key safety endpoints include frequency and severity of treatment-emergent adverse events (TEAEs) and incidence of HAHA development in relation to the TEAEs.

### **11.2. General Statistical Considerations**

This is a multicenter randomized Phase 2 study designed to evaluate the safety and efficacy of patritumab in combination with cetuximab and platinum-based therapy in recurrent/metastatic first-line SCCHN. The primary analyses for this study will occur when at least 53 PFS events have been observed in the HRG high stratum.

At the point of primary analysis for PFS, the treatment assignment for all randomized subjects will be unblinded to designated study personnel for the analysis after data are reconciled and cleaned and a snapshot of the clean database is created. To minimize potential bias, subjects and Investigators will not be informed about individual treatment assignment until study closure.

Final analyses will occur after study closure with mature OS data for the main study phase. At the time of study closure, subjects who are demonstrating clinical benefit (SD or better) from study treatment may be offered an opportunity to continue study treatment on the extension phase.

Assessments of change from baseline to post baseline or the ratio of post baseline to baseline will include only those subjects with both baseline and post baseline

measurements. The last nonmissing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis. Descriptive summary statistics (n, mean, median, standard deviation, and range) will be calculated for continuous variables, and for categorical variables, the number and percentage in each category will be displayed by treatment group.

A detailed SAP describing the methodology will be prepared and finalized prior to primary analyses being performed and prior to database unblinding. Statistical methods described here may be modified based on advances in research. Any deviations and reasons for changes from the planned statistical analyses in the protocol will be fully described in the SAP and in the clinical study report.

### **11.3. Study Population Data**

Disposition and reasons for ending the treatment and discontinuing from the study and subsequent anticancer therapy will be listed and summarized in the FAS.

Demographic and baseline characteristics such as age, race, and baseline ECOG performance status, histology subtype, HRG value, and cancer type will be summarized by treatment group and overall for the FAS as well as the HRG-high stratum of the FAS, per-protocol analysis set, and safety analysis set. If two sets of subjects are identical to each other, analysis will only be performed once.

Study drug exposure, treatment duration, and compliance with study therapy will be summarized using descriptive statistics by treatment group for the safety analysis set.

### **11.4. Efficacy Analyses**

Efficacy analyses will be performed on the FAS and per-protocol analysis set. Subjects will be analyzed according to the treatment assigned at randomization.

#### **11.4.1. Primary Efficacy Analyses**

The primary efficacy endpoint for this study is PFS. Progression free survival is defined as the time from the date of randomization to the earlier of the dates of the first objective documentation of radiographic disease progression (as per RECIST Version 1.1- see [Appendix 17.3](#)) or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the data cutoff date for PFS analysis will be censored at the date of their last evaluable tumor assessment. Detailed censoring rules for PFS analysis will be specified in the SAP.

The primary analysis is PFS comparison between the patritumab arm and the control arm in HRG-high stratum of the FAS. The testing hypotheses to compare PFS between the patritumab arm versus the control arm will be performed in two steps.<sup>25</sup> In step 1, the null hypothesis that PFS is the same for both arms in the HRG high stratum of FAS is tested at the one-sided 0.10 significance level. If this test in step 1 does not reject the null hypothesis, then in step 2A, the null hypothesis that PFS is the same for both arms in the FAS will be tested at the one-sided 0.05 significance level. If the test in step 1 is rejected, then in step 2B, the two-sided 80% confidence interval (CI) for hazard ratio (HR) of PFS



in the HRG low stratum of the FAS will be estimated. The results from both steps (PFS comparison in HRG-high stratum, and PFS comparison in FAS or PFS estimate in HRG-low stratum) will be used to guide the decision on future Phase 3 designs.

The comparison of PFS between the patritumab arm and the control arm will be performed using a log-rank test stratified by the stratification factors in both the FAS and the HRG high stratum of FAS. The stratification factors include HPV (positive vs other) and HRG (high vs. low, only for the FAS) at randomization. Kaplan-Meier methods will be used to calculate median PFS and CIs and generate Kaplan-Meier curves for PFS. Estimates of HR between 2 arms along with their two-sided 80% and 95% CIs will be calculated using stratified Cox's proportional hazards regression model. The model will include the treatment group as a covariate and the stratification factors used at randomization as strata.

The above analysis for PFS will be performed in the per-protocol analysis set.

#### **11.4.2. Secondary Efficacy Analyses**

Secondary efficacy variables include OS and ORR (CR and PR). Overall survival is defined from the date of randomization to death due to any cause and will be analyzed in the same manner as for PFS. Subjects who are alive at the time of data cut off for OS analysis will be censored at the last contact date at which the subject is known to be alive. Objective response rate is defined as the proportion of subjects with the best overall response of CR or PR. A confirmation of CR/PR is not required for this study as per RECIST Version 1.1. The differences in the ORR and OS between the control arm and patritumab arm will be presented along with two-sided 80% and 95% CIs based on the Wilson's score method with continuity correction. These analyses will be done using the FAS for HRG high and low strata.

#### **11.4.3. Exploratory Efficacy Analyses**

Exploratory efficacy endpoints include duration of response, time to response, time to disease progression, and duration of SD. Exploratory efficacy endpoints and details of corresponding analyses will be defined in the SAP.

### **11.5. Pharmacokinetic/Pharmacodynamic Analyses**

#### **11.5.1. Pharmacokinetic Analyses**

Serum concentrations for patritumab, cetuximab, and cisplatin/carboplatin will be displayed in tables of individual values and aggregated by treatment group in summary tables with descriptive statistics. To explore possible drug-drug interactions between patritumab plus cetuximab or cisplatin/carboplatin, the PK of serum cetuximab and platinum concentrations will be compared with and without patritumab. For all subjects, sparse samples for serum patritumab concentrations will be assessed using population PK methods. The relationship between exposure and response will be explored using population PK modeling.

### **11.5.2. Pharmacodynamic Analyses**

Not Applicable

### **11.5.3. Biomarker and Exploratory Analyses**

The study has baseline HRG and HPV status biomarker assessments to determine the stratification factors of HRG and HPV. Baseline HRG cutoff will be used for all specified efficacy analyses. As exploratory analyses, the HRG cutoff will be refined using graphic technique, data distribution, maximum likelihood methods, and clinical benefit of HRG-high group. Selected efficacy analyses for the HRG high stratum will be performed using the refined HRG cutoff as additional exploratory analyses. Further biomarker evaluations will be summarized descriptively.

## **11.6. Safety Analyses**

Safety analyses will be performed using the safety analysis set, and subjects will be analyzed according to their actual treatment received. Key safety analyses will also be performed for HRG high stratum of the safety analysis set. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics by treatment group. Listings of safety data will be presented using the safety analysis set.

### **11.6.1. Adverse Event Analyses**

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment, or reemerges during treatment, having been present at baseline but stopped prior to treatment, or worsens in severity since treatment relative to the pretreatment state, when the AE is continuous.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized for the number and percentage of subjects reporting treatment emergent AEs. AEs/toxicities and laboratory test results (hematology and blood chemistry) will be graded according to the NCI CTCAE, Version 4.03. The number and percentage of subjects reporting TEAEs will be tabulated by the worst CTCAE grade, system organ class, and preferred term, with a breakdown by treatment group. Similarly, the number and percentage of subjects reporting treatment emergent SAEs will be tabulated, as well as TEAEs and treatment emergent SAEs considered related to patritumab, cetuximab, and cisplatin/carboplatin.

A by-subject AE (including treatment emergent) data listing including, but not limited to, verbatim term, preferred term, system organ class, CTCAE grade, and relationship to study drug will be provided.

SAEs reported from tumor biopsies collected during Screening will be recorded, but not included in the primary analysis.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from patritumab, cetuximab, and cisplatin/carboplatin of a subject, will be listed.

### **11.6.2. Clinical Laboratory Evaluation Analyses**

Clinical laboratory data and their changes from baseline (only for continuous laboratory parameters) will be summarized by treatment group and visit (including the maximum and minimum post-treatment values and the values at the End of Treatment visit). Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized by treatment. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during the time period of interest. Shift tables for clinical laboratory data will also be presented showing change in CTCAE severity grade from baseline to each visit (and to the minimum, maximum, and last post-baseline values) for each treatment.

Laboratory test results (hematology and blood chemistry) will be graded according to the NCI CTCAE, Version 4.03. A shift table, presenting the two-way frequency tabulation for baseline and the worst post-treatment value according to the CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

### **11.6.3. Vital Sign Analyses**

Descriptive statistics will be provided for vital signs data and their changes from baseline will be summarized by treatment group and visit (including the maximum and minimum post-treatment values and the values at the End of Treatment visit).

### **11.6.4. Electrocardiogram Analyses**

The ECG parameters (PR, RR, QRS, heart rate-corrected QT interval by Bazett's or by Fridericia's formula) [QT, QTcB and QTcF]) will be summarized using descriptive statistics for actual values and for changes from baseline by treatment group by scheduled time of evaluation including end of treatment visit as well as for the maximum post treatment values.

The incidence of outliers in maximum absolute QTcF and QTcB intervals (> 450 > 480 and > 500 msec) and the maximum absolute uncorrected QT intervals (> 500 msec) over end-of-treatment evaluation, as well as in QTcF and QTcB maximum changes from baseline (> 30 and > 60 msec) over end-of-treatment evaluation will be summarized by treatment. A listing of ECG data will be provided.

### **11.6.5. Physical Finding Analyses**

A listing of physical examination findings will be provided.

### **11.6.6. Other Safety Analyses**

Key safety endpoints include frequency and severity of treatment-emergent AEs and incidence of human antihuman antibody HAHA development in relation to the TEAEs. HAHA findings from all subjects will be listed to identify subjects with positive HAHA findings and when the earliest positive HAHA findings were observed for these subjects.

Echocardiogram or MUGA data will be listed.

## **11.7. Other Analyses**

### **11.7.1. Patient Reported Outcomes**

Descriptive statistics will be computed for the specified PRO measures, the FACT-H&N (total score, subscales including the HNS, and individual symptom items) and FHNSI-10, by scheduled time of evaluation and by treatment as well as the change from baseline. Best response (improvement, stability, or deterioration) on each of the above PROs based upon published classification of responses on the same PROs will be compared between the patritumab and control arms. In addition, this study will also present the entire cumulative distribution of change from baseline in specified PROs as a continuous plot of the change from baseline on the X-axis and the cumulative percent of patients experiencing that change on the Y axis for the patritumab and control arms, as recommended in the recent FDA final guidance on PROs. Based upon the entire cumulative distributions, various categorical distributions of best responses representing alternative magnitudes of change from baseline as criteria for classification of responses will also be presented across treatment groups, as appropriate.

Change from baseline of the PRO measures will also be evaluated using mixed longitudinal modeling with treatment, time, and treatment-by-time interactions as fixed effects, subject as random effect, and baseline PRO score as covariate. Differences between the control arm and patritumab arm will be presented along with 95% CIs. These analyses on PRO measures will be considered as exploratory and further details of all analyses, including handling of missing data, will be described in the SAP.

Descriptive statistics for the actual value and change from baseline will be computed for the EQ-5D-5L health profile utilities and EQ-5D VAS by scheduled time of evaluation (including end of treatment visit) for all subjects and by treatment group. Results of the EQ VAS will be presented as a measure of overall self-rated health status. Further details of analyses will be provided in the SAP.

### **11.7.2. Eastern Cooperative Oncology Group**

ECOG performance status at baseline will be summarized. A shift table, presenting the two way frequency tabulation for baseline and end of study treatment visit, will be provided for ECOG performance status.

## **11.8. Interim Analyses**

No interim analysis is planned

## **11.9. Data Monitoring Committee**

An independent Data Monitoring Committee (DMC) will be established for this study and will review the ongoing safety of the study participants and monitor the overall conduct of the clinical trial. The DMC will review accumulating safety data when at least 25% of the target number of subjects is enrolled after the first subject is randomized. Subsequent DMC meetings will convene as needed until database lock. Based on its

ongoing review of the unblinded safety data, the DMC will outline any serious safety concerns and make recommendations to continue, modify, suspend, or terminate the study.

Details on the membership, responsibilities and working procedures of the Independent DMC will be described in the DMC Charter, provided as a separate document in the study file. The same independent Data Analysis Group statistician responsible for providing the safety data will also provide efficacy data (for proper assessment of the risk/benefits of continuing treatment and study) to the DMC for review.

### **11.10. Sample Size Determination**

The primary efficacy endpoint is PFS. The sample size for this study is based on the number of required PFS events in the HRG-high stratum. For PFS, a clinically meaningful improvement is defined as 79% increase from median PFS of 4.2 months in the control arm<sup>26</sup> to median PFS of 7.5 months in the patritumab arm (that is a HR of 0.56). A total of 70 HRG-high subjects will be randomized to observe 53 PFS events in the HRG high stratum assuming a one-sided alpha of 0.10, 80% power, and a 1:1 randomization ratio between 2 arms, a 12-month enrollment and 10-month follow-up, and 10% dropouts.

Under 2:1 (HRG high vs. low) stratification, a total of approximately 105 subjects (70 HRG high subjects and 35 HRG low subjects) will be randomized in both strata to observe at least 75 PFS events. The sample size from both strata combined will provide approximately 81% power to detect a HR=0.56 in PFS assuming one-sided alpha of 0.05 and other same assumptions above.

The sample size computation is performed using the test based on Survival Superiority Trials: Two Sample Test – Logrank Test: Given Accrual Duration and Study Duration in the EAST software (version 5.3, Cytel Inc.).

## **12. DATA INTEGRITY AND QUALITY ASSURANCE**

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

### **12.1. Monitoring and Inspections**

The Sponsor/CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals (see study monitoring plan for frequency of monitoring visits) throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from Sponsor. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories, etc) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, SOPs, ICH GCP, and applicable regulatory requirements.

### **12.2. Data Collection**

All relevant observations and data related to the study, as per the study protocol, will be recorded on eCRF pages. A representative of Daiichi Sankyo or their designee will provide instruction for completing the eCRF. Adequate and accurate case records should be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examinations, clinical assessments, a record of clinical safety laboratory sample collection, drug administration, AEs, and final evaluation.

The eCRFs must be completed for each subject who signs the ICF and undergoes screening procedures. For subjects who are screened but not randomized, minimal data will be recorded on the eCRF, including demography, subject status, and AEs. All study related data for these subjects will be maintained in the medical records at the site.

### **12.3. Data Management**

Each subject will be identified in the database by a unique subject identifier as defined by the sponsor.

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to the Sponsor or designee. Data will be vetted both electronically and manually for eCRFs the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the Electronic Data Capture application. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies.

Data received from external sources such as central labs will be reconciled to the clinical database. All data generated from external sources (i.e., central laboratory, pharmacokinetic processing, pharmacodynamics processing, and genotyping laboratory, etc.) will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

Serious AEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA.

All concomitant medications and prior cancer therapies will be coded using the World Health Organization Drug Reference List Dictionary.

### **12.4. Study Documentation and Storage**

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include (but are not limited to):

- Subject files containing completed CRFs, informed consents, and supporting copies of source documentation (if kept)
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IEC/IRB and the Sponsor

- Records related to the Investigational Product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

All essential documentation will be retained by the Investigator until at least 2 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 at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

## **12.5. Record Keeping**

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB/IEC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.



### **13. FINANCING AND INSURANCE**

#### **13.1. Finances**

Prior to starting the study, the Principal Investigator and/or Institution will sign a clinical study agreement with Sponsor or a CRO. This agreement will include the financial information agreed upon by the parties.

#### **13.2. Reimbursement, Indemnity, and Insurance**

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

#### **14. PUBLICATION POLICY**

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that Daiichi Sankyo has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of Daiichi Sankyo Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

## **15. STUDY ADMINISTRATIVE INFORMATION**

### **15.1. Protocol Amendments**

Any amendments to the study protocol as the study progresses will be communicated to the investigator by the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC within five working days. The sponsor will assure the timely submission of amendments to regulatory authorities.

### **15.2. Address List**

A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information will be kept on file and updated in the Study Operations Manual.

#### **15.2.1. Sponsor**

##### **United States**

Daiichi Sankyo, Inc.  
399 Thornall Street  
Edison, NJ 08837, United States

##### **15.2.1.1. Sponsor Medical Monitor**

[REDACTED] MD  
[REDACTED]

Daiichi Sankyo, Inc.  
399 Thornall Street  
Edison, NJ 08837, United States

Phone: [REDACTED]

Mobile: [REDACTED]

Fax: + [REDACTED]

Email: [REDACTED]

##### **15.2.1.2. Sponsor Clinical Operations Delivery Lead**

[REDACTED] MBA  
[REDACTED]

Daiichi Sankyo, Inc.

399 Thornall Street

Edison NJ 08837, United States

Tel: [REDACTED]

Fax: [REDACTED]

Email: [REDACTED]

**15.2.1.3. CRO Medical Monitor**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Munich, Germany

Tel [REDACTED]

Mobile: [REDACTED] 566

Fax: [REDACTED]

**15.2.1.4. CRO Project Manager**

[REDACTED] MD, CPM, PMP

[REDACTED]

[REDACTED]

[REDACTED] Maidenhead, SL6 3QH, UK

Phone: [REDACTED]

Mobile: [REDACTED]

[REDACTED]

**15.2.1.5. Drug Safety**

[REDACTED]

Maidenhead, UK

Phone: [REDACTED]

Fax - [REDACTED]

**15.2.2. Sponsor**

**15.2.2.1. Data Management**

Please refer to the Study Manual.

**15.2.2.2. Biological Specimens**

Please refer to the Laboratory Manual.

**15.2.2.3. Interactive Web/Voice Response System (IxRS)**

Please refer to the Study Manual.

**15.2.2.4. Pharmacogenomics Laboratory**

Please refer to the Laboratory Manual.

**15.2.2.5. Bioanalytical Laboratory (PK and HAHA)**

Please refer to the Laboratory Manual.

## 16. REFERENCES

- 
- <sup>1</sup> Investigator's Brochure—Anti-HER3 Antibody, Patritumab (U3-1287), Version 8.0. Daiichi Sankyo, 02 October 2015.
  - <sup>2</sup> Anti-proliferative effect of patritumab (U3-1287) in combination with cetuximab. Research Study Report No. RR20140120-3. U3 Pharma GmbH. June 27, 2014.
  - <sup>3</sup> Shames DS, Carbon J, Walter K, et al. High hergulin expression is associated with activated HER3 and may define an actionable biomarker in patients with squamous cell carcinomas of the head and neck. PLOS ONE. 2013;8:e56765.
  - <sup>4</sup> Li C, Brand TM, Iida M, et al. Human epidermal growth factor receptor 3 (HER 3) blockade with U3-1287/AM888 enhances the efficacy of radiation therapy in lung and head and neck carcinoma. Discovery Medicine. 2013;16:79-92
  - <sup>5</sup> Schneider M, Wenzl C, Kallus H, et al. Efficacy of patritumab (U3-1287), a fully human anti-human epidermal growth factor receptor 3 (HER3) monoclonal antibody, in head and neck cancer models. Poster presented at: Annual Meeting of European Society of Medical Oncology. September 26-30, 2014. Madrid, Spain.
  - <sup>6</sup> Deng Z, Hasegawa M, Aoki K, et al. A comprehensive evaluation of human papillomavirus positive status and p16 overexpression as a prognostic biomarker in head and neck squamous cell carcinoma. Intl J Oncol. 2014;45:67-76.
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  - <sup>8</sup> Gregoire V, Lefebvre J-L, Licitra L, Felip E, for the EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 (Suppl 5): v184-v186.
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- <sup>10</sup> Bourhis J, Rivera F, Mesia R, et al. Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2006;24:2866-72.
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## 17. APPENDICES

### 17.1. Modified Cockcroft-Gault Equation

The estimated serum creatinine clearance rate (CrCl; mL/min) will be calculated using the modified Cockcroft-Gault equation<sup>a</sup> based on actual weight, where weight is lean body mass in kilograms (1 kilogram = 2.2 pounds):

#### Conventional – serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

#### International System of Units (SI) – serum creatinine in μmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

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<sup>a</sup> Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

## **17.2. Patient-Reported Outcomes**

### **17.2.1. Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N)**

Note that the following questionnaire is provided as an example only of the FACT-H&N. Do not give this questionnaire to subjects for completion. Actual questionnaires to be given to subjects for completion will be provided under separate cover.

**FACT-H&N (Version 4)**

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
QP1	I have a lack of energy .....	0	1	2	3	4
QP2	I have nausea .....	0	1	2	3	4
QP3	Because of my physical condition, I have trouble meeting the needs of my family .....	0	1	2	3	4
QP4	I have pain .....	0	1	2	3	4
QP5	I am bothered by side effects of treatment .....	0	1	2	3	4
QP6	I feel ill .....	0	1	2	3	4
QP7	I am forced to spend time in bed .....	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
QS1	I feel close to my friends .....	0	1	2	3	4
QS2	I get emotional support from my family .....	0	1	2	3	4
QS3	I get support from my friends .....	0	1	2	3	4
QS4	My family has accepted my illness .....	0	1	2	3	4
QS5	I am satisfied with family communication about my illness .....	0	1	2	3	4
QS6	I feel close to my partner (or the person who is my main support) .....	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
QS7	I am satisfied with my sex life .....	0	1	2	3	4

**FACT-H&N (Version 4)**

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
OE1	I feel sad .....	0	1	2	3	4
OE2	I am satisfied with how I am coping with my illness .....	0	1	2	3	4
OE3	I am losing hope in the fight against my illness .....	0	1	2	3	4
OE4	I feel nervous .....	0	1	2	3	4
OE5	I worry about dying .....	0	1	2	3	4
OE6	I worry that my condition will get worse .....	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
OF1	I am able to work (include work at home) .....	0	1	2	3	4
OF2	My work (include work at home) is fulfilling .....	0	1	2	3	4
OF3	I am able to enjoy life .....	0	1	2	3	4
OF4	I have accepted my illness .....	0	1	2	3	4
OF5	I am sleeping well .....	0	1	2	3	4
OF6	I am enjoying the things I usually do for fun .....	0	1	2	3	4
OF7	I am content with the quality of my life right now .....	0	1	2	3	4

**FACT-H&N (Version 4)**

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like .....	0	1	2	3	4
H&N2	My mouth is dry .....	0	1	2	3	4
H&N3	I have trouble breathing .....	0	1	2	3	4
H&N4	My voice has its usual quality and strength .....	0	1	2	3	4
H&N5	I am able to eat as much food as I want .....	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look.....	0	1	2	3	4
H&N7	I can swallow naturally and easily .....	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products .....	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.).....	0	1	2	3	4
H&N 10	I am able to communicate with others .....	0	1	2	3	4
H&N 11	I can eat solid foods.....	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck .....	0	1	2	3	4

**17.2.2. EuroQoL-5D-5L Health Questionnaire**

Note that the following questionnaire is provided as an example only of the EQ-5D-5L Health Questionnaire. Do not give this questionnaire to subjects for completion. Actual questionnaires to be given to subjects for completion will be provided under separate cover.



**Health Questionnaire**

**English version for the UK**

SAMPLE

*UK (English) v.2 © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group*

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**SELF-CARE**

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN / DISCOMFORT**

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**ANXIETY / DEPRESSION**

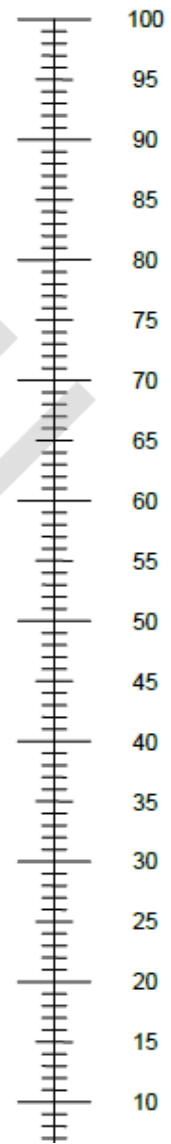
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.  
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health  
you can imagine



### **17.3. Assessment of Tumor Response**

Assessment of tumor responses will be performed according to revised RECIST guidelines, Version 1.1. Some of these definitions and criteria are highlighted below.

#### **17.3.1. Measurement of Tumor at Baseline**

##### **17.3.1.1. Definitions**

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

##### **17.3.1.1.1. Measurements**

Tumor lesions: Must 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 (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

##### **17.3.1.1.2. Non-measurable**

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

##### **17.3.1.1.3. Special Considerations Regarding Lesion Measurability**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

##### **Bone Lesions**

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such<sup>b</sup> as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

### **Cystic Lesions**

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

### **Lesions with prior local treatment:**

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion since the therapy

## **17.3.1.2. Specifications by Methods of Measurements**

### **17.3.1.2.1. Measurement of Lesions**

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

### **17.3.1.2.2. Method of Assessment**

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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<sup>b</sup> 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(2):228-247.

## **17.3.2. Tumor Response Evaluation**

### **17.3.2.1. Assessment of Overall Tumor Burden and Measurable Disease**

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only subjects with measurable disease at baseline should be included in the study.

### **17.3.2.2. Baseline Documentation of ‘Target’ and ‘Non-Target’ Lesions**

When more than one measurable lesion is present at “baseline” all lesions up to a total of two lesions per organ and a maximum of five lesions total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions, respectively will be recorded).

Target lesions should be selected on the 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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance that the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm  $\times$  30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis  $\geq 10$  mm but  $< 15$  mm) should be considered non-target lesions. Nodes that have a short axis  $< 10$  mm are considered non-pathological and should not be recorded or followed.

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

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

#### **17.3.2.3. Response Criteria**

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

#### **17.3.2.4. Evaluation of Target Lesions**

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

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

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

##### **17.3.2.4.1. Special Notes on the Assessment of Target Lesions**

**Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

**Target lesions that become ‘too small to measure’:** While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently

surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

#### **17.3.2.5. Evaluation of Non-Target Lesions**

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

**CR:** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

##### **17.3.2.5.1. Special Notes on Assessment of Progression of Non-target Disease**

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

##### **17.3.2.6. New Lesions**

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion

should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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

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

#### **17.3.2.7. Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. No confirmatory measurement for CR or PR is required in this study.

The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

##### **17.3.2.7.1. Time Point Response**

It is assumed that at each protocol-specified time point, a response assessment occurs. [Table 17.1](#) provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

**Table 17.1: Time Point Response: Subjects With Target (+/-Non-Target) Disease**

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Not Evaluable.

#### 17.3.2.7.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

#### 17.3.2.7.3. Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject are known.

Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline, 6 weeks. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.



#### **17.3.2.7.4. Special Notes on Response Assessment**

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'clinical progression.' Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease. If a radiographic tumor assessment has not been performed within 4 weeks of the time of clinical progression, then another radiographic assessment should be performed without waiting for the next regularly scheduled scan.

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

#### **17.3.2.8. Frequency of Tumor Re-evaluation**

In this study, tumor measurement will be conducted at Screening, and then at every 6 weeks for the first 24 weeks. After 24 weeks, tumor assessments will be performed every 12 weeks, or sooner if clinically indicated. Tumor measurement will be performed during the end of treatment visit unless it was performed within the previous 6 weeks or the previous assessment demonstrated disease progression.

Baseline tumor assessments must be performed within 2 weeks (14 days) prior to the first dose of treatment (Section 6.1.2). Existing radiographic scans can be used for the baseline evaluation if the scans were performed within 4 weeks prior to randomization.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of the chest and abdomen. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and non-target sites are evaluated at each time point of tumor assessment.

## **17.4. Schedule of Events**

**Table 17.2: Schedule of Events for Main Study**

Assessment	Tissue screen	Screen	Randomization	Cycle 1 (Weeks 1-3)							Cycles 2 & 3	Cycle 4 & all Subsequent Cycles	End of Cycle 6 & Every 4 Cycles	Every 6 weeks	End-of-Study Treatment Visit	40 Days After Last Dose <sup>a</sup>		
				Day 1			Day 2	Day 3	Day 8	Day 15							Day 1	Day 1
				Predose	Dosing	EOI												
<b>Visit Window (Days)</b>		-14 unless otherwise indicated												21 days after last dose <sup>a</sup>				
Informed consent for tumor tissue	X																	
Informed consent (s) <sup>b</sup>		X																
Medical history (including smoking history) & demographics		X																
Inclusion / Exclusion		X																
Physical exam		X		X				X	X	X*	X*			X				
Vital signs		X		X		X		X	X	X*	X*			X				
Height & weight <sup>c</sup>		X		X <sup>d</sup>						X* <sup>d</sup>	X* <sup>d</sup>			X <sup>d</sup>				
ECOG		X		X				X	X	X	X			X				
Echo or MUGA <sup>e</sup>		X								X <sup>e</sup>	X <sup>e</sup>			X				
ECG (12-lead) <sup>e</sup>		X												X				
Con Meds		X		X		X		X	X	X*	X*			X				
Adverse Events	X <sup>f</sup>	X		X		X		X	X	X*	X*			X	X <sup>g</sup>			
PRO assessments <sup>h</sup>				X						X	X			X				
CBC differential & platelets <sup>i</sup>		X		X <sup>d</sup>				X <sup>d</sup>	X <sup>d</sup>	X* <sup>d</sup>	X* <sup>d</sup>			X <sup>d</sup>				
Serum chemistries <sup>i</sup>		X		X <sup>d</sup>				X <sup>d</sup>	X <sup>d</sup>	X* <sup>d</sup>	X* <sup>d</sup>			X <sup>d</sup>				
GFR or estimated serum creatinine clearance <sup>j</sup>		X		X						X	X							
Coagulation		X																
Urinalysis		X												X				
IxRS			X															
Intense PK <sup>k</sup>				X <sup>d</sup>		X	X	X	X	X <sup>f</sup>								
Sparse PK (all) <sup>l</sup>				X <sup>d</sup>		X				X				X				
HAHA sample <sup>l</sup>				X <sup>d</sup>						X				X				
Pregnancy test <sup>m</sup>		X												X				

Assessment	Tissue screen	Screen	Randomization	Cycle 1 (Weeks 1-3)						Cycles 2 & 3	Cycle 4 & all Subsequent Cycles	End of Cycle 6 & Every 4 Cycles	Every 6 weeks	End-of-Study Treatment Visit	40 Days After Last Dose <sup>a</sup>			
				Day 1			Day 2	Day 3	Day 8							Day 15	Day 1	Day 1
				Pre-dose	Dosing	EOI												
Patritumab Adm <sup>n</sup>					X						X	X						
Cetuximab Adm <sup>o</sup>					X				X	X	X	X						
Platinum Adm <sup>p</sup>					X						X	X						
PGx sample <sup>q</sup>				X <sup>d</sup>														
Tumor assessments <sup>r</sup>		X											X <sup>s</sup>	X				
Survival follow-up															X <sup>t</sup>			
Additional biomarker blood samples <sup>u</sup>				X <sup>u</sup>							X <sup>u</sup>		X <sup>u</sup>		X <sup>u</sup>			

a Last dose of any study drug administered.

b Informed consent for main study (mandatory) and pharmacogenomics (optional).

c Height measured only at Screening.

d These assessments can be performed within 3 days prior to visit.

e Echocardiograms/MUGA scans will be performed at Screening, Cycle 3, at every third subsequent cycle, and End-of-Study Visit. Additional echocardiograms/MUGA scans and electrocardiograms may be performed at the discretion of the investigator. The same test (echocardiogram or MUGA) must be used for a subject throughout the study.

f Collect SAEs only related to the biopsy procedure.

g At 40 days after the last dose of study drug, a telephone call will be placed to the subject to record adverse events.

h PRO assessments will be administered before any study-related procedures are performed.

i Results must be available prior to dosing.

j At Screening, either GFR or the estimated serum creatinine clearance (mL/min) as an estimate of GFR will be calculated. The estimated serum creatinine clearance rate (CrCl; mL/min) will be calculated using the modified Cockcroft-Gault equation ([Appendix 17.1](#)). The estimated GFR will also be calculated before each cisplatin or carboplatin administration. This will be performed only until completion of chemotherapy.

k Intensive serum PK in a subgroup of 30 subjects samples will be collected. See [Table 8.2](#) for detailed information on sampling times.

l See [Table 8.1](#) for detailed information on sampling times.

m Pregnancy test must be confirmed negative before dosing. Additional pregnancy testing may be done at the discretion of the Investigator and/or if required by local regulations for women of child-bearing potential.

n Patritumab administered initially at 18 mg/kg and thereafter 9 mg/kg every 3 weeks as a continuous intravenous infusion over 60 minutes (±10 minutes). Infusion times can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60-minute infusion.

o Cetuximab infusions administered initially at 400 mg/m<sup>2</sup> IV over 2 hours and 250 mg/m<sup>2</sup> over 1 hour weekly. Cetuximab is administered 60 minutes after patritumab administration. Cetuximab is given on Days 1, 8, and 15.

p Cisplatin infusions administered at 100 mg/m<sup>2</sup> IV over 1 hour and every 3 weeks up to a maximum of 6 cycles. For pre- and post-treatment hydration see [Section 3.1.2.1](#) and according to institutional standards. Creatinine clearance required prior to cisplatin administration. Cisplatin administered 1 hour after cetuximab administration. If carboplatin is selected instead of cisplatin, administer carboplatin at AUC of 5 over 30-60 minutes every 3 weeks for a maximum of 6 cycles. See [Section 3.1.2.1](#) for carboplatin.

q Genetic sampling is optional.

- r Tumor measurements will be assessed per RECIST Version 1.1. Baseline scans to be performed as part of eligibility during Screening. Existing radiographic scans can be used for the baseline evaluation if the scans were performed within 4 weeks prior to randomization.
  - s Tumor assessments are to be performed every 6 weeks to Week 24 (+/- 3 days), then every 12 weeks (+/- 7 days) thereafter.
  - t After discontinuation from study treatment, follow-up information for survival will be obtained per telephone approximately every 3 months for a minimum of 13 months.
  - u Additional biomarker samples:
    - Collect blood sample for cfDNA predose Cycle 1 Day 1, predose Cycle 2 Day 1, End of Cycle 6, predose every 4 Cycles, at progression (end of study treatment), and 40 days after last dose of study drug administered.
    - Collect blood samples for exosome at: predose Cycle 1 Day 1, predose Cycle 2 Day 1, and End of Cycle 6. Refer to the laboratory manual for instructions on collection and management of samples.
- \* Can be collected on Days 8 and 15 in all subsequent cycles at the discretion of the Investigator.
- † Corresponds to Cycle 1, Day 21 (504 hrs)—see [Table 8.2](#).

**Table 17.3: Schedule of Events for Extension Phase**

	Additional cycles		Every 3 months	End of Treatment	40 days after last dose <sup>a</sup>
	Predose	Dosing			
<b>Visit Window (Days)</b>					
Physical Exam	X			X	
Vital Signs	X			X	
Adverse Events	X				X
CBC diff and platelets <sup>b</sup>	X <sup>b</sup>			X <sup>b</sup>	
Serum chemistries <sup>b</sup>	X <sup>b</sup>			X <sup>b</sup>	
HAHA and PK sample <sup>c</sup>			X		
Patritumab Adm <sup>d</sup>		X			
Cetuximab Adm <sup>e</sup>		X			
Additional biomarker blood samples			X	X	X

a Last dose of any study drug administered.

b CBC and chemistries must be performed within 3 days of dosing.

c For subjects with positive HAHA at the End of Study Treatment visit, additional serum HAHA samples should be collected every 3 months up to 1 year from the last dose of study drug or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

d Patritumab administered at 9 mg/kg every 3 weeks as a continuous intravenous infusion over 60 minutes ( $\pm 10$  minutes). Infusion times can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion.

e Cetuximab is infused at 250 mg/m<sup>2</sup> over 1 hour weekly. Cetuximab can be administered directly after patritumab administration.