STATISTICAL ANALYSIS PLAN
(SAP)

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

VERSION 1.0, 29 NOVEMBER 2016

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STATISTICAL ANALYSIS PLAN SYNOPSIS

Protocol Number:	U31287-A-U203
Protocol Version and Date:	VERSION 4.0 13 JUN 2016
Name of Investigational Product:	Patritumab (U3-1287)
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
Study Phase:	Phase 2
Study Objectives:	**Primary Objective** • 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. **Secondary Objectives** • Evaluate overall survival (OS) • Evaluate overall response rate (ORR) • Refine the cutoff between heregulin high and low expression based on clinical data from this study • Assess the population PK of patritumab in subjects with Squamous cell carcinoma of the head and neck (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 sub group (n = 30) of subjects • Evaluate the incidence of human antihuman antibody (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

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. There will be two treatment arms 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 Approximately 105 subje ts will be randomized to the patritumab and the control arms in a 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.
Number of Planned Study Centers:	Approximately 35 sites in Europe.

Planned Sample Size:	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 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 r ndomized 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.).
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.

Summary of Eligibility Criteria:	Key Inclusion Criteria 1. Adult subjects ≥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 ≥ 1.5 x 10^9/L – Platelet count ≥ 100 x 10^9/L – Hemoglobin ≥ 10 g/dL 8. Renal function, as follows: – Estimated serum creatinine clearance (mL/min) or glomerular filtration rate (GFR) ≥ 60 mL/min for cisplatin and ≥ 30 mL/min for carboplatin

9. Hepatic function, as follows:

- Aspartate aminotransferase ≤ 2.5 x upper limit of normal (ULN) (if liver metastases are present, < 5 x ULN)
- Alanine aminotransferase ≤ 2.5 x ULN (if liver metastases are present, < 5 x ULN)
- Alkaline phosphatase ≤ 2.0 x ULN (if bone or liver metastases are present, < 5 x ULN)
- Bilirubin ≤ 1.5 x ULN

10. Prothrombin time or partial thromboplastin time ≤ 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 vasec omy, 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 hormonereleasing 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
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 ≥ 2 years
10. Known history of brain metastases or currently active brain metastases
11. Uncontrolled hyperten ion (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 ≥ 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)
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 Endpoint:	• 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 complete response (CR) or partial response (PR) regardless of whether it is confirmed or unconfirmed • Pharmacokinetic parameters: $AUC_{0\text{-}21d}$ 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 – ≥ 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
Stopping Criteria:	NA
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 th 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 [stable disease (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.
Statistical Analysis for the Primary Endpoint:	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. 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 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 also be performed in the per-protocol analysis set.

Statistical Analysis for the Secondary Endpoints:	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 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. Safety data will be analyzed descriptively. 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.

SAP U31287-A-U203
Version 1.0, 29 November 2016

GENERAL INFORMATION

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
$AUC_{0\text{-}21d}$	Area under curve at last time point
C_{max}	Maximum observed circulating concentration
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EOI	End of infusion
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
EWB	Emotional well-being
FACT-H&N	Functional Assessment of Cancer Therapy-Head and Neck
FHNSI	FACT-Head and Neck Symptom Index
FWB	Functional well-being
GFR	Glomerular filtration rate
HAHA	Human antihuman antibody
HNS	FACT-Head and Neck Subscale
HPV	Human p pilloma virus
HRG	Heregulin (product neuregulin-1 gene [nRG1])
ILD	Interstitial Lung Disease
IV	Intraven us
IXRS	Interactive Web/Voice Response System
LD	longest diameters
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated acquisition (scan)
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetic or pharmacokinetics
PR	Partial response
PROs	Patient reported outcomes
PWB	Physical well-being
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

ABBREVIATION	DEFINITION
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SWB	Social well-being
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White Blood Count

1. SCOPE

This Statistical Analysis Plan (SAP) is created based on Protocol U31287-A-U203 version 4.0, 13 JUN 2016. This version describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol. The analysis plan may change due to unforeseen circumstances. Any deviations to the planned statistical analyses specified within the SAP will be justified in writing and presented within the clinical study report.

2. STUDY OBJECTIVES

2.1. 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

2.2. 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 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

2.3. Exploratory Objectives

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

3. STUDY DESIGN

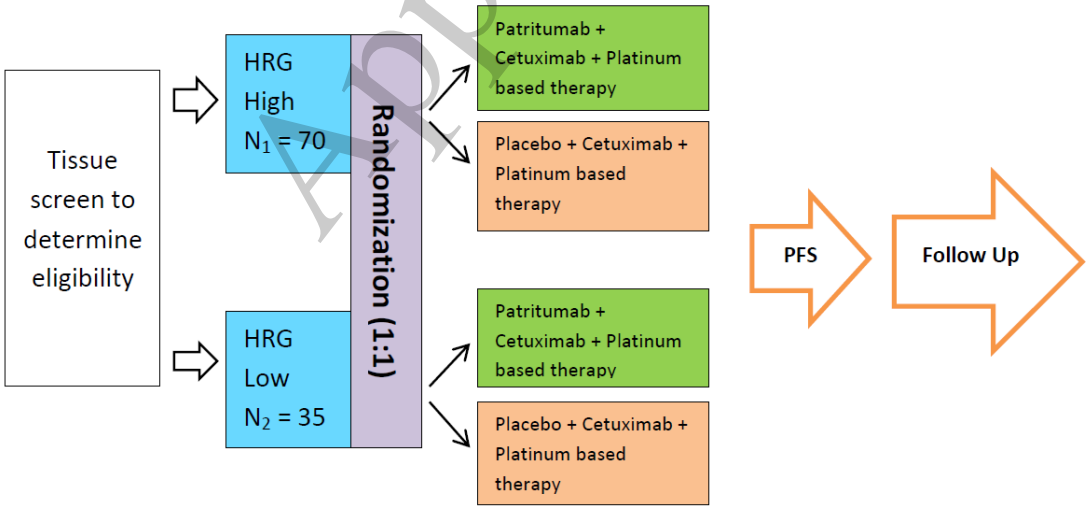
3.1. General Study Design and Plan

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.

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.

Approximately 105 subjects will be randomized 1:1 to the patritumab and the control arms stratified by HRG value (high versus low) and HPV status (positive vs negative). Approximately 70 HRG-high and approximately 35 HRG-low subjects will be randomized. When one HRG stratum is filled with the required sample size, the enrollment in that HRG stratum will cease. The initial cut-off for HRG high versus low before randomization was set using the median HRG delta Ct value (0.93) of commercial tissue samples and was increased based on further samples to 1.50 on 29JUL2016. See Figure 3.1.1 for a schematic of the study design

Figure 3.1.1: Phase 2 Study Design



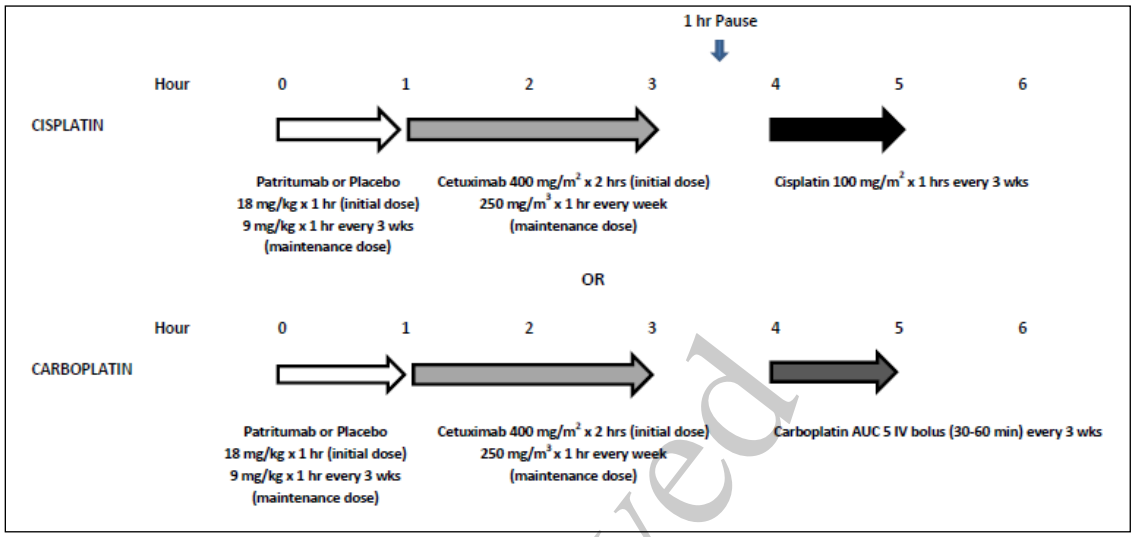
The enrolled subjects will be stratified by HRG (high, low) and HPV (positive, negative)

There will be two treatment arms:

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

Figure 3.1.2 illustrates the order and timing of the treatments involved.

Figure 3.1.2: Order and Timing of Treatments



Patritumab initial loading dose is 18 mg/kg IV (or placebo) over 60 minutes followed in cycle 2 and beyond with a maintenance dose of 9 mg/kg IV over 60 minutes (± 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^2 IV is given as a 2-hour infusion followed by 250 mg/m^2 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^2 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 posttreatments 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. AUC 5 is the target. The carboplatin dose will be calculated using the Calvert formula: Carboplatin Dose (mg) = 5 x (glomerular filtration rate [GFR] + 25). Estimated serum creatinine clearance (mL/min) calculated using the modified Cockcroft-Gault equation 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.

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.

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 CR, partial response PR, or 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 demonstrate 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.

The study evaluation schedule is provided in Table 3.1.1 and Table 3.1.2

Table 3.1.1: Schedule of Events

Assessment	Tissue screen	Screen	Random-ization	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[a]
				Day 1			Day 2	Day 3	Day 8	Day 15	Day 1	Day 1				
				Predose	Dosing	EOI										
Visit Window (Days)		-14 unless otherwise indicated													21 days after last dose [a]	
Informed consent for tumor tissue	X															
Informed consent (s) [b]		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 [c]		X		X [d]							X*[d]	X*[d]			X[d]	
ECOG		X		X					X	X	X	X			X	
Echo or MUGA [e]		X									X [e]	X [e]			X	
ECG (12-lead) [e]		X													X	
Con Meds		X		X		X			X	X	X*	X*			X	
Adverse Events	X [f]	X		X		X			X	X	X*	X*			X	X [g]
PRO assessments [h]				X							X	X			X	
CBC differential & platelets [i]		X		X [d]					X [d]	X [d]	X*[d]	X*[d]			X[d]	
Serum chemistries [i]		X		X [d]					X [d]	X [d]	X*[d]	X*[d]			X[d]	
GFR or estimated serum creatinine clearance [j]		X		X							X	X				
Coagulation		X														
Urinalysis		X													X	
IxRS			X													
Intense PK [k]				X [d]		X	X	X	X	X	X[†]					
Sparse PK (all) [l]				X [d]		X					X				X	
HAHA sample [l]				X [d]							X				X	
Pregnancy test [m]		X													X	

Assessment	Tissue screen	Screen	Random-ization	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[a]
				Day 1			Day 2	Day 3	Day 8	Day 15	Day 1	Day 1				
				Predose	Dosing	EOI										
Patritumab Adm [n]					X						X	X				
Cetuximab Adm [o]					X				X	X	X	X				
Platinum Adm [p]					X						X	X				
PGx sample [q]				X [d]												
Tumor assessments [r]		X												X [s]	X	
Survival follow-up																X [t]
Additional biomarker blood samples [u]				X [u]							X [u]		X [u]		X [u]	X [u]

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, every third subsequent cycle, and End-of-Study Visit. Additional echocardiograms/MUGA scans and electrocardiograms may be performed at the discretion of th inve tigator. 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 e pl ced to the subject to record adverse events.
h PRO assessments will be administered before any study-rela ed procedures are performed.
i Results must be available prior to dosing.
j At Screening, either GFR or the estimated serum creatinin clear nce (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 **Error! Reference source not found.** in the protocol for detailed information on sampling times.
l See **Error! Reference source not found.** in the protocol 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^2 IV over 2 hours and 250 mg/m^2 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^2 IV over 1 hour and every 3 weeks up to a maximum of 6 cycles. For pre- and post-treatment hydration see Section **Error! Reference source not found.** in the protocol 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 **Error! Reference source not found.** in the protocol 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 **Error! Reference source not found.** in the protocol.

Table 3.1.2: Schedule of Events for Extension Phase

	Additional cycles		Every 3 months	End of Treatment	40 days after last dose[a]
	Predose	**Dosing**			
Visit Window (Days)					
Physical Exam	X			X	
Vital Signs	X			X	
Adverse Events	X				X
CBC diff and platelets [b]	X [b]			X [b]	
Serum chemistries [b]	X [b]			X [b]	
HAHA and PK sample [c]			X		
Patritumab Adm [d]		X			
Cetuximab Adm [e]		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 (±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^2 over 1 hour weekly. Cetuximab can be administered directly after patritumab administration.

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3.2. Study Population

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

3.3. Randomization and Blinding

3.3.1. Randomization

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)

The IXRS will manage the number of HRG-high and HRG-low patients randomized. Once the maximum number of HRG-low subjects has been randomized, the IXRS will not allow enrollment of additional HRG-low subjects. To ensure balance between treatment groups, subjects will additionally b stratified according to HPV status (positive, negative).

Randomization to treatment groups will be achieved using IXRS. The time between randomization and the initiation of treatment should be as short as possible and no more than 3 business days.

3.3.2. Blinding

This study is randomized, placebo-controlled, double blinded study. The treatment assignments will be blinded to the subjects, the investigators, site staff, and all persons involved in reviewing the clinical data, including CRO personnel in clinical and trial management and Sponsor personnel, with the exception of the Data Monitoring Committee, who will review the unblinded clinical data on an ongoing basis.

3.3.2.1. Unblinding at Primary Analysis

At the point of primary analysis, as defined in Section 7 of this SAP, the treatment assignment for all subjects randomized will only be unblinded to CRO and sponsor statisticians and programmers directly involved in performing the analyses 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. Any datasets containing potentially unblinded information (i.e., patritumab PK and HAHA) will have their access restricted. The study statistician will maintain a list of the individuals who have access to individual treatment assignments and/or data that potentially unblinds the study. This list will include the date and level of unblinding and rationale for unblinding.

3.3.2.2. Unblinding at Study Closure

For the purpose of database lock and generation of the clinical study report (CSR), the study will be considered closed when OS data will be considered mature. At study closure, all subjects will be unblinded for final analysis after the final database is locked. Any subject remaining on study treatment and appears to continue to benefit (ie, SD or better) from treatment may continue to receive study treatment.

3.3.2.3. 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 further course of medical treatment. 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. 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 subinvestigator 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. A detailed procedure is described in the protocol.

3.4. Study Assessments

The table in Section 3.1, above, presents the visit schedule and procedures of the study to be conducted at each visit.

4. 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 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 bo h 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 if HRG high stratum does not show statistical significance in PFS.

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.).

5. STUDY VARIABLES

5.1. Efficacy Variables

Efficacy variables include PFS, OS, ORR (CR and PR), duration of response, time to response, time to disease progression, and duration of SD.

Tumor response assessments, including subjects who discontinued from treatment, will be performed every 6 weeks (± 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 (± 7 days).

5.1.1. Primary Efficacy Variable

The primary efficacy variable is PFS. PFS 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) or death due to any cause. Progressive Disease is defined as ≥ 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.

The rules for censored cases are defined as follows:

1. Subjects who are alive with no objective documentation of radiographic disease progression by the data cut-off date for the PFS analyses will be censored at the date of the last post-baseline evaluable tumor assessment. The evaluable tumor assessment is defined as the overall response for tumor assessment being not "Inevaluable" recorded on the Case Report Form (CRF) page "overall tumor assessment". If there is no post-baseline evaluable tumor assessment, the subject will be censored at the date of randomization.

2. Subjects who start other anti-cancer therapy including surgical or radiologic intervention given with curative intent prior to progression or death will be censored at the date of the last post-baseline evaluable tumor assessment prior to starting other anti-cancer therapy. If there is no post-baseline evaluable tumor assessment prior to starting other anti-cancer therapy, the subject will be censored at the date of randomization.
3. Subjects who progress or die after ≥2 consecutive missed tumor assessment visits will be censored at the date of the last evaluable tumor assessment prior to progression or death. In this study, progression or death after ≥2 consecutive missed tumor assessment visits is defined as progression or death that occurs more than 13 weeks (two tumor assessment visits plus 1 week visit window) since the last post-baseline evaluable tumor assessment. If there is no post-baseline evaluable tumor assessment prior to the tumor assessment of progressive disease or death and progression or death occurs more than 13 weeks since the date of randomization, the subject will be censored at the date of randomization;
4. Subjects without baseline tumor assessment will be censored at the date of randomization.

5.1.2. Secondary Efficacy Variables

Secondary efficacy variables include OS and ORR (CR and PR).

5.1.2.1. Overall Survival (OS)

OS is defined as the time from the date of randomization to death due to any cause. 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.

Survival status data will be obtained from deaths reported in the CRFs and Survival follow-up communications every 3 months after a subject discontinues from study treatment.

The last contact date is defined as the last date the subject was known to be alive at the analysis cut-off. The date will be the latest date among the following:

- Last non-missing assessment/onset date captured under the following eCRF pages (or if a date of assessment/onset is not available the "date of visit" for the eCRF page can be used): adverse events, vital signs, physical examination, ECOG PS, ECG, Echocardiogram or MUGA scan, safety laboratory test, tumor assessment, patient-reported outcomes assessment, hospitalization and also assessment date in third-party data such as PK, HAHA etc.
- Last dosing date of study medication, last date of concomitant medications, and last date of non-drug treatments/procedures.
- Start date of subsequent anti-cancer therapy administered after study treatment discontinuation.
- Date of Last Contact collected on the survival follow up page of the eCRF.

- Date of Last Contact collected on the final subject status (or end of study status) page of the eCRF.

5.1.2.2. Object Response Rate (ORR)

ORR 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 best overall response is defined as the best response (in the order of CR, PR, SD, and PD) among all overall responses recorded from the start of treatment until the subject is withdrawn from the study.The best overall response of PD corresponds to disease progression (assessment based upon tumor measurements and recorded on the CRF page "overall tumor assessment") for the first valid post-treatment tumor assessment. If there is no post-treatment tumor assessment, the best overall response will be assigned as "Inevaluable". In the case of a best overall response of SD, measurements must have met the SD criteria at least once after study entry at a minimum time interval from baseline. A best overall response of SD must be assessed a minimum of 39 days (6 weeks – 3 day visit window) after the date of randomization. If this minimum requirement is not met, the best overall response will be determined starting with the next tumor assessment. If there is no next tumor assessment, the best overall response will be assigned as "Inevaluable".

5.1.3. Exploratory Efficacy Variables

Duration of response, time to response, time to disease progression and duration of SD will be exploratory efficacy variables examined in this study.

5.1.3.1. Duration of Response

Duration of response is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of progressive disease (disease progression as assessed based upon tumor measurements and recorded on the CRF page "overall tumor assessment"). If a subject is discontinued or is lost to follow-up with no documentation of progressive disease, duration of response is defined as the time from the date of the first documentation of objective response to the date of the last evaluable tumor assessment as a censored value. The rules for censored cases are defined as follows:

Subjects who progress after ≥2 consecutive missed tumor assessment visits will be censored at the date of the last evaluable tumor assessment prior to the tumor assessment of progressive disease. In this study, progression after ≥2 consecutive missed tumor assessment visits is defined as progression that occurs more than 13 weeks (two tumor assessment visits plus 1 week visit window) since the last post-baseline evaluable tumor assessment. Subjects who start other anti-cancer therapy prior to progression will be censored at the date of the last post-baseline evaluable tumor assessment prior to starting other anti-cancer therapy.

Duration of response will be measured for responding subjects (PR or CR) only.

5.1.3.2. Time to Response

Time to response is defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR). Time to response will be measured for responding subjects (PR or CR) only.

5.1.3.3. Time to Disease Progression (TTP)

Time to progression is defined as the time from the randomization date to the date of first objective documentation of radiographic disease progression (per RECIST v1.1 as assessed by investigator). Objective documentation of disease progression is based upon "Overall Response" recorded as "Progressive Disease (PD)" on the CRF page: "overall tumor assessment". The rules for censored cases of TTP and duration of response are similar to the censoring of PFS, except that subjects who die before disease progression is document are censored for the former.

5.1.3.4. Duration of Stable Disease (SD)

Duration of stable disease is defined for subjects whose best response is SD as the time from the date of randomization to the date of the first documentation of progressive disease (disease progression as assessed based upon tumor measurements and recorded on the CRF page "overall tumor assessment"). Censoring rules are the same as described above for duration of response.

5.2. Safety Variables

5.2.1. Adverse Events

The following safety variables will be assessed in this study according to the Schedule of Events (Table 3.1.1 and Table 3 1.2) in Section 3.1.

- A Treatment-eme g nt adverse event (TEAE) is defined as an Adverse Event (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, Version XX.X), and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.
- AEs of Special Interest

– Interstitial Lung Disease (ILD)

  ILD is defined as an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever.

– Combined Elevations of Aminotransferases and Bilirubin

  Hepatic events, both serious and nonserious, presenting with combined abnormalities meeting criteria for a potential "Hy's law" case [i.e., Alanine

aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥ 3 x ULN, with simultaneous total bilirubin ≥ 2 x ULN].

5.2.2. 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 (WBC) with 5 part differential (including absolute neutrophil count), 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 β-HCG pregnancy t st

At Screening, creatinine clearance (mL min) or GFR will be calculated. This will also be done before each cisplatin or carboplatin administration.

5.2.3. Vital Signs

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

5.2.4. ECG

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.

5.2.5. Physical Examinations

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.

5.2.6. Other Safety Variables

An echocardiogram or multigated acquisition (MUGA) scan will be performed at screening, and at End-of-Study Treatment visit and during the study at the discretion of the Investigator.

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. 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.

5.3. Pharmacokinetic Variables

5.3.1. Concentration Data

Serum concentrations for patritumab will be collected at Cycles 1- 3 and at End of Study Treatment (Table 8.1 of the Protocol).

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 (Table 8.2 of the Protocol) This will be an intense pharmacokinetic (PK) assessment.

5.3.2. Pharmacokinetic (PK) Parameters

PK parameters ($AUC_{0\text{-}21d}$ and Cmax) will be calculated from the individual concentrations of patritumab, cetuximab, cisplatin and carboplatin using non-compartmental methods. PK parameters will be derived for the intensive PK sampling (i.e. Cycle 1) for patritumab, cetuximab cisplatin and carboplatin.

5.4. Pharmacodynamic (PD) Variables

Not Applicable.

5.5. Biomarkers

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.

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.

5.6. Other Variables

5.6.1. Eastern Cooperative Oncology Group Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status will be determined at Screening, and then at each scheduled visit throughout the study.

5.6.2. 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.

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

The FACT-H&N contains 4 general subscales (total 27 items) measuring physical well-being (PWB), functional well-being (FWB), social well-being (SWB), emotional well-being (EWB), and a Head and Neck Cancer symptom-sp cific subscale – the 12-item Head and Neck Additional Concerns Subscale (HNS). Each of the 39 FACT- H&N items is rated on 5-point scales, ranging from 0=not at all to 4=very much, where higher scores represent more favorable patient-reported outcomes.

Combining the 10 symptom-related items out of the 39 FACT-H&N items – "I have a lack of energy" (PWB item 1), "I have nausea" (PWB item 2), "I have pain" (PWB item 4), "I worry that my condition will get worse" (EWB item 6), "I am content with the quality of my life right now" (FWB item 7), "I have trouble breathing" (Additional Concerns item 3), "I can swallow naturally and easily" (Additional Concerns item 7), "I am able to communicate with others" (Additional Concerns item 10), "I can eat solid foods" (Additional Concerns item 11), and "I have pain in my mouth, throat or neck" (Additional Concerns item 12) - yields a 10-item FACT-Head and Neck Symptom Index (FHNSI).

Specifically, 7 specific summary scores will be evaluated,

- PWB score
- FWB score
- SWB score
- EWB score
- HNS score
- FHNSI score
- FACT-H&N total score

The FACT-H&N Total Score ranges from 0-156. The PWB score, SWB score and EWB score range from 0 to 28. The EWB score ranges from 0 to 24. The HNS score and the FHNSI score ranges from 0 to 48. The FACT-H&N total score, PWB score, FWB score,

SWB score, EWB score, HNS score and FHNSI score will be analyzed as exploratory efficacy parameters.

Use following algorithm to determine the individual subscale scores:

- Physical well-being (PWB): PWB score = Sum (GP1-GP7) x 7/number of nonmissing items. If the number of missing items (GP1-GP7) is greater than 3, then set PWB score = missing.
- Social well-being (SWB): SWB score = Sum (GS1-GS7) x 7/number of nonmissing items. If the number of missing items (GS1-GS7) is greater than 3, then set SWB score = missing.
- Emotional well-being (EWB): EWB score = Sum (GE1-GE6) x 6/number of nonmissing items. If the number of missing items (GE1-GE6) is greater than 3, then set EWB score = missing.
- Functional well-being (FWB): FWB score = Sum (GF1-GF7) x 7/number of nonmissing items. If the number of missing items (GF1-GF7) is greater than 3, then set FWB score = missing.
- Additional Concern (HNS): HCS score = Sum (H&N1-H&N12) x 12/number of nonmissing items. If the number of missing above items is greater than 6, then set HCS score = missing.
- Additional Concern (HNS): HCS score = Sum (H&N1-H&N12) x 12/number of nonmissing items. If the number of missing above items is greater than 6, then set HCS score = missing.
- FHNSI: FHNSI score = Sum of 10 symptom-related items x 10/number of nonmissing items. If the number of missing above items is greater than 5, then set FHNSI score = missing.
- FACT-H&N total score: FACT-H&N score = Sum (PWB, SWB, EWB, GFB, HCS). If any of the above items is missing, then set FACT-H&N score = missing.

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.

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 (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5). 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.

As index-based values have not been evaluated for the EQ-5D-5L at this time, crosswalk value sets developed based on the EQ-5D-3L index-based values will be applied. The crosswalk value set for the United Kingdom will be used for analyses overall and for all regions. The value set provides an index score for each health state and can be accessed at:
(http://www.euroqol.org/fileadmin/user_upload/Documenten/Excel/Crosswalk_5L/EQ-5D-5L_Crosswalk_Value_Sets.xls).

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.

6. ANALYSIS SETS

6.1. Analysis Sets Definitions

6.1.1. Full Analysis Set

The full analysis set (FAS) will be based on the intent-to-treat principle and will comprise all subjects randomized into the study. Subjects will be analyzed as randomized.

6.1.2. 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.

6.1.3. 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.

6.1.4. Pharmacokinetic Analysis Set

The PK analysis set will include all sub ects who have received at least 1 dose of study drugs and have evaluable patritumab or cetuximab concentrations.

6.1.5. Patient Reported Outcome Analysis Set

There will be 2 PRO Analysis Sets:

- FACT-H&N An lysis Set
- EQ-5D Analysis Set.

The FACT-H&N Analysis Set will include all subjects in the Full Analysis Set who complete the FACT-H&N assessment at Cycle 1 Day 1, at least partially in a manner that permits imputation of missing responses, according to the approach described in Section 5.6.2.

The EQ-5D Analysis Set will include all subjects in the Full Analysis Set who complete the EQ-5D assessment at Cycle 1 Day 1, at least partially in a manner that permits imputation of missing responses, according to the approach described in Section 5.6.2.

6.2. Protocol Deviations

A list of protocol deviations for the study report will be presented in a data listing.

6.3. Treatment Misallocations

The following rules of reporting efficacy and safety results (eg, under which treatment group) for subjects with errors in treatment allocation will be applied.

If subjects are:

- Randomized but not treated, then they will be reported under their randomized treatment group for efficacy analysis. However, they are by definition excluded from the safety analysis as actual treatment is missing.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing, but they will be reported under the treatment they actually received for all safety analyses.
- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses, but will be reported under the treatment they actually received for all safety analyses.

7. 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 (i.e., when all subjects have died or a minimum of 13 months after the last subject is randomized whichever comes first). 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 b seline 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 imput d 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.

Study Day is calculated as *<date - 1st study treatment date + 1>*. The date of the first study treatment is Day 1

7.1. Adjustment for Covariates

No other covariate adjustments will be applied for primary and secondary efficacy analyses, except for the stratification variables if applicable. The PRO analyses will use baseline values of the dependent variable as a covariate in a mixed model.

7.2. Handling of Dropouts or Missing Data

For a description of the handling of censored data for efficacy endpoints such as OS, PFS and TTP, see Section 5.1 above. Imputation of partial or missing AE onset date and concomitant medication date, incomplete tumor assessment dates, and incomplete dates for last contact or death are specified in Section 11.1. The missing data handling for the analyses on patient reported outcomes is described in 5.6.2.1.

7.3. Interim Analyses and Data Monitoring

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 at periodical basis. 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.

7.4. Multicenter Studies

There will be approximately 35 sites in Europe. Site as a factor will not be formally examined in this study.

7.5. Multiple Comparisons/Multiplicity

This study has only one primary efficacy variable PFS. The testing hypotheses to compare PFS the patritumab arm versus the control arm will be performed in two sequential steps in pre-defined populations (Freidlin 2012 et al). The primary analysis is PFS comparison between the patritumab arm and the control arm in HRG-high stratum of the FAS (Step 1). If the testing in Step 1 is significant, then no further testing will be performed in Step 2 and the 80% confid n e intervals of the hazard ratio in HRG low stratum will be estimated. If the testing in Step 1 is not significant, then the testing in FAS (HRG high + low) will be performed in Step 2 (See Section 8.2.1). The results from both steps will be used to guide the decision on future Phase 3 designs. Since this is a proof of concept study, no adjustment for multiplicity will be performed.

7.6. Examination of Subgroups

As exploratory analyses, subgroup analysis (e.g. age, sex, HRG, HPV, primary tumor site, etc) for selective efficacy endpoints will be conducted (Section 8.2.4).

8. STATISTICAL ANALYSIS

8.1. Study Population Data

8.1.1. Subject Disposition

Subject disposition will be summarized by randomized treatment group and overall for All Screened Subjects. The number and percentage of subjects in the Full Analysis Set, the Per Protocol Analysis Set, the Safety Analysis Set, the Pharmacokinetics Analysis Set, and the PRO Analysis Sets will be presented. Subject status (ongoing, if any, and discontinued from study treatment) and the reasons for discontinuation (as reported on CRF EOT page) will be summarized in this table. All percentages, except those for All Screened Subjects, will be based on the Full Analysis Set. A listing will present data relevant to subject disposition.

8.1.2. Protocol Deviations

Protocol deviations collected by clinical team, as well as those identified in the CRF data will be provided in a listing.

Protocol deviations will be finalized prior to database lock.

8.1.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics 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 (if substantial differences such as >5% as compared to the FAS), and Safety Analysis Set. If two sets of subjects are identical to each other, analysis will only be performed once.

Demographic characteristics consist of age, gender, race, and ethnicity. A subject's age in years is calculated using the informed consent date and the birth date [(consent date-birthdate)/365.25]. Age will additionally be categorized as (≤ 65, > 65) for reporting purposes.

Baseline characteristics consist of height, weight, tumor stage at study entry, tumor grade, prior systemic cancer therapy (Yes or No), prior radiation therapy (Yes or No), time from diagnosis of SCCHN to study treatment, histology subtype, HRG value, HPV Status, tobacco history (cigarettes and cigars), ECOG performance status, and ECG findings at baseline.

Individual subject listings of all demographic, baseline characteristics, SCCHN cancer history, medical and surgical history including prior cancer history and prior cancer surgery, and prior cancer therapy will be provided.

8.2. Efficacy Analyses

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

8.2.1. Analysis of Primary Efficacy Variables

The primary efficacy endpoint is PFS as defined in Section 5.1.1 of this SAP. Progression will be determined based on the investigators' assessment.

The primary efficacy analysis will be the comparison of PFS between the patritumab arm and the control arm in HRG-high stratum of the FAS using the stratified log-rank test. For a description of the handling of censored data for efficacy endpoint PFS, see Section 5.1 above.

The testing hypotheses to compare PFS for the patritumab arm versus the control arm will be performed in two sequential steps (Freidlin 2012 et al). 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 (HRG high stratum + low stratum) will be t s ed at the one-sided 0.05 significance level. If the test in step 1 is rejected, then in st p 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 comparison of PFS between the patritumab arm and the control arm will be performed using a log-rank test stratified by the stratification factors.

Hypothesis testing for superioritywith regard to PFS will be performed with a 1-sided hypotheses setting.

Suppose that $S_A(t)$ and $S_P(t)$ are the cumulative survival functions for PFS in patritumab and control treatment groups, respectively. The null hypothesis H_0 with PFS:

H_0: $S_A(t) = S_P(t)$ for all $t \geq 0$ (identical survival functions for both groups)

will be tested against the 1-sided alternative hypothesis H_A:

H_A: $S_A(t) \geq S_P(t)$ for all $t \geq 0$ and $S_A(t) > S_P(t)$ for at least some $t > 0$

(improvement in PFS in the patritumab group over the control group)

The stratified log-rank test will be conducted using SAS PROC LIFETEST where the STRATA statement will include the treatment group and the stratification factors [HPV (positive vs other) and HRG (high vs. low, only for the FAS) at randomization]. The 1-sided p-value will therefore be obtained and H_0 will be rejected if p-value $\leq$ the pre-specified 1-sided alpha.

The Kaplan-Meier product-limit method will be used to estimate the distribution of PFS for the patritumab arm versus the control arm. The median PFS for each treatment group will be based on the Kaplan-Meier estimate and the 95% confidence intervals for each treatment group will be calculated using the method of Brookmeyer and Crowley. The

median and confidence interval will be reported in months, and days will be converted to months by dividing by 30.4. The corresponding Kaplan-Meier curves will also be presented.

Estimates of HR between 2 arms along with their two-sided 80% and 95% CIs will be calculated using stratified Cox proportional hazards regression model. SAS PROC PHREG with the treatment group as the model covariate and stratification factors [HPV (positive vs other) and HRG (high vs. low) at randomization] as the STRATA variables will be used for this model. The Efron's method will be used to handle ties.

The above analysis for PFS will be repeated for the per-protocol analysis set. A separate analysis which includes clinical progression as a PFS event will be done as a sensitivity analysis.

8.2.2. Analysis of Secondary Efficacy Variables

8.2.2.1. Overall Survival

OS will be analyzed in the same manner as for PFS. Estimates of HR between the patritumab arm and the control arm along with their two-sided 80% and 95% CIs will be calculated using stratified Cox proportional hazards regression model. SAS PROC PHREG with the treatment group as the model covariate and stratification factors at randomization as the STRATA variables will be used for this model. The Efron's method will be used to handle ties. The corresponding Kaplan-Meier curves will also be presented.

8.2.2.2. Objective Response Rate

The number and the percentage of the subjects with the best overall tumor responses of either CR or PR (the objective response) will be tabulated by treatment group. Percentages will be calculated based on the number of subjects in the respective treatment group. The differences in the ORR 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.

In addition, the percent change from baseline will be calculated for the sum of longest diameters (LD) for all target lesions at each post-treatment evaluation for each subject, if applicable. The percent change in the sum of longest diameters from baseline in target lesions will be summarized by treatment group and assessment time with descriptive statistics; the largest decrease from baseline will also be summarized and displayed in the waterfall plots.

Best overall response and tumor assessments (target lesions, non-target lesions and overall) will be listed for all subjects in the Full Analysis Set. Percent change from the nadir (i.e., minimum sum of LD, including baseline, if that is the minimum value, up to the preceding tumor assessment) will be presented in the listing for target lesions.

8.2.2.3. Cutoff for HRG Expression

HRG expression value will be summarized by treatment group for overall, HRG-high, and HRG-low group with summary statistics. The distribution of HRG values will be plotted with histogram and normal curves.

HRG expression values will be dichotomized at alternative cutoffs to form new HRG-high and HRG-low groups. Analysis of PFS and OS specified in Section 8.2.1 and Section 8.2.2.1 will be performed for newly classified HRG high and low groups at alternative cutoffs. The results will be used to select optimum HRG cutoff.

8.2.3. Analysis of Exploratory Efficacy Variables

Exploratory efficacy endpoints include duration of response, time to response, time to disease progression, and duration of SD.

8.2.3.1. Duration of Response

The distribution of duration of response as defined in Section 5.1.4.1 of this SAP will be presented as Kaplan Meier plot, together with response duration quartiles for responding subjects (PR or CR). Median time to response will be estimated along with two-sided 80% and 95% CIs using Kaplan-Meier methods

8.2.3.2. Time to Response

The distribution of time to response as defined in Section 5.1.4.2 of this SAP will be presented as Kaplan Meier plot, together with response duration quartiles for responding subjects (PR or CR). Median time to response will be estimated along with two-sided 80% and 95% CIs using Kaplan Meier methods.

8.2.3.3. Time to Disease Progression

Median time to disease progression will be estimated along with two-sided 80% and 95% CIs using Kaplan-Meier methods by treatment. In addition, summary statistics for 25% and 75% percentiles will be estimated using Kaplan-Meier methods.

8.2.3.4. Duration of Stable Disease

The distribution of duration of stable disease as defined in Section 5.1.4.4 of the SAP will be presented as Kaplan Meier plot, together with response duration quartiles for responding subjects with the best response of stable disease. In addition, median duration of stable disease will be estimated along with two-sided 80% and 95% CIs using Kaplan-Meier methods.

8.2.4. Sensitivity and Subgroup Analysis

8.2.4.1. Sensitivity Analysis

Sensitivity analysis for PFS will be performed by including both RECIST progression disease and clinical progression as PFS events. If HRG cutoff is changed during subject enrollment and stratification, the subject HRG status (High versus Low) will be redefined

using the changed HRG cutoff into new HRG high and low cohorts. Statistical analysis for PFS and key secondary endpoints will be conducted for the new HRG cohorts as a sensitivity analysis.

8.2.4.2. Subgroup Analysis

The subgroup analyses for PFS and OS specified in Section **Error! Reference source not found.** and Section **Error! Reference source not found.** will be performed for the subgroups below if data warrants:

- Age (≤65, > 65 yrs)
- Sex (Female, Male)
- Race (White, Non-white)
- HPV status (Postive, Negative)
- HRG subgroups (alternative cutoffs)
- Primary tumor site (oral cavity, oropharynx, hypopharynx, and larynx)
- ECOG performance status (0, 1)
- Platinum-based therapy (cisplatin carboplatin; n.b., subjects treated with both will be excluded)
- Tumor grade (well- or mod rately differentiated, poorly differentiated)
- Previous treatment (neoadjuvant chemotherapy, radiochemotherapy)
- Baseline FACT-H&N total score (≤ median, > median)

A Cox proportional hazards regression with treatment as the only covariate will be applied. Forest plots will be presented for both PFS and OS.

8.3. Safety Analyses

All analyses involving safety data (extent of exposure, TEAEs, clinical laboratory results, vital signs, ECG, echocardiograms/MUGAs, physical exam, HAHA, and ECOG performance status) will be performed on the Safety Analysis Set. No inferential statistical analysis is planned for safety data. Descriptive statistics will be calculated for quantitative safety data and frequency counts and percentages will be compiled for classification of qualitative safety data. All percentages will be calculated based on the number of subjects in the Safety Analysis Set. If the number of subjects with available data does not allow for the reliable estimation of variability at a scheduled time point, no summary statistics will be presented for that time point. Unless otherwise noted, baseline values will be the last non-missing assessment collected prior to first dose of study drug.

8.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as an adverse event that has an onset date on or after the first dose of patritumab/Placebo, or worsens in severity after the first dose of patritumab/Placebo relative to the pre-treatment state. An adverse event that occurs more than 30 days after the last dose of study medication will not be included as a TEAE, unless it is considered drug related.

Adverse events will be coded using the Medic l 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 serious adverse events (SAEs) will be tabulated, as well as TEAEs and treatment emergent SAEs considered related to patritum b, cetuximab, and cisplatin/carboplatin.

At each level of subject summarization, a subject will be counted once if he/she reports one or more occurrences of the same system organ class/preferred term/grade. For treatment-emergent (serious) adverse event toxicity tables tabulated on subject level, a subject with two or more treatment-emergent adverse events with the same preferred term will be counted only once for that term using the most severe toxicity. For a given subject, if the toxicity grade is missing for all treatment-emergent adverse events with the same preferred term, the treatment-emergent adverse events will be counted only once for that term under the "Missing" CTCAE toxicity category. In the presence of a subject who has both missing and non-missing CTCAE toxicity grades for adverse events with the same preferred term, the missing CTCAE toxicity of the adverse event will be treated as the lowest toxicity grade. In addition, a subject who reported two or more treatment-emergent adverse events with the same system organ class will be counted only once in the system organ class total, and subjects with two or more treatment-emergent adverse events in different system organ classes will be counted only once in the overall total.

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 of subjects from patritumab, cetuximab, and cisplatin/carboplatin will be listed.

8.3.2. Clinical Laboratory Evaluations

For continuous laboratory parameters, values and their changes from baseline at each visit will be summarized, as well as the maximum and minimum post-treatment values, and values for the last observation on treatment. Last observation on treatment is defined as the last non-missing value on or prior to end of treatment duration plus 7 days.

Repeated or unscheduled tests will not be summarized fo each scheduled visit, but will be included for summaries of maximum and minimum post-treatment values.

Clinical laboratory test results (hematology and blood chemistry) will be graded according to the NCI CTCAE, Version 4.03. Test results will also be flagged as low or high relative to the normal reference ranges. For each test, subjects will be characterized based on their worst severity grade observed during post-baseline period, based on CTCAE criteria and/or normal reference ranges. For parameters where CTCAE criteria are applicable, a shift table presenting the 2-way frequency tabulation of baseline and the worst post-baseline CTCAE grades will be provided. If absolute neutrophil or lymphocyte counts are not reported in the lab data, but percent differentials and total WBC are available, the absolut counts will be derived by the formula: differential count = 100*differential(%)/WBC and will be reported with the same units as WBC. Derived differentials will be used for NCI-CTCAE toxicity grading, and will not be reported with a normal range. Derived values that do not meet the NCI-CTCAE criteria for grade 2 or higher toxicity will be reported as grade <1 and as being within normal range. If the result of a liver function test is below a certain threshold (e.g., AST reported as <10), then it will be reported as grade <1 and as being within normal range.

Abnormal clinical laboratory test results deemed of clinical significance or of CTCAE Grade 3 or 4 will be listed.

8.3.3. Liver Function Parameters

Subjects with elevated post-baseline ALT, AST or Total Bilirubin that fall into the following categories will be identified. Number and percentage of these subjects will be tabulated for each cohort and in total.

- AST >= 3 × Upper Limit of Normal range (ULN)
- ALT >= 3 × ULN
- AST >= 3 × ULN or ALT >= 3 × ULN

- AST >= 5 × ULN
- ALT >= 5 × ULN
- AST >= 5 × ULN or ALT >= 5 × ULN
- Total Bilirubin >= 2×ULN
- AST >= 3 × ULN and Total Bilirubin >= 2×ULN[a]
- ALT >= 3 × ULN and Total Bilirubin >= 2×ULN
- (AST >= 3 × ULN or ALT >= 3 × ULN) and Total Bilirubin >= 2×ULN

Total Bilirubin >= 2×ULN is defined as at least one case of post-dose ≥ 2 x ULN occurred between the first incidence date and 30 days after the last incidence date of ALT ≥ 3 x ULN post treatment. Same rule applies to the last 2 categories.

8.3.4. Vital Signs

Values and change from baseline for vital signs, incl ding systolic blood pressure, diastolic blood pressure, pulse, body temperature, and weight will be summarized by treatment group and scheduled time of evaluation (including end-of-treatment visit), as well as for the maximum and minimum post-treatment values, the values at the end-of-treatment visit, and values for the last observation on treatment for the Safety Analysis Set. Last observation on treatment is defined as the last non-missing value on or prior to end of treatment duration plus 7 days.

Repeated or unscheduled tests will not be summarized for each scheduled visit, but will be included for summaries of maximum and minimum post-treatment values. A comprehensive listing of vital signs will be provided.

8.3.5. ECG

Values and change from baseline for ECG parameters, including heart rate, PR interval, RR interval, QRS duration, QT interval, QTcB (QT / RR**1/2), and QTcF (QT / RR**1/3), will be summarized for each treatment group and in total at scheduled time of evaluation (including end-of-treatment visit).

In addition, the following notable ECG interval values for each parameter will be evaluated:

QTcB and QTcF:

- New >450 msec
- New >480 msec
- New >500 msec
- Increase from baseline >30 msec
- Increase from baseline >60 msec

Note that "New" implies a newly occurring ECG abnormality. It is defined as an abnormal ECG finding at post-baseline that is not present at baseline, e.g., QTc New > 480 msec implies QTc > 480 msec pose-baseline and QTc ≤ 480 msec at baseline.

A subject with multiple occurrences of a newly occurring abnormality is counted only once per abnormality.

The percentage of subjects with newly occurring qualitative ECG abnormalities is based on the total number of subjects who are at risk of developing this abnormality in the category. For each individual abnormal finding, this is defined as the number of subjects with both baseline and post baseline evaluations and a normal value at baseline.

If a QTc record is missing but the records of QT interval and RR are available then QTc should be derived using the formula above. If RR is missing but heart rate (HR) is available, QTc should be derived using the following formulae:

- $QTcF = QT \times (HR/60)^{1/3}$
- $QTcB = QTx (HR/60)^{1/2}$

Data from ECGs will also be presented in the data listings using the Safety Analysis Set.

8.3.6. Dosing and Extent of Exposure

The number of IV received will be summarized for patritumab, cetuximab, and cisplatin/carboplatin, respectively, for subj cts in Safety Analysis Set.

Treatment duration in weeks for patritumab and cisplatin/carboplatin is calculated as (date of the last dose – date of the first dose + 21)/7.

Cycle duration in days is calculated as (date of Day 1 of next cycle – date of Day 1 of present cycle). Cycle duration is not calculated for the last cycle. Average cycle duration will be calculated for each subject.

Treatment duration for cetuximab is calculated as Duration (weeks): (date of the last dose – date of the first dose + 7)/7

For all study treatment expect carboplatin:

- Total cumulative dose (mg/kg) is defined as the sum of all doses (mg/kg) taken by a subject.
- Total cumulative dose (mg) is calculated as total cumulative dose (mg/kg) x weight (kg).
- Dose intensity (mg/kg/cycle/dose) is calculated as 3*(total cumulative dose(mg/kg)/(Duration(weeks)*(number of planned doses/cycle))
- Relative dose intensity (%) is calculated as 100*(dose intensity/(planned protocol dose)

For carboplatin:

- Total cumulative dose (mg) is defined the sum of all doses (mg) taken by a subject.

- Dose intensity is calculated as 3*(total cumulative dose(mg)/Duration(weeks)
- Relative dose intensity (%) is calculated as 100*(dose intensity)(planned protocol dose (mg)) where the planned protocol dose is 5x(creatinine clearance + 25) (i.e., target of 5 AUC), and the creatinine clearance is calculated using the modified Cockcroft-Gault equation (Protocol Appendix 17.1).

For the purpose of counting cycle, a subject is considered to be treated in a cycle if they receive the Day 1 dose. Treatment duration (in weeks and cycles), total cumulative dose, dose intensity, relative dose intensity, doses not completed, dose reductions, and number of IV received will be summarized using descriptive statistics, and listed for each subject in the Safety Analysis Set. Average cycle duration and number of cycles delayed, defined as time from last cycle > 21 days,) will be reported for patritumab. Subjects' dose modification will also be listed for patritumab, cetuximab, and cisplatin/carboplatin.

8.3.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary. Prior and concomitant medications will be summarized by treatment group, ATC2 class, and preferred term. A subject who takes one or more medications under any given ATC2 class and preferred term will be counted once for the ATC2 class and preferred term.

For the summary, medications taken prior to the first dose of study medication will be classified as prior medications, while medications taken on or after the first dosing will be classified as concomitant medications. Medications taken prior to the first dosing but with a missing stop date or with a stop date either on or after the first dosing or marked as "continuing" will also be considered concomitant medications for the summary. A listing of prior and concomitant medications by subject will be provided for the Safety Analysis Set.

8.3.8. Physical Examinations

A listing of physical examination data by subject for the Safety Analysis Set will be provided.

8.3.9. Analysis of Other Safety Variables

HAHA results (positive as determined by titer values, if positive on screening, and detection of neutralizing antibody, if needed) will be listed to identify subjects with positive HAHA.

ECOG performance status at baseline and scheduled time of evaluation (including end of Treatment visit) will be summarized by treatment group and in total for Safety Analysis Set. A two-way frequency tabulation for baseline and each study visit will be provided for ECOG performance status.

Left ventricular ejection fraction (LVEF) will be summarized using descriptive statistics for actual values and for changes from baseline by cohort by scheduled time of evaluation including the end of treatment visit as well as for the minimum and maximum post-baseline values and for the last observation on treatment. The last observation on

treatment value is defined as the last non-missing value on or prior to end of treatment duration plus 7 days. Repeated or unscheduled tests will not be summarized for each scheduled visit, but will be included for summaries of maximum and minimum post-baseline values and the last observation on treatment.

A listing of ECOG performance status will be presented.

A listing of echocardiogram by subject for the Safety Analysis Set will be provided.

8.4. Pharmacokinetic Analyses

8.4.1. Concentration Data

Concentrations below the lower limit of quantitation (BLQ) will be set to zero for the calculation of descriptive statistics. If any of the concentrations at a time point is BLQ, the geometric mean of the concentrations at this particular time point will not be calculated and will be presented as "NC" in the summary tables. PK data will be listed for the pharmacokinetic analysis sets.

8.4.1.1. Sparse Patritumab PK

Serum concentrations for patritumab at Cycles 1-3 and at End of Study Treatment will be listed and summarized with descriptive statistics using the PK Analysis set. Mean plasma concentration of patritumab versus time will be plotted on both linear scale and semi-logarithm scale.

8.4.1.2. Intensive PK

Intensive PK refers to samples taken during Cycle 1 (Day 1 to Day 21 for patritumab, Day 1 to Day 8 for cetuximab Day 1 to Day 3 for cisplatin or carboplatin). Individual concentration profiles versus time by treatment group for each study drug will be plotted on linear and logarithmic scales. Concentrations will be summarized by treatment and nominal timepoint. Individual PK parameters will be listed and summarized by treatment.

The PK parameters, area under curve at last time point (AUC_{last}) and C_{max} will be summarized and listed by treatment groupfor each drug using the PK Analysis set. Box plots of AUC_{last} and C_{max} versus treatment will be presented.

8.4.2. Analysis of Pharmacokinetic (PK) Parameters

The intensive PK parameters, area under curve at last time point (AUC_{last}) and C_{max} will be summarized and compared for cetuximab and platinum concentration by treatment arms for the PK Analysis set. The 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 using an ANOVA model with treatment as factor. AUC_{last} and C_{max} will be log-transformed prior to analysis. The geometric mean ratios and their two-sided 90% CIs for AUC_{last} and C_{max} between the patritumab arm and the placebo arm will be calculated using the exponentiation of the differences and their CIs between treatments least square mean from the ANOVA. The ratios and their two-sided 90% CIs will be expressed relative to the placebo arm.

8.4.3. Population Pharmacokinetic (PK) and Exposure Response

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. These analyses are outside the scope of this SAP and details of those analyses will be included in a separate document for population PK and exposure response analyses.

8.5. Pharmacodynamic (PD) Parameters

Not Applicable.

8.6. Biomarkers Analyses

The study has baseline HRG biomarker and HPV status 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.

Baseline HRG values will be summarized and listed.

8.7. Other Variables Analyses

8.7.1. Patient Reported Outcomes

The FACT-H&N total score (FACT-G +disease specific subscale score), the FACT-H&N individual subscale scores (Physical Well Being (PWB), Social Well Being (SWB), Emotional Well Being (EWB), Functional Well Being (FWB)), FACT-G total score, and the FACT-H&N FHNSI sco and change from baseline will be summarized by visit and treatment group using the FACT-H&N Analysis Set.

For each post-baseline assessment:

- Observed range; Mean (SD) by treatment group (overall, HPV+ and HPB-) will be reported for each of the scores listed above.
- The entire Cumulative Distribution Function (CDF) of change from baseline on FACT-G, FACT-H&N FHNSI and FACT-H&N total score will be presented as a continuous plot of the change from baseline on the X-axis and the cumulative percent of subjects experiencing that change on the Y-axis for each treatment group.

Change from baseline in the FACT-H&N total score (FACT-G +disease specific subscale score), the FACT-H&N individual subscale scores, FACT-G total score, and the FACT-H&N FHNSI score, will also be evaluated using mixed longitudinal modeling for the FACT-H&N Analysis Set. The model will include treatment, time, treatment-by-time interaction, and baseline as fixed effects. The unstructured option for the REPEATED statement in PROC MIXED will be used to model the within subject covariance

structure. LS means along with 95% CIs by timepoint and LS mean differences between the control arm and patritumab arm along with two-sided 95% CIs for each timepoint will be derived.

For these analyses, PRO values obtained at the end of treatment visit or at any scheduled timepoint with fewer than 5 subjects in the placebo arm or patritumab arm will not be included.

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 using the EQ-5D Analysis Set. Results of the EQ VAS will be presented as a measure of overall self-rated health status.

9. CHANGES FROM THE PROTCOL SPECIFIED STATISTICAL ANALYSES

No changes have been issued.

10. REFERENCES

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11. APPENDICES

11.1. Data Derivation Details

11.1.1. Windows Convention for Handling Partial and Missing Dates

No imputation will be performed for any dates other than adverse event onset dates and concomitant medication start and stop dates. A complete date may be necessary in order to determine if an adverse event or medication should be included in the summary/analysis (i,e., if the event is treatment emergent or the medication is prior or concomitant). The conventions specified below will be used for this purpose only. The original partial or missing dates rather than the imputed dates will be presented in the listing.

Adverse Events Onset Date

If the AE onset date is missing in which the day, month, and year are all unknown or only the day is known, the AE onset date is set to the date of first dose of study medication.

For the partial AE onset date,

- If the year is present and the month and day are missing or the year and day are present and the month is m ssing
  - If year = year of first dose then set month and day to month and day of first dose
  - If year < year of first dose, then set month and day to December 31st.
  - If year > year of first dose, then set month and day to January 1st.
- If the month and year are present and the day is missing:
  - If year=year of first dose and

    if month = month of first dose then set day to day of first dose date

    if month < month of first dose then set day to last day of month

    if month > month of first dose then set day to 1st day of month

    If year < year of first dose then set day to last day of month

    If year > year of first dose then set day to 1st day of month
- If the imputed AE onset date is after AE stop date, then set the onset date to the AE stop date.

Prior and Concomitant Medications Date

If the start date of medication is completely missing in which the day, month, and year are all unknown or only the day is known, then the start date will not be imputed.

For the partial start date of medication,

- If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to January 1.
- If the year and month are present and the day is missing, set day to 1st day of month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

If the end date of medication is completely missing which the day, month, and year are all unknown or only the day is known, then the end date will not be imputed.

For the partial end date of medication,

- If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to December 31.
- If the year and month are present and the day is missing, set day to last day of the month.

Incomplete Tumor Assessment Dates

All dates for tumor assessment must be completed with day, month and year.

- If one or more measurement dates (e.g. X-ray, CT-scan for target and non-target tumor lesions) are incomplete but other measurement dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date.
- If all measurement dates have no day recorded, the 1st of the month is used.
- If the month is not completed, for any of the assessments, the respective assessment will be onsidered to be at the midpoint of previous and following assessment dates.

Incomplete Dates for Last Contact or Death

All dates are expected to be completed with day, month, and year.

If the day/month is missing, the 1st of the month/year will be used for incomplete death dates or dates of last contact.

11.2. Interim Analysis Statistical Analysis Plan

Safety data and efficacy data will be prepared for the purpose of DMC reviews, and the frequency and extent of such data reviews will follow the DMC charter for Study U31287-A-U203. In general, the statistical methodology and TLF shells in the SAP will be a framework to generate outputs for DMC reviews. The independent Data Analysis Group (DAG) will perform the analysis. Operating details of the DAG are included in the DMC charter.

11.3. Formula for Wilson Method

Wilson Method

Use the following formula to compute a (1-α)% confidence interval for a single proportion using the Wilson method with continuity correction:

$$L = \frac{\hat{p}_i + \frac{z^2}{2n_i} - \frac{1}{2n_i} - z\sqrt{\frac{\hat{p}_i[n_i(1-\hat{p}_i)+1]}{{n_i}^2} + \frac{z^2 - 2 - 1/n_i}{4{n_i}^2}}}{1 + \frac{z^2}{n_i}}$$

$$U = \frac{\hat{p}_i + \frac{z^2}{2n_i} + \frac{1}{2n_i} + z\sqrt{\frac{\hat{p}_i[n_i(1-\hat{p}_i)-1]}{{n_i}^2} + \frac{z^2 + 2 - 1/n_i}{4{n_i}^2}}}{1 + \frac{z^2}{n_i}}$$

where $\hat{p}_i$ denotes the sample proportion for group i and n the group sample size. All statistical constants will be computed using appropriate SAS functions. Note: if $\hat{p}_i$=0, L must be taken as 0; if $\hat{p}_i$=1, U is then 1. In case L is calculated to be less than 0, set L to 0; and similarly set U to 1 if U is calculated to be larger than 1.

Confidence limits for the difference in ORR between each of the U3-1287 (AMG888) groups and placebo based on Wilson (Newcombe) score will use the method below.

Denote the lower and upper Wilson score (with continuity correction) confidence limits for p_1 as L_1 and U_1 and the lower and upper confidence limits for p_2 as L_2 and U_2 (where L and U are defined above). The Wilson score (with continuity correction) confidence limits for the proportion diff ence ($d=p_1-p_2$) are computed as

$$d_L = (\hat{p}_1 - \hat{p}_2) - z\sqrt{L_1(1-L_1)/n_1 + U_2(1-U_2)/n_2}$$

$$d_U = (\hat{p}_1 - \hat{p}_2) + z\sqrt{U_1(1-U_1)/n_1 + L_2(1-L_2)/n_2}$$

11.4. Mock-up Tables and Listings

The date on which the first dose of study medication (including placebo) is administered is considered as Day 1 of the study. For events occurring on or after the start of treatment, study day is calculated as the event date minus the date of first administration of study medication plus 1 day. For events occurring before the start of treatment, study day is calculated as the event date minus the date of first administration of study medication.

Raw measurements will be reported to the number of significant digits as captured electronically or on the CRF. The mean and median will be displayed to one decimal place beyond the number of decimal places the original parameter is presented, and the measure of variability (e.g., standard deviation) will be displayed to two decimal places beyond the number of decimal places the original parameter is presented. Minimums and maximums will be reported to the same number of significant digits as the parameter. Calculated percentages will be reported with 1 decimal place. When count data are presented as category frequencies and corresponding percentages, the percent will be suppressed when the count is zero. Show a 'Missing row' after the last category if there are missing observations for the variable.

P-values will be reported to 4 decimal places (SAS format pvalue6.4). Values less than 0.0001 will be displayed as <0.0001. Values greater than 0.9995 will be displayed as 1.0000. Unless otherwise indicated, 1-sided p-values are presented in the tables.

All tables will summarize data for the overall study population and by the high and low HRG expression strata. For disposition tables and safety tables the order will be overall, high, and low. For efficacy tables the order will be high, low, and overall.

Listings will be presented for each part and sorted by subject ID. When available, listings will also be sorted by study day.

Unless otherwise indicated continuous variables will be summarized using the following descriptive statistics: the number of subjects (n), mean, standard deviation, median, minimum, and maximum. The frequency and percentage of observed levels will be reported for categorical measures. Percentages will be based on the number of subjects in the relevant analysis set. All statistical analyses will be performed in SAS Version 9.1 or higher

Table 15.1.1: Subject Disposition
All Screened Analysis Set

HRG High

Subject Accounting	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Screened			
Screened, But Not Randomized			xxx [a]
Randomized			
Randomized but Not Dosed	xxx (xx.x)	xxx (x.x)	xxx (xx.x)
Analysis Set			
Full Analysis Set (Intent to Treat Set)[b]	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Safety Analysis Set	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Per-Protocol Analysis Set	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
PK Analysis Set	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
FACT-H&N Analysis Set	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
EQ-5D Analysis Set	xxx (xxx)	xxx (xxx.x)	xxx (xxx.x)
Treatment Status			
Ongoing on the Study Treatment	xx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Discontinued from Study Treatment	xxx xx.x)	xxx (xxx.x)	xxx (xxx.x)
Primary Reason for Discontinuation from Study Treatment			
Adverse Event	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Progressive Disease per RECIST	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Clinical Progression	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Lost to Follow-up	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Death	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Protocol Violation	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Withdrawal by subject	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Study Terminated by Sponsor	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Other	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Notes: Percentages are based on the number of subjects in the Full Analysis Set.
[a] Subjects who had signed ICF and were screened but not randomized are not included in the total number of Full Analysis Set.
[b] The full analysis set (FAS) will be based on the intent-to-treat principle and will include all subjects randomized into the study.
[c] On-study Death is defined as death occurred on or after first dose date till 21 days after last dose date of any study drug.
Source Data: adam.adsl; Listing 16.2.1.1

Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.1: Subject Disposition
All Screened Analysis Set

HRG High

Subject Accounting	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Extension Treatment Status			
Ongoing on the Study Treatment	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Discontinued from Study Treatment	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Primary Reason for Discontinuation from Study Treatment			
Adverse Event	xxx (xxx.x)	xxx (xxx)	xxx (xxx.x)
Clinical Progression	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Lost to Follow-up	xxx (xxx.x)	xxx (xxx x)	xxx (xxx.x)
Death	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Protocol Violation	xxx (xxx.x)	x (xxx.x)	xxx (xxx.x)
Withdrawal by subject	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Study Terminated by Sponsor	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Progressive Disease per RECIST	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Other	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
On-Study Death [c]	xxx (xxx.x	xxx (xxx.x)	xxx (xxx.x)
Primary cause of On-Study Death			
Adverse Event	xx (x x x)	xxx (xxx.x)	xxx (xxx.x)
Disease Progression	xx (xxx x)	xxx (xxx.x)	xxx (xxx.x)
Unknown	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Other	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Notes: Percentages are based on the number of subjects in the Full Analysis Set.
[a]: Subjects who had signed ICF and were screened but not randomized are not included in the total number of Full Analysis Set.
[b] The full analysis set (FAS) will be based on the intent-to-treat principle and will comprise all subjects randomized into the study.
[c] On-study Death is defined as death occurred on or after first dose date till 21 days after last dose date of any study drug.
Source Data: adam.adsl; Listing 16.2.1.1
Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.2.1: Demographic and Baseline Characteristics
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Age (yrs) [a]			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
<=65	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>65	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gender			
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<=65			
>65			
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<=65			
>65			
Race			
White	xx (xx. %)	xx (xx.x%)	xx (xx.x%)
Black or African American	(xx.x%)	xx (xx.x%)	xx (xx.x%)
Asian	xx (x.x%)	xx (xx.x%)	xx (xx.x%)
American Indian or Alaskan Native	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Native Hawaiian/Pacific Islander	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other/Specify	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Denominator for percentages is the number of subjects in the Full Analysis Set.
The baseline value is defined as the last non-missing value before initial administration of study treatment.
[a] Age in years is calculated using the informed consent date and the birth date.
Source Data: adam.adsl; Listing 16.2.4.1, 16.2.4.4.1, 16.2.4.4.2, 16.2.4.4.3, 16.2.4.4.4, 16.2.4.6, 16.2.8.3.2, 16.2.8.3.4, 16.2.8.4.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.2.1: Demographic and Baseline Characteristics
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Height (cm)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Weight (kg)			
n	xx	xx	xx
Mean	xx.x	x x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Histology			
Squamous	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (x x%)	xx (xx.x%)	xx (xx.x%)
Histologic Grade			
Well Differentiated	xx (x.x%)	xx (xx.x%)	xx (xx.x%)
Moderately Differentiated	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Poorly Differentiated	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Undifferentiated	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not applicable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Denominator for percentages is the number of subjects in the Full Analysis Set.
The baseline value is defined as the last non-missing value before initial administration of study treatment.
[a] Age in years is calculated using the informed consent date and the birth date.
Source Data: adam.adsl; Listing 16.2.4.1, 16.2.4.4.1, 16.2.4.4.2, 16.2.4.4.3, 16.2.4.4.4, 16.2.4.6, 16.2.8.3.2, 16.2.8.3.4, 16.2.8.4.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.2.1: Demographic and Baseline Characteristics
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Tumor Staging at Study Entry			
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
I	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
IIA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
IIB	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
III	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
IVA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
IVB	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
IVC	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Time from Initial Diagnosis of SCCHN to Study Treatment (month) [b]			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
<6 months	xx xx.x%)	xx (xx.x%)	xx (xx.x%)
6-12 months	xx (xx x%)	xx (xx.x%)	xx (xx.x%)
>12 months	xx (xx.x%	xx (xx.x%)	xx (xx.x%)
Cancer Type			
Oral Cavity	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Oropharynx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hypopharynx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Larynx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Denominator for percentages is the number of subjects in the Full Analysis Set.
The baseline value is defined as the last non-missing value before initial administration of study treatment.
[a] Age in years is calculated using the informed consent date and the birth date.
[b] For the partial Initial Diagnosis of SCCHN date, if the month and year are present and the day is missing, then set day to the 1st day of month.
Source Data: adam.adsl; Listing 16.2.4.1, 16.2.4.4.1, 16.2.4.4.2, 16.2.4.4.3, 16.2.4.4.4, 16.2.4.6, 16.2.8.3.2, 16.2.8.3.4, 16.2.8.4.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.2.1: Demographic and Baseline Characteristics
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Cigarette Use			
Current	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Former	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Never	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Duration of Cigarette (years)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Cigar Use			
Current	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Former	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Never	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Duration of Cigar (years)			
n	x	xx	xx
Mean	xx.x	xx.x	xx.x
SD	x.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx

Notes: Denominator for percentages is the number of subjects in the Full Analysis Set.
The baseline value is defined as the last non-missing value before initial administration of study treatment.
[a] Age in years is calculated using the informed consent date and the birth date.
[b] For the partial Initial Diagnosis of SCCHN date, if the month and year are present and the day is missing, then set day to the 1st day of month.
Source Data: adam.adsl; Listing 16.2.4.1, 16.2.4.4.1, 16.2.4.4.2, 16.2.4.4.3, 16.2.4.4.4, 16.2.4.6, 16.2.8.3.2, 16.2.8.3.4, 16.2.8.4.2.

Table 15.1.2.1: Demographic and Baseline Characteristics
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Prior Systemic Cancer Therapy			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Best Response to Prior Systemic Cancer Therapy			
CR	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PR	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SD	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PD	xx (xx.x%)	xx (x.x%)	xx (xx.x%)
Not Applicable	xx (xx.x%)	xx (xx %)	xx (xx.x%)
Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Prior Radiation Therapy			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Baseline ECOG Performance Status			
0 - Fully Active	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1 - Restricted in Physically Strenuous Activity	xx (x.x%)	xx (xx.x%)	xx (xx.x%)
2 - Ambulatory and Capable of All Self-Care	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Capable of Only Limited Self Care	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Completely Disabled	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Denominator for percentages is the number of subjects in the Safety Analysis Set.
The baseline value is defined as the last non-missing value before initial administration of study treatment.
[a] Age in years is calculated using the informed consent date and the birth date.
Source Data: adam.adsl; Listing 16.2.4.1, 16.2.4.4.1, 16.2.4.4.2, 16.2.4.4.3, 16.2.4.4.4, 16.2.4.6, 16.2.8.3.2, 16.2.8.3.4, 16.2.8.4.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.2.1: Demographic and Baseline Characteristics
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Baseline 12-Lead ECG			
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Not Clinically Significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Clinically Significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Performed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Heregulin (HRG)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.x	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx

Notes: Denominator for percentages is the number of subjects in the Safety Analysis Set
The baseline value is defined as the last non-missing value before in al administration of study treatment.
[a] Age in years is calculated using the informed consent date a d the irth date.
Source Data: adam.adsl; Listing 16.2.4.1, 16.2.4.4.1, 16.2.4.4.2, 16 2 4.4.3, 16.2 4.4.4, 16.2.4.6, 16.2.8.3.2, 16.2.8.3.4, 16.2.8.4.2.
Programming Note: continue for HRG Low and Overall on the next page

Programming note: Present 'Missing' as a category if here is at least one subject in a row.

Using the table shell of 15.1.2.1 for following 3 tables:

Table 15.1.2.2: Demographic and Baseline Characteristics
Per Protocol Analysis Set

Change first line footnote to: Denominator for percentages is the number of subjects in Per Protocol Analysis Set

Table 15.1.2.3: Demographic and Baseline Characteristics
Safety Analysis Set

Change first line footnote to: Denominator for percentages is the number of subjects in Safety Analysis Set

Daiichi Sankyo Pharma Development
Protocol U31278-A-U203
<Run Type> (Data Cut Date: DDMMMYYYY; Data Extraction Date: DDMMMYYY)

Table 15.1.3: Study Drug Exposure
Safety Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin				Placebo + cetuximab + cisplatin or carboplatin			
	Patritumab (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)	Placebo (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)
Treatment Duration (weeks)								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Treatment Duration (cycles)								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx. xx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Number of IVs Received per Subject								
n	xx	xx	x	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	x.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.x	xx.x	x x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Number of Subjects with <5 IVs	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Subjects with 5 - <10 IVs	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Subjects with 10 - <15 IVs	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Subjects with 15 - <20 IVs	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Subjects with >20 IVs	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: For Patritumab, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/21.
For Cetuximab, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 7)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 7)/21.
For Carboplatin or Cisplatin, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/21.
[a] Refer to SAP Section 8.3.6 for definitions for Cumulative Dose Received per Subject, Dose Intensity, and Relative Dose Intensity, and Cycle Duration..

Source Data: adam.adex, adam.adda; Listing 16.2.5.1.1, 16.2.5.1.3.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.3: Study Drug Exposure
Safety Analysis Set

HRG High

	Patritumab+ cetuximab + cisplatin or carboplatin				Placebo + cetuximab + cisplatin or carboplatin			
	Patritumab (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)	Placebo (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)
Cumulative Dose Received per Subject (mg) [a]								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.x	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.x	xx.x	xx.x	xx.x	x.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Cumulative Dose Received per Subject (mg/kg)								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	x	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	Xx
Dose Intensity (mg/kg/cycle/dose) [a]								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx xx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	xx

Notes: For Patritumab, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/21.
For Cetuximab, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 7)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 7)/21.
For Carboplatin or Cisplatin, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/21.
[a] Refer to SAP Section 8.3.6 for definitions for Cumulative Dose Received per Subject, Dose Intensity, and Relative Dose Intensity, and Cycle Duration..

Source Data: adam.adex; Listing 16.2.5.1.1, 16.2.5.1.2, 16.2.5.1.3.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.1.3: Study Drug Exposure
Safety Analysis Set

Overall

	Patritumab+ cetuximab + cisplatin or carboplatin				Placebo + cetuximab + cisplatin or carboplatin			
	Patritumab (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)	Placebo (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)
Relative Dose Intensity (%) [a]								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx. xx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.x	xx.x	xx.x	xx.x	xx x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Cycle Duration (Days)								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx. x	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.x	xx.x	xx.x	x.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	Xx
Cycles Delayed								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	x	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	xx

Notes: For Patritumab, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/21.
For Cetuximab, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 7)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 7)/21.
For Carboplatin or Cisplatin, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/21.
[a] Refer to SAP Section 8.3.6 for definitions for Cumulative Dose Received per Subject, Dose Intensity, and Relative Dose Intensity, and Cycle Duration..

Source Data: adam.adex; Listing 16.2.5.1.1, 16.2.5.1.2, 16.2.5.1.3.

Table 15.1.3: Study Drug Exposure
Safety Analysis Set

Overall

	Patritumab+ cetuximab + cisplatin or carboplatin				Placebo + cetuximab + cisplatin or carboplatin			
	Patritumab (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)	Placebo (N=xxx)	Cetuximab (N=xxx)	Carboplatin (N=xxx)	Cisplatin (N=xxx)
Cycles Delayed								
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>=2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Dose Reductions								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.x	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	x	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx	xx	Xx
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>=2	xx (xx.x%)	xx (xx.x%)	xx (x.x%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: For Patritumab, treatment duration (in weeks) is calculated as (date of th last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/2 .
For Cetuximab, treatment duration (in weeks) is calcu ated as (date of the last dose – date of the first dose + 7)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first do + 7)/21.
For Carboplatin or Cisplatin, treatment duration (in weeks) is calculated as (date of the last dose – date of the first dose + 21)/7. Treatment duration (in cycles) is calculated as (date of the last dose – date of the first dose + 21)/21.
[a] Refer to SAP Section 8.3.6 for definitions for Cumulative Dose Received per Subject, Dose Intensity, and Relative Dose Intensity, and Cycle Duration..

Source Data: adam.adex; Listing 16.2.5.1.1, 16.2.5.1.2, 16.2.5.1.3.

Table 15.1.4.1: Prior Medications by ATC Class and Preferred Term
Safety Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Subjects with any Prior Medications	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC 2 Class x	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (x.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx x)	xx (xx.x)
Preferred Term 3	xx (xx.x)	x (xx.x)	xx (xx.x)
Preferred Term n	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC 2 Class y	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term n	xx (xx x)	xx (xx.x)	xx (xx.x)
ATC 2 Class z	xx (x.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term n	x (xx.x)	xx (xx.x)	xx (xx.x)

Notes: Denominator for percentages is the number of subjects in the Safety Analysis Set.
Medications taken prior to the first dose of study medication will be classified as prior medications.
Subjects may have more than one medication per ATC classification and preferred term. At each level of subject summarization, a subject was counted once if he/she reported one or more medications.
Medications were coded using the WHO Drug Dictionary (Version XXX).

Source Data: adam.adcm; Listing 16.2.4.5
Programming Note: continue for HRG Low and Overall on the next page

Use tables shell of 15.1.6.1 to generate 15.16.2:

Table 15.1.4.2: Concomitant Medications by ATC Class and Preferred Term
Safety Analysis Set

Programming note: Replace the second sentence with “Medications taken on or after the first dose of study medication will be classified as concomitant medications”.
First row should state ‘Subjects with any Concomitant Medications’

Table 15.2.1.1: Analysis of Progression Free Survival (PFS)
Full Analysis Set

HRG High

Statistics	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	
Subject (%) with Events	xx (xx.x%)	xx (xx.x%)	
Subject (%) without Events (Censored)	xx (xx.x%)	xx (xx.x%)	
Median PFS (months) [a]	xx.x	xx.x	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
Stratified Log-rank p-value [b]			0.xxxx
Log-rank p-value (Unstratified) [c]			0.xxxx
Stratified Cox Regression Analysis [b]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx
Unstratified Cox Regression Analysis [c]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx
PFS Rate at 3 Months [d]	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 6 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 9 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 12 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases.
[a] Median PFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.
[b] Stratified log-rank test adjusted for stratification factors: HRG (high vs low; overall only) and HPV (positive vs other) at randomization.
[c] Log-rank test did not adjust for stratification factors.
[d] Estimate and CI for PFS rate at the specified timepoint are from Kaplan-Meier analysis.

Source Data: adam.adtte; Listing 16.2.6.1
Programming Note: continue for HRG Low and Overall on the next page

Programming note: If insufficient #'s of subject progress then certain proportions are not estimable and the estimate and corresponding confidence interval will be omitted.

Use table shell of 15.2.1.1 to generate following tables:

Table 15.2.1.2**:** Analysis of Progression Free Survival (PFS)
Per Protocol Analysis Set

Table 15.2.1.3: Subgroup Analysis of Progression Free Survival (PFS)
Full Analysis Set

Overall

Subgroup/ Statistic	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	
Age			
<65			
Median PFS (months) [a]	xx.x	xx.x	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
Hazard Ratio (relative to Placebo)[b]			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx
>=65			
Median PFS (months) [a]	xx.x	xx.x	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
Hazard Ratio (relative to Placebo)[b]			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx
Sex			
Female			
Median PFS (months) [a]	xx.x	xx.x	
95% CI	x.x; xx.x]	[xx.x; xx.x]	
Hazard Ratio (relative to Placebo)[b]			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx
Male			
Median PFS (months) [a]	xx.x	xx.x	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
Hazard Ratio (relative to Placebo)[b]			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases.
[a] Median PFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.
[b] Log-rank test did not adjust for stratification factors.

Source Data: adam.adtte; Listing 16.2.6.1
Programming note: Continue for subgroups in Section 8.2.4.2 of SAP.

Table 15.2.1.4: Analysis of Progression Free Survival (PFS) for Different HRG Cutoffs
Full Analysis Set

HRG Cutoff: HRG >= XX.XX

Statistics	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	
Subject (%) with Events	xx (xx.x%)	xx (xx.x%)	
Subject (%) without Events (Censored)	xx (xx.x%)	xx (xx.x%)	
Median PFS (months) [a]	xx.x	xx.x	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
Stratified Cox Regression Analysis [b]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
80% CI for Hazard Ratio			[x.xxxx, x.xxxx]
Unstratified Cox Regression Analysis [c]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
80% CI for Hazard Ratio			[x.xxxx, x.xxxx]
PFS Rate at 3 Months [d]	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 6 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 9 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 12 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases.
[a] Median PFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.
[b] Stratified Cox PH regression adjusted for stratification factors: HPV (positive vs other) and HRG (high vs. low, only for the FAS) at randomization.
[c] Cox PH regression did not adjust for stratification factors.
[d] Estimate and CI for PFS rate at the specified timepoint are from Kaplan-Meier analysis.

Programming note: If insufficient #'s of subject progress then certain proportions are not estimable and the estimate and corresponding confidence interval will be omitted.
Programming Note: continue for different HRG Cutoff

Table 15.2.2.1: Analysis of Overall Survival (OS)
Full Analysis Set

HRG High

Statistics	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	
Subject (%) with Events	xx (xx.x%)	xx (xx.x%)	
Subject (%) without Events (Censored)	xx (xx.x%)	xx (xx.x%)	
Median PFS (months) [a]	xx.x	xx.x	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
Stratified Log-rank p-value [b]			0.xxxx
Log-rank p-value (Unstratified) [c]			0.xxxx
Stratified Cox Regression Analysis [b]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx
Unstratified Cox Regression Analysis [c]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
p-value for hazard ratio equal to one			0.xxxx
PFS Rate at 3 Months [d]	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 6 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 9 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 12 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases.
[a] OS is defined as the time from the date of randomization to death due to any cause.
[b] Stratified log-rank test adjusted for stratification factors: HPV (positive vs other) at randomization.
[c] Log-rank test did not adjust for stratification factors.
[d] Estimate and CI for OS rate at the specified timepoint are from Kaplan-Meier analysis.

Source Data: adam.adtte; Listing 16.2.6.1
Programming Note: continue for HRG Low and Overall on the next page

Use table shell of 15.2.2.1 to generate following tables:

Table 15.2.2.2 Analysis of Overall Survival (OS)
Per Protocol Analysis Set

Change the first line of footnote to: OS is defined as the time from the date of randomization to death due to any cause.
Change the PFS in table and footnotes to OS.

Use table shell of 15.2.1.3 to generate following tables:

Table 15.2.1.3: Subgroup Analysis of Overall Surviva (OS)
Full Analysis Set

Change the first line of footnote to: OS is defined as the time from the date of randomization to death due to any cause.
Change the PFS in table and footnotes to OS.

Table 15.2.2.3: Analysis of Overall Survival (OS) for Different HRG Cutoffs
Full Analysis Set

HRG Cutoff: HRG <= XX.XX

Statistics	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	
Subject (%) with Events	xx (xx.x%)	xx (xx.x%)	
Subject (%) without Events (Censored)	xx (xx.x%)	xx (xx.x%)	
Median PFS (months) [a]	xx.x	xx.x	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
Stratified Cox Regression Analysis [b]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
80% CI for Hazard Ratio			[x.xxxx, x.xxxx]
Unstratified Cox Regression Analysis [c]			
Hazard Ratio (relative to Placebo)			x.xxxx
95% CI for Hazard Ratio			[x.xxxx, x.xxxx]
80% CI for Hazard Ratio			[x.xxxx, x.xxxx]
PFS Rate at 3 Months [d]	xx.x%	xx.x%	
95% CI	x.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 6 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 9 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	
PFS Rate at 12 Months	xx.x%	xx.x%	
95% CI	[xx.x; xx.x]	[xx.x; xx.x]	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See the SAP for the handling of censored cases.
[a] OS is defined as the time from the date of randomization to death due to any cause..
[b] Stratified Cox PH regression adjusted for stratification factors: HPV (positive vs other) at randomization.
[c] Cox PH regression did not adjust for stratification factors.
[d] Estimate and CI for OS rate at the specified timepoint are from Kaplan-Meier analysis.

Programming note: If insufficient #'s of subject progress then certain proportions are not estimable and the estimate and corresponding confidence interval will be omitted.
Programming Note: continue for different HRG Cutoff

Table 15.2.3.1: Best Overall Tumor Response and Objective Response Rate (ORR)
Full Analysis Set

HRG High

Subjects with measurable disease	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	
Subject with Measurable Disease at Baseline, n (%)	xx (xx.x)	xx (xx.x)	
Objective Response (CR, PR)			
n (%)	xx (xx.x%)	xx (xx.x%)	
95% CI [a]	[xx.x; xx.x]	[xx. ; xx x]	
Between-arm difference (relative to placebo)			
95% CI [b]			[xx.x; xx.x]
80% CI [b]			[xx.x; xx.x]
Complete Response (CR)			
n (%)	xx (xx.x%)	xx (xx.x%)	
95% CI [a]	[xx.x; x x]	[xx.x; xx.x]	
Partial Response (PR)			
n (%)	xx (xx.x)	xx (xx.x%)	
95% CI [a]	[xx.x; xx.x]	[xx.x; xx.x]	95% CI [a]
Stable Disease (SD)			
n (%)	xx (xx.x%)	xx (xx.x%)	
95% CI [a]	[xx.x; xx.x]	[xx.x; xx.x]	
Progressive Disease (PD)			
n (%)	xx (xx.x%)	xx (xx.x%)	
95% CI [a]	[xx.x; xx.x]	[xx.x; xx.x]	
Inevaluable			
n (%)	xx (xx.x%)	xx (xx.x%)	

Note: Denominator for percentages is the number of subjects with measurable disease.
The best overall response is the best response (in the order of CR, PR, SD, and PD) among all overall responses recorded from the start of treatment until the subject withdraws from the study. If there is no post-baseline tumor assessment or all post-baseline tumor assessments with overall response of Inevaluable captured in the CRF, the best overall response is classified as Inevaluable.
[a] Based on Wilson's score method for single proportion with continuity correction.
[b] Based on Wilson's score method for the difference of two proportions with continuity correction.

Source Data: adam.adrs; Appendices 16.2.6.1.3, 16.2.6.3
Programming Note: continue for HRG Low and Overall on the next page

The following table follows Table 15.2.3.1:

Table 15.2.3.2 Best Overall Tumor Response and Objective Response Rate (ORR)
Per Protocol Analysis Set

Programming Note: continue for different HRG Cutoff.

Table 15.2.4: Duration of Objective Response/Stable Disease and Time to Response/Disease Progression in Months
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)
Duration of Objective Response [a]		
Subjects with Objective Response	xx	xx
n. (%) subjects with radiographic disease progression	xx (xx.x%)	xx (xx.x%)
Median	xx.xx	xx.xx
95% CI for Median	[xx.xx, xx.xx]	[xx.xx, xx.xx]
80% CI for Median	[xx.xx, xx.xx]	[xx.xx, xx.xx]
1st Quantile	xx.xx	xx.xx
3rd Quantile	xx.xx	xx.xx
Min, Max	xx.x xx.x*	xx.x*, xx.x
Duration of Stable Disease [a]		
Subjects with Stable Disease	xx	xx
n (%) subjects with radiographic disease progression	xx (xx.x%)	xx (xx.x%)
Median	xx.xx	xx.xx
95% CI for Median	[xx.xx, xx.xx]	[xx.xx, xx.xx]
80% CI for Median	[xx.xx, xx.xx]	[xx.xx, xx.xx]
1st Quantile	xx.xx	xx.xx
3rd Quantile	xx.xx	xx.xx
Min, Max	xx.x, xx.x*	xx.x*, xx.x

Notes:
Duration of objective response is defined for subjects with CR/PR as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of progressive disease.
Duration of SD is defined for subjects whose best response is SD as the time from the randomization date to the date of the first documentation of progressive disease.
Time to response is defined as the time from the randomization date to the date of the first documentation of objective response (CR or PR).
Time to disease progression is defined as the time from the randomization date to the date of first objective documentation of disease progression.
See the SAP for the handling of censored cases.
[a] Median, 1st and 3rd quantiles are from Kaplan-Meier Estimate. CI for median was computed using the Brookmeyer-Crowley method. Minimum and maximum include the censored observations where using "+" after value indicates censoring.

Source Data: adam.adtte; Listing 16.2.6.2, 16.2.6.3
Programming Note: continue for HRG Low and Overall on the next page

Table 15.2.4.: Duration of Objective Response/Stable Disease and Time to Response/Disease Progression in Weeks
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)
Time to Response [a]		
n. (%) subjects with objective response	xx (xx.x%)	xx (xx.x%)
Median	xx.xx	xx.xx
95% CI for Median	[xx.xx, xx.xx]	[xx.xx, xx.xx]
80% CI for Median	[xx.xx, xx.xx]	[xx.xx, xx.xx]
1st Quantile	xx.xx	xx.xx
3rd Quantile	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x
Time to Disease Progression [a]		
n. (%) subjects with radiographic disease progression	xx (x.x%)	xx (xx.x%)
Median	xx.xx	xx.xx
95% CI for Median	[x xx, xx.xx]	[xx.xx, xx.xx]
80% CI for Median	[xx.xx, xx.xx]	[xx.xx, xx.xx]
1st Quantile	xx.xx	xx.xx
3rd Quantile	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x

Notes
Duration of objective response is defined for subjects with CR/PR as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of progressive disease.
Duration of SD is defined for subjects whose best response is SD as the time from the randomization date to the date of the first documentation of progressive disease.
Time to response is defined as the time from the randomization date to the date of the first documentation of objective response (CR or PR).
Time to disease progression is defined as the time from the randomization date to the date of first objective documentation of disease progression.
See the SAP for the handling of censored cases.
[a] Median, 1st and 3rd quantiles are from Kaplan-Meier Estimate. CI for median was computed using the Brookmeyer-Crowley method. Minimum and maximum include the censored observations where using "+" after value indicates censoring.

Source Data: adam.adtte; Listing 16.2.6.2, 16.2.6.3
Programming Note: continue for HRG Low and Overall on the next page

Table 15.2.5: Summary of Change and the Percent Change from Baseline in the Sum of Longest Diameters (mm) of Target Lesions
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N-xxx)			Placebo + cetuximab + cisplatin or carboplatin (N=xxx)		
Visit	Result (mm)	Change (mm)	% Change	Result	Change	% Change
Baseline						
n	xx			xx		
Mean	xx.x			xx.x		
SD	xx.xx			xx.xx		
Median	xx.x			xx.x		
Minimum	xx.			xx.		
Maximum	xx			xx		
Week X						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.	xx	xx.	xx.	xx.	xx.
Maximum	xx	xx	xx	xx	xx	xx

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. Time points with data from fewer than 5 subjects overall are not summarized. Repeated or unscheduled tests are not summarized for each scheduled visit, but are included for summaries of minimum post -baseline values.

Source Data: adam.adrs; Listing 16.2.6.1.3

Programming Note: continue for HRG Low and Overall on the next page

Table 15.2.5: Summary of Change and the Percent Change from Baseline in the Sum of Longest Diameters (mm) of Target Lesions
Full Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N-xxx)			Placebo + cetuximab + cisplatin or carboplatin (N=xxx)		
Visit	Result (mm)	Change (mm)	% Change	Result	Change	% Change
Week N						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.	xx.	xx	xx.	xx.	xx.
Maximum	xx	xx	xx	xx	xx	xx
Minimum Post-baseline Value (Nadir)						
n	xx		xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.	xx.	xx.	xx.	xx.	xx.
Maximum	xx	xx	xx	xx	xx	xx

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. Time points with data from fewer than 5 subjects overall are not summarized. Repeated or unscheduled tests are not summarized for each scheduled visit, but are included for summaries of minimum post-baseline values.
Source Data: adam.adrs; Listing 16.2.6.1.3
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.1.1: Overview of Number (%) of Subjects Reporting Treatment-Emergent Adverse Events
Safety Analysis Set

HRG High

	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Treatment-Emergent Adverse Events (TEAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Worst CTCAE Grade			
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing			
TEAE Related to Patritumab	xx (xx.x%)	xx (x x%)	xx (xx.x%)
Worst CTCAE Grade			
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…..	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE Related to Cetuximab	xx (xx x%)	xx (xx.x%)	xx (xx.x%)
Worst CTCAE Grade			
5	xx (xx.x%	xx (xx.x%)	xx (xx.x%)
4	xx (x x%)	xx (xx.x%)	xx (xx.x%)
...			
>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE Related to Cisplatin			
Worst CTCAE Grade			
…			
TEAE Related to Carboplatin			
Worst CTCAE Grade			
…			

Notes: In the presence of a subject who has both missing and non-missing CTCAE grades for adverse events, the missing CTCAE grade of the adverse event is treated as the lowest severity grade.
Adverse events were coded using the MedDRA dictionary, Version XXX.

Source Data: adam.adae; Listing 16.2.7.2.
Programming Note: continue for HRG Low and Overall on the next page

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Table 15.3.1.1: Overview of Number (%) of Subjects Reporting Treatment-Emergent Adverse Events
Safety Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Treatment-Emergent SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Worst CTCAE Grade			
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing			
Treatment-Emergent SAE Related to Patritumab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Worst CTCAE Grade			
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
...			
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment-Emergent SAE Related to Cetuximab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Worst CTCAE Grade			
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (x.x%)	xx (xx.x%)	xx (xx.x%)
...			
>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment-Emergent SAE Related to Cisplatin			
Worst CTCAE Grade			
…			
Treatment-Emergent SAE Related to Carboplatin			
Worst CTCAE Grade			
…			

Notes: In the presence of a subject who has both missing and non-missing CTCAE grades for adverse events, the missing CTCAE grade of the adverse event is treated as the lowest severity grade.
Adverse events were coded using the MedDRA dictionary, Version XXX.
Source Data: adam.adae; Listing 16.2.7.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.1.1: Overview of Number (%) of Subjects Reporting Treatment-Emergent Adverse Events
Safety Analysis Set

HRG High

	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Discontinued Patritumab Due to TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cetuximab Due to TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cisplatin Due to TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Carboplatin Due to TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Patritumab Interruption	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Patritumab Interruptio Related to Patritumab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Patritumab Dose Reduction	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Patritumab Dose Reduction Related to Patritumab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Patritumab Due to TEAE Related to Patritumab	x (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cetuximab Due to TEAE Related to Cetuximab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cisplatin Due to TEAE Related to Cisplatin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Carboplatin Due to TEAE Related to Carboplatin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Patritumab Due to Treatment Emergent SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cetuximab Due to Treatment Emergent SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cisplatin Due to Treatment Emergent SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Carboplatin Due to Treatment Emergent SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: In the presence of a subject who has both missing and non-missing CTCAE grades for adverse events, the missing CTCAE grade of the adverse event is treated as the lowest severity grade.
Adverse events were coded using the MedDRA dictionary, Version XXX.
Source Data: adam.adae; Listing 16.2.7.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.1.1: Overview of Number (%) of Subjects Reporting Treatment-Emergent Adverse Events
Safety Analysis Set

HRG High

	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Discontinued Patritumab Due to Treatment Emergent SAE Related to Patritumab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cetuximab Due to Treatment Emergent SAE Related to Cetuximab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Cisplatin Due to Treatment Emergent SAE Related to Cisplatin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Carboplatin Due to Treatment Emergent SAE Related to Carboplatin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Death Related to Patritumab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Death Related to Cetuximab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Death Related to Cisplatin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE leading to Death Related to Carboplatin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: In the presence of a subject who has both missing and non-m ssing CTCAE grades for adverse events, the missing CTCAE grade of the adverse event is treated as the lowest severity grade.
Adverse events were coded using the MedDRA dict onar Versio XXX.

Source Data: adam.adae; Listing 16.2.7.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.1.2: Number and Percentage of Subjects with Treatment-emergent Adverse Events Summarized by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

HRG High

System Organ Class	Preferred Term	Worst CTCAE Grade	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx) n (%)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx) n (%)	Total (N=xxx) n (%)
Subjects with any TEAEs		Any Grade	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		5	xx (xx.x%)	xx (x x%)	xx (xx.x%)
		4	xx (xx.x%)	xx (xx %)	xx (xx.x%)
		3	xx (xx.x%)	xx (xx.x)	xx (xx.x%)
		2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		1	xx (xx.x%)	xx (x x%)	xx (xx.x%)
		>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #1	Any Preferred Term	Any Grade	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		3	xx (x x%)	xx (xx.x%)	xx (xx.x%)
		2	xx (xx. %)	xx (xx.x%)	xx (xx.x%)
		1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Missing	x (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: In the presence of a subject who has both missing and non-mis ing CTCAE grades for adverse events with the same preferred term, the missing CTCAE grade of the adverse event is treated as the lowes sever y grade.
Subjects may have more than one event per system organ class and preferred term. At each level of subject summarization, a subject was counted once if he/she reported one or more adverse events.
Adverse events were coded using the MedDRA dictionary, Version XXX.
Source Data: adam.adae; Listing 16.2.7.2.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.1.2: Number and Percentage of Subjects with Treatment-emergent Adverse Events Summarized by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

HRG High

System Organ Class	Preferred Term	Worst CTCAE Grade	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx) n (%)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx) n (%)	Total (N=xxx) n (%)
System Organ Class #1	Preferred Term #1	Any Grade	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		5	xx (xx.x%)	xx (x x%)	xx (xx.x%)
		4	xx (xx.x%)	xx (xx. %)	xx (xx.x%)
		3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		2	xx (xx.x%)	xx (x.x%)	xx (xx.x%)
		1	xx (xx.x%)	x (xx x%)	xx (xx.x%)
		>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #1	Preferred Term N	Any Grade	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		5	xx (xx x%)	xx (xx.x%)	xx (xx.x%)
		4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		3	xx (x x%)	xx (xx.x%)	xx (xx.x%)
		2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		1	xx (x.x%)	xx (xx.x%)	xx (xx.x%)
		>=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class N	Any Preferred Term Etc.				

Notes: In the presence of a subject who has both missing and non-missing CTCAE grades for adverse events with the same preferred term, the missing CTCAE grade of the adverse event is treated as the lowest severity grade.
Subjects may have more than one event per system organ class and preferred term. At each level of subject summarization, a subject was counted once if he/she reported one or more adverse events.
Adverse events were coded using the MedDRA dictionary, Version XXX.
Source Data: adam.adae; Listing 16.2.7.2.
Programming Note: continue for HRG Low and Overall on the next page

The following table follows 15.3.1.2:

Table 15.3.1.3: Number and Percentage of Subjects with Treatment-emergent Serious Adverse Events Summarized
by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any treatment emergent SAEs

Table 15.3.1.4: Number and Percentage of Subjects with Treatment-emergent Adverse Events Related to Patritumab/Placebo Summarized
by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any TEAEs related to Patritumab

Table 15.3.1.5: Number and Percentage of Subjects with Treatment-emerg t Adverse Events Related to Cetuximab Summarized
by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any TEAEs related to Cetuximab

Table 15.3.1.6: Number and Percentage of Subjects with reatment-emergent Adverse Events Related to Cisplatin/Carboplatin Summarized
by Worst CTCAE Grade System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any TEAEs related to Cisplatin/ Carbop atin

Table 15.3.1.7: Number and Percentage of Subjects with Treatment-emergent Serious Adverse Events Related to Patritumab/Placebo Summarized
by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any treatment emergent SAEs related to Patritumab

Table 15.3.1.8: Number and Percentage of Subjects with Treatment-emergent Serious Adverse Events Related to Cetuximab Summarized
by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any treatment emergent SAEs related to Cetuximab

Table 15.3.1.9: Number and Percentage of Subjects with Treatment-emergent Serious Adverse Events Related to Cisplatin/Carboplatin Summarized

by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any treatment emergent SAEs related to Cisplatin/Carboplatin

Table 15.3.1.10: Number and Percentage of Subjects with Adverse Events of Interest by Worst CTCAE Grade, System Organ Class, and Preferred Term
Safety Analysis Set

First Row: Subjects with any adverse events of interest

Table 15.3.4.1: Summary of Results and Change from Baseline in Laboratory Tests – Hematology
Safety Analysis Set

HRG High

Lab Test (units)	Patritumab+ cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Placebo + cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Total ____(N=xxx)_____	
Visit	Result	Change	Result	Change	Result	Change
Lab Test #1 (SI unit)						
Baseline						
n	xx		xx		xx	
Mean	xx.x		xx.x		xx.x	
SD	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Cycle X Day X						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	x	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx

Note: The baseline value is defined as the last non-missing value before initia administration of study treatment. Repeated or unscheduled tests are not summarized for each scheduled visit, but are included for summaries of last observation on trea en maximum and minimum post-baseline values. Last observation on treatment is defined as the last non-missing value on or prior to end of treatment duration + 7. Perce tages are b sed on the number of subjects meeting the defined criteria (m); the number of subjects with non-missing observations for the specified visit (n) is the denominator.
Source Data: adam.adlb; Listing 16.2.8.1.1

Programming Note: do not summarize Cycle 1 Day 1. Do not summarize coagulation parameters.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.4.1: Summary of Results and Change from Baseline in Laboratory Tests – Hematology
Safety Analysis Set

HRG High

Lab Test (units)	Patritumab+ cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Placebo + cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Total ____(N=xxx)_____	
Visit	Result	Change	Result	Change	Result	Change
Lab Test #1 (SI unit)						
End of Treatment						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
Last Observation on Treatment						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
Maximum Post-Baseline Value						
Minimum Post-Baseline Value						
Lab Test N….						

Note: The baseline value is defined as the last non-missing value before initial administration of study treatment. Repeated or unscheduled tests are not summarized for each scheduled visit, but are included for summaries of last observation on treatment, maximum and minimum post-baseline values. Last observation on treatment is defined as the last non-missing value on or prior to end of treatment duration + 7. Percentages are based on the number of subjects meeting the defined criteria (m); the number of subjects with non-missing observations for the specified visit (n) is the denominator.
Source Data: adam.adlb; Listing 16.2.8.1.1

Programming Note: do not summarize Cycle 1 Day 1. Do not summarize coagulation parameters.
Programming Note: continue for HRG Low and Overall on the next page

The following table follows Table 15.3.4.1:

Table 15.3.4.2: Summary of Results and Change from Baseline in Laboratory Tests - Chemistry
Safety Analysis Set

Source Data: adam.adlb; Listing 16.2.8.1.2

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Table 15.3.4.3: Shift Table of CTCAE Grade in Laboratory Tests – Hematology
Safety Analysis Set

HRG High

Condition (Unit) Treatment	Baseline CTCAE Grade	Worst Post-baseline CTCAE Grade: < 1 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	3 or 4 n (%)	Total n (%)	Missing n
Condition #1									
Patritumab+ cetuximab + cisplatin or carboplatin (n=xxx)		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	< 1								xx
	1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	x (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx xx x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	4	xx (xx.x%)	xx (xx.x%)	xx (xx x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	3 or 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx (xx x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Missing	xx	xx	xx	xx	xx	xx	xx	xx
Placebo + cetuximab + cisplatin or carboplatin (n=xxx)		xx (xx.x%)	xx (xx x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	< 1								xx
	1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	2	xx (xx.x%)	x (x .x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	4	xx (xx. %)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	3 or 4	x (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Missing	x	xx	xx	xx	xx	xx	xx	xx

Condition #2 . . . etc.

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment.
For each condition, percentages are based on the number of subjects in the Safety Analysis Set for each cohort with a baseline and at least one post-baseline assessment (that is, n in the first column). Subjects classified as missing have a missing test result.
Source Data: adam.ad b; Listing 16.2.8.1.1

Programming note: do not summarize coagulation parameters.
Programming Note: continue for HRG Low and Overall on the next page

The following table follows 15.3.4.3:

Table 15.3.4.4: Shift Table of CTCAE Grade in Laboratory Tests - Chemistry
Safety Analysis Set

Source Data: adam.adlb; Listing 16.2.8.1.2

Table 15.3.4.5: Number and Percentage of Subjects with Liver Enzymes (ALT, AST) and Total Bilirubin (TBL) Elevation
Safety Analysis Set

HRG High

Category	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Total (N=xxx)
Subjects with post-baseline AST			
AST >= 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 5 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 8 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 10 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 20 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with post-baseline ALT			
ALT >= 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT >= 5 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT >= 8 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT >= 10 x ULN	x (xx.x)	xx (xx.x)	xx (xx.x)
ALT >= 20 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with post-baseline AST or ALT			
AST >= 3 x ULN or ALT >= 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 5 x ULN or ALT >= 5 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 8 x ULN or ALT >= 8 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 10 x ULN or ALT >= 10 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 20 x ULN or ALT >= 20 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
TBL >= 2 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concurent TBL >= 2 x ULN and AST >= 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concurent TBL >= 2 x ULN and ALT >= 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concurent TBL >= 2 x ULN and AST or ALT >= 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concurent TBL >= 2 x ULN and AST or ALT >= 3 x ULN and ALP >= 2 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concurent TBL >= 2 x ULN and AST or ALT >= 3 x ULN and ALP <= 2 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: ULN = Upper limit of normal ranges.
Concurent is defined as at least one case of post-dose TBL >= 2 x ULN occurred between the first incidence date and 30 days after the last incidence date of the corresponding liver enzyme(s) >= 3 x ULN
Source Data: adam.adlb; Listing 16.2.8.1.1
Programming Note: continue for HRG Low and Overall on the next page

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Table 15.3.5: Summary of Vital Signs and Change from Baseline
Safety Analysis Set

HRG High

Vital Sign (units) / Visit	Patritumab+ cetuximab + cisplatin or carboplatin ____(N=xxx)_____ Result	Change	Placebo + cetuximab + cisplatin or carboplatin ____(N=xxx)_____ Result	Change	Total ____(N=xxx)_____ Result	Change
Systolic Blood Pressure (mmHg)						
Baseline						
n	xx		xx		xx	
Mean	xx.x		xx.x		xx.x	
SD	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Cycle 1 Day 1						
Pre-infusion						
n	xx		xx		xx	
Mean	xx.x		xx		xx.x	
SD	xx.xx		xx.xx		xx.xx	
Median	xx.x		x x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Post-infusion						
n	xx	xx	xx	xx	xx	xx
…						
Cycle N Day N						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. Repeated or unscheduled tests are not summarized for each scheduled visit, but are included for summaries of last observation on treatment, maximum and minimum post-baseline values. The End of Treatment value is based on the CRF visit. Last observation on treatment is defined as the last non-missing value on or prior to end of treatment duration + 7.

Source Data: adam.advs; Listing 16.2.8.3.1.
Programming note: continue table for Diastolic Blood Pressure, Pulse Rate,Temperature and Weight
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.5: Summary of Vital Signs and Change from Baseline
Safety Analysis Set

HRG High

Vital Sign (units) Visit	Patritumab+ cetuximab + cisplatin or carboplatin ____(N=xxx)_____ Result	Change	Placebo + cetuximab + cisplatin or carboplatin ____(N=xxx)_____ Result	Change	Total ____(N=xxx)_____ Result	Change
Systolic Blood Pressure (mm Hg)						
End of Treatment						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	x.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
Last Observation on Treatment						
n	xx	xx	xx	x	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
Maximum Post-baseline Value						
N	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	x.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
Minimum Post-baseline Value						

Lab Test N (SI unit)

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. Repeated or unscheduled tests are not summarized for each scheduled visit, but are included for summaries of last observation on treatment, maximum and minimum post-baseline values. The End of Treatment value is based on the CRF visit. Last observation on treatment is defined as the last non-missing value on or prior to end of treatment duration + 7.

Source Data: adam.advs; Listing 16.2.8.3.1.
Programming note: continue table for Diastolic Blood Pressure, Pulse Rate, Respiratory Rate, Body Temperature and Weight
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.6.1: Summary of 12-Lead ECG and Change from Baseline
Safety Analysis Set

HRG High

Parameter (units)	Patritumab+ cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Placebo + cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Total ____(N=xxx)_____	
Visit	Result	Change	Result	Change	Result	Change
Heart Rate (bpm)						
Baseline						
n	xx		xx		x	
Mean	xx.x		xx.x		xx.x	
SD	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
End of Treatment						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.x	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	x.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	x	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. The End of Treatment value is based on the CRF visit

Source Data: adam.adeg; Listing 16.2.8.3.2.
Programming note: continue with PR interval, RR interval, QRS duration, QT interval, QTcB, and QTcF
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.6.2: Summary of Subjects Meeting Pre-Specified QT and QTcB/QTcF Criteria
Safety Analysis Set

HRG High

Maximum Over All Post- Baseline Evaluations	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx) n (%)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx) n (%)	Total (N=xxx) n (%)
Subjects with at least one baseline and one post-baseline ECG evaluation	xx	xx	xx
QTcB			
New > 450 msec	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
New > 480 msec	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
New > 500 msec	xx (xx.x%)	xx (x x%)	xx (xx.x%)
Change from baseline >30 msec	xx (xx.x%)	xx xx.x%)	xx (xx.x%)
Change from baseline > 60 msec	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
QTcF			
New > 450 msec	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
New > 480 msec	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
New > 500 msec	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Change from baseline >30 msec	xx (x.x%)	xx (xx.x%)	xx (xx.x%)
Change from baseline > 60 msec	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. Percentages are based on the number of subjects in the Safety Analysis Set for each cohort with at least one baseline and one post-baseline ECG assessment. “New” means the category of the QTc abnormality was not present at baseline and became present at least one post-baseline ECG assessment.
Source Data: adam.adeg; Listing 16.2.8.3.2.
Programming Note: continue for HRG Low and Overall on the next page

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Table 15.3.7: Shift Table of ECOG Status
Safety Analysis Set

HRG High

Time Point / Treatment	Baseline ECOG PS	Post-Baseline ECOG PS 0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	Total n (%)	Missing n
Cycle 1 Day 1									
Patritumab+ cetuximab + cisplatin or carboplatin (n=xxx)		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	0								xx
	1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Missing	xx	xx	xx	xx	xx	xx	xx	xx
Placebo + cetuximab + cisplatin or Carboplatin (n=xxx)		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	0								xx
	1	xx (xx.x%)	xx (xx.x%)	xx (xx x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx
	Missing	xx	xx	xx	xx	xx	xx	xx	xx
Cycle x Day 1									
End of Treatment									
Last Observation on Treatment									
Maximum Post-baseline Value									
Minimum Post-baseline Value									
...									

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. For each test, percentages are based on the number of subjects in the Safety Analysis Set for each cohort with a baseline and at least one post-baseline ECOG assessment (that is, n in the first column).
Subjects classified as missing have a missing test result.
Source Data: adam.adqs; Listing 16.2.8.3.4.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.3.8: Summary of Left Ventricular Ejection Fraction (LVEF) Value and Change from Baseline
Safety Analysis Set

HRG High

Parameter (units)	Patritumab+ cetuximab + cisplatin or carboplatin (N=xxx)		Placebo + cetuximab + cisplatin or carboplatin (N=xxx)		Total (N=xxx)	
Visit	Result	Change	Result	Change	Result	Change
LVEF (%)						
Baseline						
n	xx		xx		xx	
Mean	xx.x		xx.x		xx.x	
SD	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Cycle X Day X						
n	xx	xx	x	xx	xx	xx
Mean	xx.x	xx.x	xx	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	x	xx	xx	xx	xx
Cycle N Day N						
End of Treatment						
Last Observation on Treatment						
Maximum Post-baseline Value						
Minimum Post-baseline Value						

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment. Repeated or unscheduled tests are not summarized for each scheduled visit, but are included for summaries of last observation on treatment, maximum and minimum post-baseline values. The End of Treatment value is based on the CRF visit. Last observation on treatment is defined as the last non-missing value on or prior to end of treatment period + 7.
Source Data: adam.adeg; Listing 16.2.8.3.5.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.1.1: Summary of Patritumab Concentration (ug/mL) from Sparse PK Sampling
Pharmacokinetic Analysis Set

HRG High

	Sample Times					
Treatment	C1D1 Pre-Infusion	C1D1 End of Infusion	C2D1 Pre-Infusion	C3D1 Pre-Infusion	C3D1 End of Infusion	End of Treatment
Patritumab+ cetuximab + cisplatin or carboplatin						
n	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
CV%	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SEM	xx	xx	xx	xx	xx	xx
Geom. Mean	xx	xx	xx	xx	xx	xx
Geom. CV%	xx	xx	xx	xx	xx	xx
Minimum	xx.xxx	xx.xxx	xx.xxx	x.xxx	xx.xxx	xx.xxx
1st Quartile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx
3rd Quartile	xx.xxx	xx.xxx	x xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx. xx	xx.xxx	xx.xxx	xx.xxx

Notes: Concentrations below the lower limit of quantitation (BLQ) are et to zero fo the calculation of descriptive statistics. If any concentration at a time point is BLQ, the geometric mean at that time po t is not c lculated and is presented as “NC”.
CxDx = Cycle x Day x
Source Data: adam.adpk; Listing 16.2.5.2.1.

Programming Note: List scheduled times as shown in table 8.1 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.1.2: Summary of Patritumab Concentration (ug/mL) from Intensive PK Sampling at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Sample Times						
Treatment	C1D1 Pre-Infusion	C1D1 End of Infusion	C1D1 3 Hours Post Infusion	C1D1 4 Hours Post Infusion	C1D1 5 Hours Post Infusion	C1D1 6 Hours Post Infusion	C1D1 7 Hours Post Infusion
Patritumab+ cetuximab + cisplatin or carboplatin							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx. xx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
CV%	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SEM	xx	xx	xx	xx	xx	xx	xx
Geom. Mean	xx	xx	xx	xx	xx	xx	xx
Geom. CV%	xx	xx	xx	xx	xx	xx	xx
Minimum	xx.xxx	xx.xxx	xx.xxx	x xxx	xx.xxx	xx.xxx	xx.xxx
1st Quartile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx x x	xx.xxx	xx.xxx	xx.xxx	xx.xxx
3rd Quartile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx

Notes: Concentrations below the lower limit of quantitation (BLQ) a set t zero for the calculation of descriptive statistics. If any concentration at a time point is BLQ, the geometric mean at that time point is not calculated and is presented as "NC".
CxDx = Cycle x Day x
Source Data: adam.adpk; Listing 16.2.5.2.1.

Programming Note: List scheduled times as shown in table 8.2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.1.2: Summary of Patritumab Concentration (ug/mL) from Intensive PK Sampling at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Sample Times				
Treatment	C1D2 24 Hours Post Infusion	C1D3 48 Hours Post Infusion	C1D8 168 Hours Post Infusion	C1D15 336 Hours Post Infusion	C1D21 504 Hours Post Infusion
Patritumab+ cetuximab + cisplatin or carboplatin					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx xxx	xx.xxx
CV%	xx.xxx	xx.xxx	xx.xxx	xx xx	xx.xxx
SEM	xx	xx	xx	xx	xx
Geom. Mean	xx	xx	xx	xx	xx
Geom. CV%	xx	xx	xx	xx	xx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
1st Quartile	xx.xxx	xx.xxx	xx.x x	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xx	xx.xxx	xx.xxx
3rd Quartile	xx.xxx	xx.xxx	x.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx

Notes: Concentrations below the lower limit of quantitation (BLQ) ar set to ero r the calculation of descriptive statistics. If any concentration at a time point is BLQ, the geometric mean at that time point is not alculated and is presented as "NC".
CxDx = Cycle x Day x
Source Data: adam.adpk; Listing 16.2.5.2.1.

Programming Note: List scheduled times as shown in table 8 2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.1.3: Summary of Cetuximab Concentration (ug/mL) from Intensive PK Sampling at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Sample Times					
Treatment	C1D1 Pre-Infusion	C1D1 End of Infusion	C1D1 4 Hours Post Infusion	C1D1 5 Hours Post Infusion	C1D1 6 Hours Post Infusion	C1D1 7 Hours Post Infusion
Patritumab + cetuximab + cisplatin or carboplatin						
N	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	x .xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx. xx	xx.xxx	xx.xxx
CV%	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SEM	xx	xx	xx	xx	xx	xx
Geom. Mean	xx	xx	xx	xx	xx	xx
Geom. CV%	xx	xx	xx	xx	xx	xx
Minimum	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx
1st Quartile	xx.xxx	xx.xxx	x.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	x .xxx	xx.xxx	xx.xxx	xx.xxx
3rd Quartile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Placebo + cetuximab + cisplatin or carboplatin						
N	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
…						

Continue above

Notes: Concentrations below the lower limit of quantitation (BLQ) are set to zero for the calculation of descriptive statistics. If any concentration at a time point is BLQ, the geometric mean at that time point is not calculated and is presented as "NC".
CxDx = Cycle x Day x
Source Data: adam.adpk; Listing 16.2.5.2.2.

Programming Note: List scheduled times as shown in table 8.2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.1.3: Summary of Cetuximab Concentration (ug/mL) from Intensive PK Sampling at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Sample Times		
Treatment	C1D2 24 Hours Post Infusion	C1D3 48 Hours Post Infusion	C1D8 168 Hours Post Infusion
Patritumab+ cetuximab + cisplatin or carboplatin			
n	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx
CV%	xx.xxx	xx.xxx	xx.xxx
SEM	xx	xx	xx
Geom. Mean	xx	xx	xx
Geom. CV%	xx	xx	xx
Minimum	xx.xxx	xx.xxx	xx.xxx
1st Quartile	xx.xxx	xx.xxx	xx.x x
Median	xx.xxx	xx.xxx	xx.xx
3rd Quartile	xx.xxx	xx.xxx	x.xxx
Maximum	xx.xxx	xx.xxx	xx xxx
Placebo + cetuximab + cisplatin or carboplatin			
N	xx	xx	xx
Mean	xx.xxx	xx.xx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx
…			
Continue above			

Notes: Concentrations below the lower limit of quantitation (BLQ) are set to zero for the calculation of descriptive statistics. If any concentration at a time point is BLQ, the geometric mean at that time point is not calculated and is presented as "NC".
CxDx = Cycle x Day x
Source Data: adam.adpk; Listing 16.2.5.2.2.

Programming Note: List scheduled times as shown in table 8.2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.1.4: Summary of Cisplatin Concentration (ug/mL) from Intensive PK Sampling at Cycle 1
Pharmacokinetic Analysis Set

HRG HIgh

	Sample Times					
Treatment	C1D1 Pre-Infusion	C1D1 End of Infusion	C1D1 6 Hours Post Infusion	C1D1 7 Hours Post Infusion	C1D2 24 Hours Post Infusion	C1D3 48 Hours Post Infusion
Patritumab + cetuximab + cisplatin						
N	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx xx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
CV%	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SEM	xx	xx	xx	xx	xx	xx
Geom. Mean	xx	xx	xx	xx	xx	xx
Geom. CV%	xx	xx	xx	xx	xx	xx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
1st Quartile	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx
3rd Quartile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	x xxx	xx.xxx	xx.xxx	xx.xxx
Placebo + cetuximab + cisplatin						
N	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
…						

Continue above

Notes: Concentrations below the lower limit of quantitation (BLQ) are set to zero for the calculation of descriptive statistics. If any concentration at a time point is BLQ, the geometric mean at that time point is not calculated and is presented as "NC".
CxDx = Cycle x Day x
Source Data: adam.adpk; Listing 16.2.5.2.3.

Programming Note: List scheduled times as shown in table 8.2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.1.5: Summary of Carboplatin Concentration (ug/mL) from Intensive PK Sampling at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Sample Times						
Treatment	C1D1 Pre-Infusion	C1D1 End of Infusion	C1D1 5 Hours Post Infusion	C1D1 6 Hours Post Infusion	C1D1 7 Hours Post Infusion	C1D2 24 Hours Post Infusion	C1D3 48 Hours Post Infusion
Patritumab + cetuximab + carboplatin							
N	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx. xx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
CV%	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SEM	xx	xx	xx	xx	xx	xx	xx
Geom. Mean	xx	xx	xx	xx	xx	xx	xx
Geom. CV%	xx	xx	xx	xx	xx	xx	xx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx
1st Quartile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
3rd Quartile	xx.xxx	xx.xxx	xx xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx. xx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Placebo + cetuximab + carboplatin							
N	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
…							
Continue above							

Notes: Concentrations below the lower limit of quantitation (BLQ) are set to zero for the calculation of descriptive statistics. If any concentration at a time point is BLQ, the geometric mean at that time point is not calculated and is presented as "NC".
CxDx = Cycle x Day x
Source Data: adam.adpk; Listing 16.2.5.2.4.

Programming Note: List scheduled times as shown in table 8.2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.2.1: Summary of Patritumab PK Parameters at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	
Cycle	AUC_{last} (ug.day/mL)	C_{max} (ug/mL)
Cycle 1		
Geometric mean		
Geometric CV%		
Arithmetic mean		
Arithmetic SD		
Median		
Min		
Max		
N		

Note: If there are less than 3 values in the data series only the min, max, an N a e presented. The other summary statistics are denoted as not calculated (NC).
If one or more of the values in a data series is zero, then do not calculate the geometric mean and geometric CV% and denote them as not applicable (NA).
If an entire concentration-time profile is BLQ, PK parameters will b reported as NC and set to missing for summary statistics.
For the calculation for summary statistics of PK parame ers, al NR a d NC values in a data series are set to missing.

Source Data: adam.adpk; Listing 16.2.5.2.1.

Programming Note: List scheduled times as shown in table 8.2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Table 15.4.2.2: Summary of Cetuximab PK Parameters at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)		Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	
Cycle	AUC_{last} (ug.day/mL)	C_{max} (ug/mL)	AUC_{last} (ug.day/mL)	C_{max} (ug/mL)
Cycle 1				
Geometric mean				
Geometric CV%				
Arithmetic mean				
Arithmetic SD				
Median				
Min				
Max				
N				

Note: If there are less than 3 values in the data series only the min ma and N are presented. The other summary statistics are denoted as not calculated (NC).
If one or more of the values in a data series is zero, then do not ca culate the geometric mean and geometric CV% and denote them as not applicable (NA).
If an entire concentration-time profile is BLQ PK param ters w ll be ported as NC and set to missing for summary statistics.
For the calculation for summary statistics of K paramete all NR and NC values in a data series are set to missing.

Source Data: adam.adpk; Listing 16.2.5.2.1.

Programming Note: List scheduled times as shown in table 8 2 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

The following table follows Table 15.4.2.2:

Table 15.4.2.3 Summary of Cisplatin PK Parameters at Cycle 1
Pharmacokinetic Analysis Set

Table 15.4.2.4 Summary of Carboplatin PK Parameters at Cycle 1
Pharmacokinetic Analysis Set

Table 15.4.2.5: Statistical Analysis of Cetuximab, Cisplatin, and Carboplatin PK Parameters at Cycle 1
Pharmacokinetic Analysis Set

HRG High

	Geometric LS Mean (95% CI)		Ratio of Geometric LS means (90% CI)
PK Parameter	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Patritumab/Placebo
Cetuximab			
AUC_{last}	xx.x	xx.x	xx.x
	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]
C_{max}	xx.x	xx.x	xx.x
	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]
Cisplatin			
AUC_{last}	xx.x	xx.x	xx.x
	[xx.x, xx.x]	[xx.x xx x]	[xx.x, xx.x]
C_{max}	xx.x	xx.x	xx.x
	[xx.x, xx.x]	[x .x, xx.x]	[xx.x, xx.x]
Carboplatin			
AUC_{last}	xx.x	xx.x	xx.x
	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]
C_{max}	xx.x	xx.x	xx.x
	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]

Note: AUC_{last} and C_{max} will be log-transformed prior o nalysis. The geometric mean ratios and their two-sided 90% CIs for AUC_{last} and C_{max} between the patritumab arm and the placebo arm will be calculated using the e ponentiation of the differences and their CIs between treatments least square mean from the ANOVA. The ratios and their two-sided 90% CIs will be expressed relative to the placebo arm.

Source Data: adam.adpk; Listing 16.2.5.2.2
Programming Note: continue for HRG Low and Overall on the next page

Table 15.5.1.1: Summary of Actual Results and Change from Baseline in FACT-H&N Total Score, FACT-H&N Subscale (HNS) Score, HNS Individual Symptom Score, and FACT-H&N Symptom Index (FHNSI) Score
FACT-H&N Analysis Set

HRG High

PRO Measure / Visit	Patritumab + cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Placebo + cetuximab + cisplatin or carboplatin ____(N=xxx)_____	
	Result	Change	Result	Change
FACT-H&N Total Score				
Baseline				
n	xx		xx	
Mean	xx.x		xx.x	
SD	xx.xx		xx.xx	
Minimum	xx		xx	
Median	xx.x		xx.x	
Maximum	xx		xx	
Cycle 2 Day 1				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx
Cycle 3 Day 1				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx

...
Continue with Cycle 4 Day 1, Cycle 5 Day 1 and additional cycles as required. Last visit will be End of Study Treatment. Then continue with FACT-H&N Subscale (HNS) Score, HNS Individual Symptom Score, and FACT-H&N Symptom Index (FHNSI) Score

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment.
PRO assessments obtained at the end of treatment visit or at scheduled timepoints with fewer than 5 subjects in any treatment arm are not included.

Source Data: adam.adqs; Listing 16.2.9.1, 16.2.9.2
Programming Note: continue for HRG Low and Overall on the next page

Table 15.5.1.2**:** Statistical Analysis of the Change from Baseline in the FACT-H&N total score, the FACT-H&N HNS, HNS individual symptom score, and the FACT-H&N FHNSI score
FACT-H&N Analysis Set

HRG High

		LS mean (95% CI)		Difference between LS means (95% CI)
PRO Measure	Timepoint	Patritumab + cetuximab + cisplatin or carboplatin (N=xxx)	Placebo + cetuximab + cisplatin or carboplatin (N=xxx)	Patritumab - placebo
FACT-H&N total score	Cycle 2 Day 1	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
	Cycle 3 Day 1	xx.x [xx.x, xx.x]	xx. [xx.x, xx.x]	xx.x [xx.x, xx.x]
	Cycle 5 Day 1	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
	Overall			xx.x [xx.x, xx.x]

Programming notes: display all timepoints with at least five bser ations per group. Continue with the FACT-H&N HNS, Each of HNS individual symptom score, and the FACT-H&N FHNSI score

Notes: The mixed model includes treatment, timepoint, treatment x timepoint, and baseline as fixed effects and subject as random effect. If the interaction effect was not significant (p >0.10), the model was rerun without the interaction term and the overall LS mean differences and CIs were estimated.
PRO assessments obtained at the end of treatment visit or at scheduled timepoints with fewer than 5 subjects in any treatment arm are not included.
The final model [included] [did not include] an interaction term. The xxx covariance structure was used to estimate the interaction model.
The xxx covariance structure was used to estimate the final model.

Programming note: Specify in footnote whether final model included an interaction term. Overall LS mean differences are not displayed if the interaction term is significant.
Source Data: adam.adqs; Listing 16.2.9.1, 16.2.9.2
Programming Note: continue for HRG Low and Overall on the next page

Table 15.5.1.3: Summary of Actual Results and Change from Baseline in EQ-5D Index
EQ-5D Analysis Set

HRG High

PRO Measure / Visit	Patritumab + cetuximab + cisplatin or carboplatin ____(N=xxx)_____		Placebo + cetuximab + cisplatin or carboplatin ____(N=xxx)_____	
	Result	Change	Result	Change
Baseline				
n	xx		xx	
Mean	xx.x		xx.x	
SD	xx.xx		xx.xx	
Minimum	xx		xx	
Median	xx.x		xx.x	
Maximum	xx		xx	
Cycle 2 Day 1				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx
Cycle 3 Day 1				
n	x	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx

...

Notes: The baseline value is defined as the last non-missing value before initial administration of study treatment.
PRO assessments obtained at the end of treatment visit or at scheduled timepoints with fewer than 5 subjects in any treatment arm are not included.

Source Data: adam.adqs; Listing 16.2.9.1, 16.2.9.2
Programming Note: continue for HRG Low and Overall on the next page

The following table follows Table 15.5.1.3:

Table 15.5.1.4 Summary of Actual Results and Change from Baseline in VAS Score
EQ-5D Analysis Set

Figure 15.1.1
CONSORT Diagram

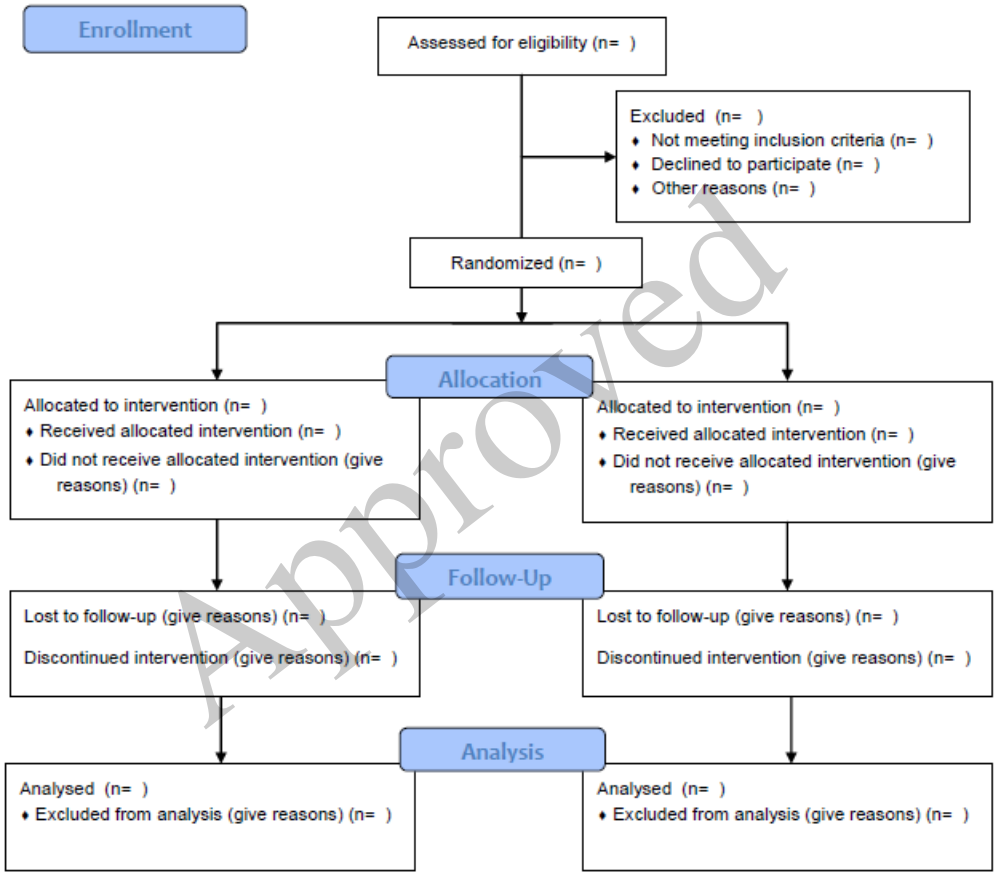
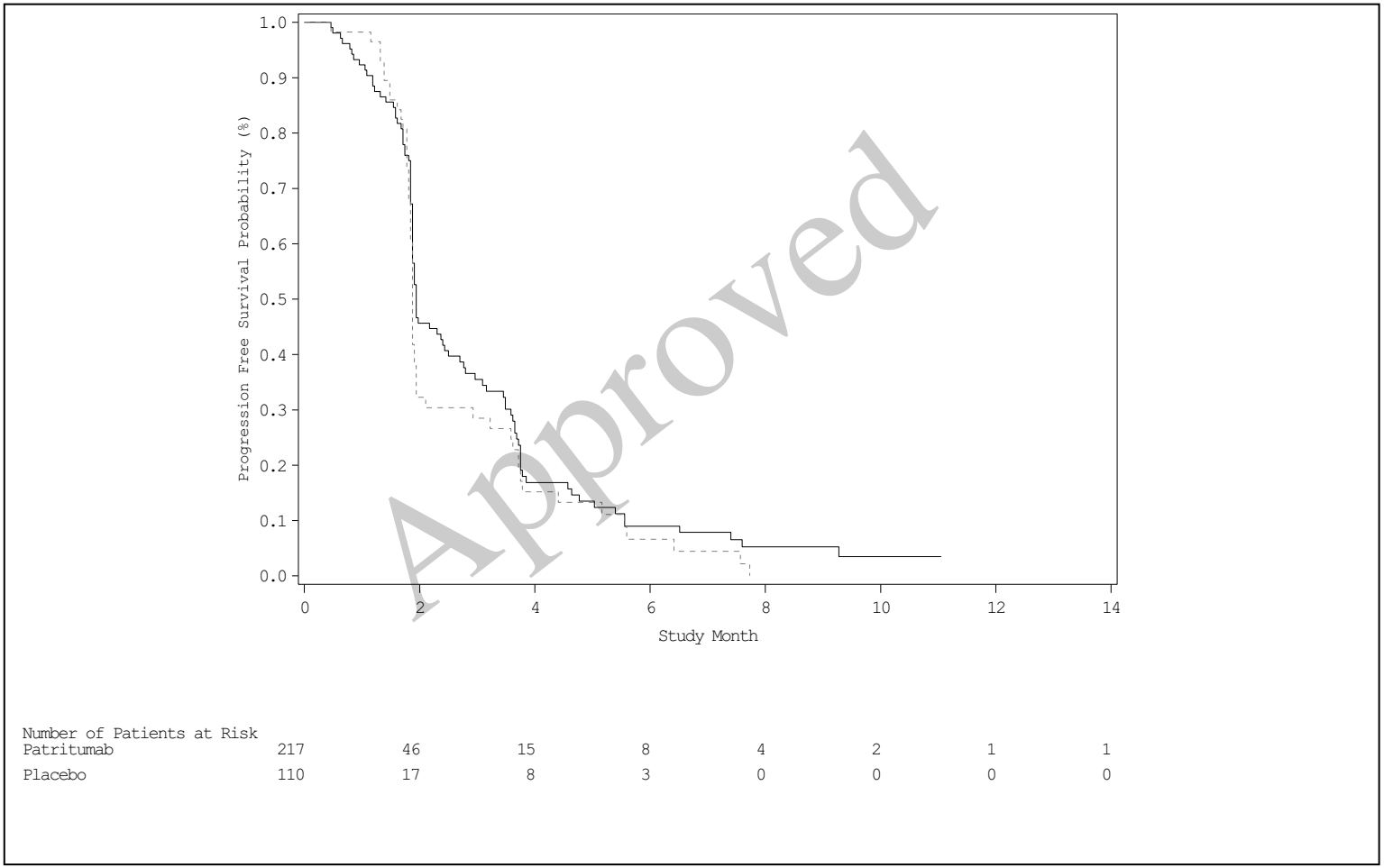


Figure 15.2.1.1 Kaplan-Meier Plot of Progression Free Survival (PFS) by Treatment Group
Full Analysis Set

HRG High



Source Data: adam.adtte; Listing 16.2.6.1
Programming Note: continue for HRG Low and Overall on the next page

Programming note: Add the legend for different treatment arms in the plot.
Show the timepoint in the survival line when there is censored subject.

Replace the second sentence with “Medications taken on or after the first dose of study medication will be classified as concomitant medications”.

The following figure follows Figure 15.2.1.1 and change the label for the y-axis accordingly.

Figure 15.2.1.3 Kaplan-Meier Plot of Progression Free Survival (PFS) for Different HRG Cutoffs by Treatment Group
Full Analysis Set

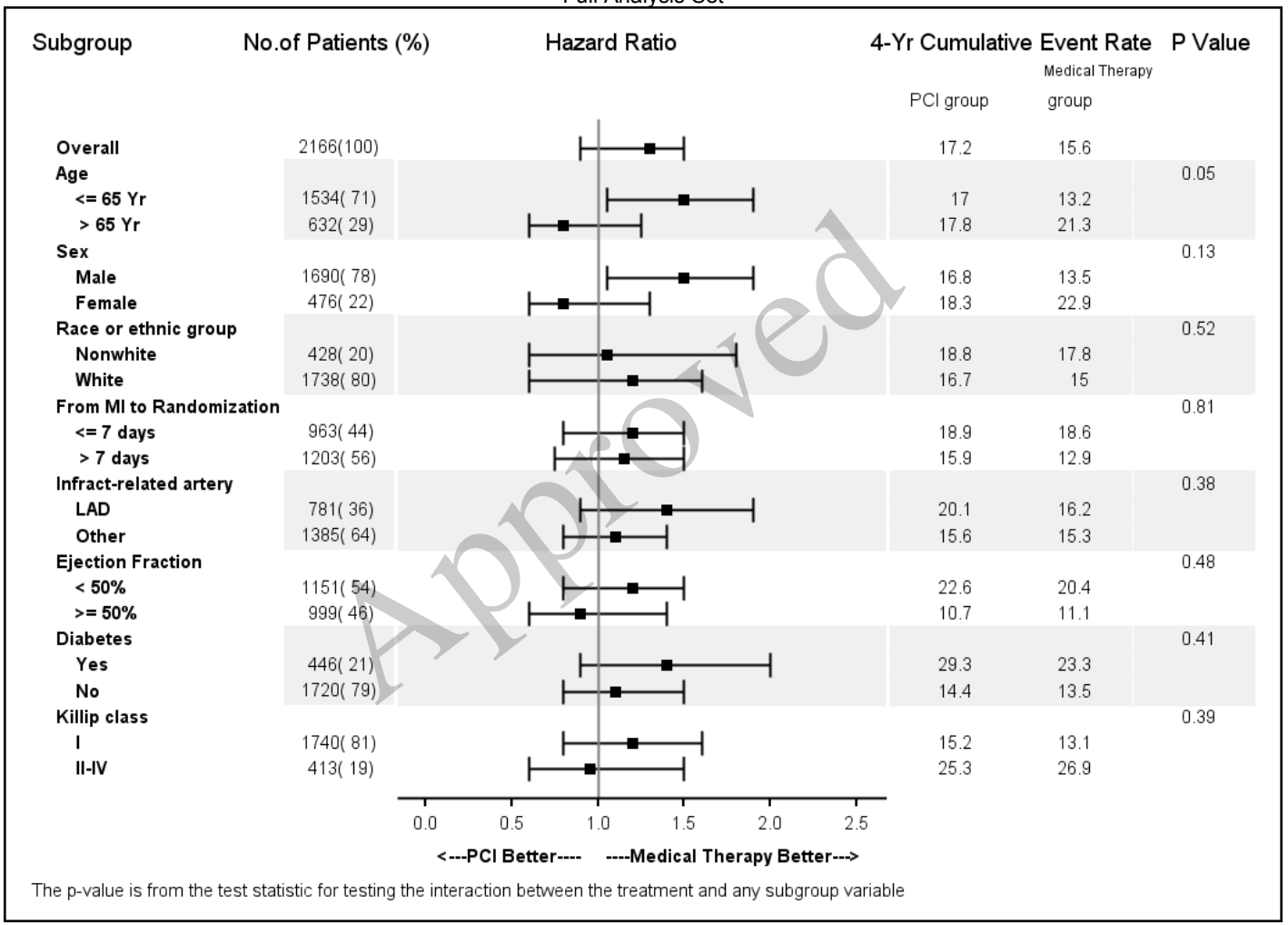
Programming Note: Change the subtitle to “HRG Cutoff: XX; HRG High of Cutoff” and continue for HRG Cutoff: XX; HRG Low of Cutoff XX and HRG Cutoff: XX; Overall of Cutoff XX. Continue for Different HRG cuteoffs.

Figure 15.2.2.1 Kaplan-Meier Plot of Overall Survival (OS) by Treatment Group
Full Analysis Se

Figure 15.2.2.3 Kaplan-Meier Plot of Overall Surv val (O) for Different HRG Cutoffs by Treatment Group
F l Ana ysis Set

Programming Note: Change the subtitle to “HRG Cutoff: XX; HRG High of C toff” a d continue for HRG Cutoff: XX; HRG Low of Cutoff XX and HRG Cutoff: XX; Overall of Cutoff XX. Continue for Different HRG cuteoffs.

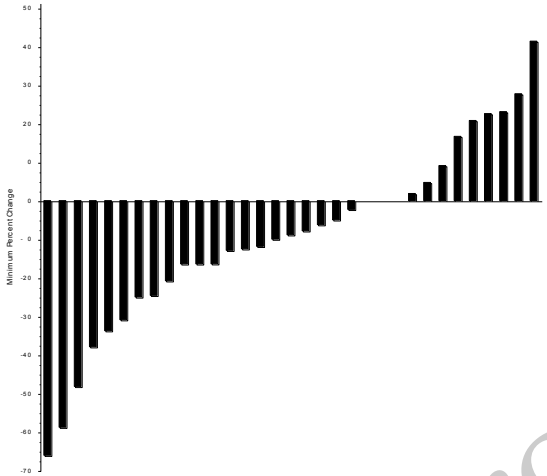
Figure 15.2.1.2 Forest Plot of Progression Free Survival (PFS) for Selected Subgroups
Full Analysis Set



The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

Figure 15.2.3: Waterfall Plot of Best (Minimum) Percent Change in Sum of Longest Diameters from Baseline in Target Lesions
Full Analysis Set

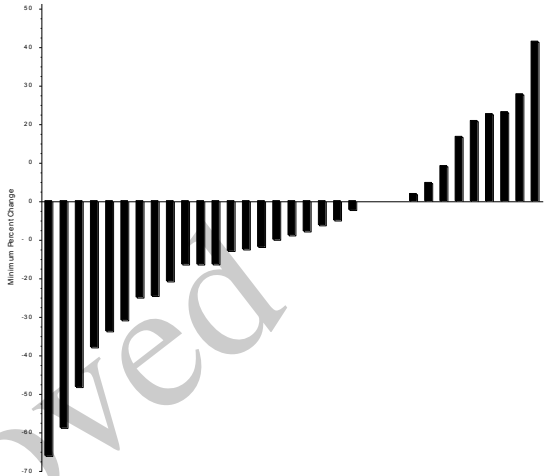
HRG High



Patritumab + cetuximab + cisplatin or carboplatin

Minimum Change (%)

n	Mean	SD	Median	Minimum	M ximum
xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx



Placebo + cetuximab +cisplatin or carboplatin

Minimum Change (%)

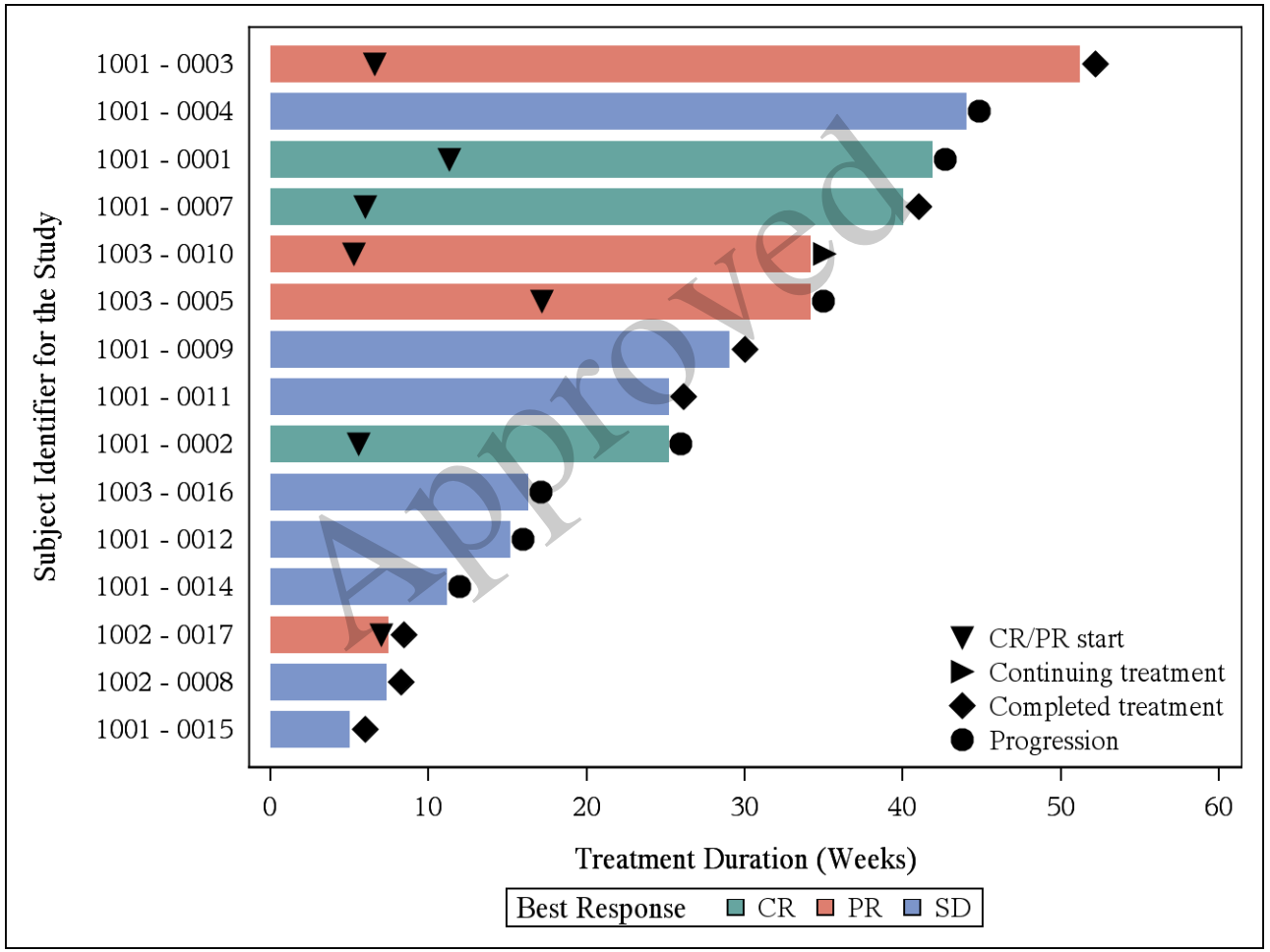
n	Mean	SD	Median	Minimum	Maximum
xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx

Note: For each subject, the minimum percent change from baseline in the sum of Longest Diameters for all target lesions is represented by a vertical line.

Source Data: adam.adrs; Listing xxxx
Programming Note: continue for HRG Low and Overall on the next page

Figure 15.2.4: Swimmer Plot of Tumor Response and Treatment Duration
Full Analysis Set

HRG High
Treatment: Patritumab + cetuximab + cisplatin or carboplatin

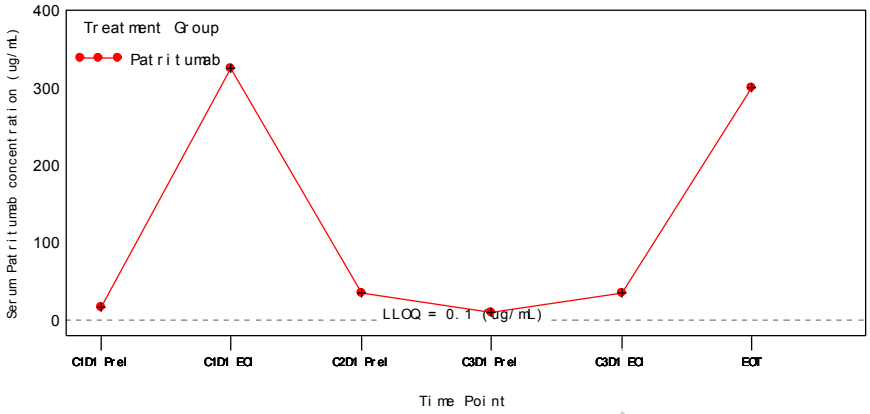


Source Data: adam.adrs; Listing xxxx

Programming Note: continue for Placebo + cetuximab +cisplatin or carboplatin . Continue for HRG Low.

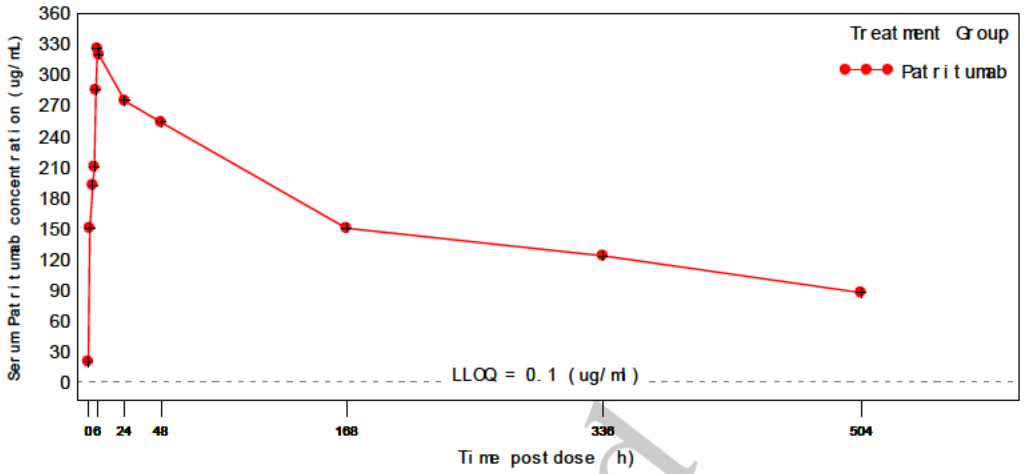
1. Please sort RS by date first then do the best response
2. Sort the plot by largest AVAL1. Each subject is a bar.
3. Add symbol of CR/PR start date of CR/PR subject (AVAL2).
4. Add symbol for status at the end of each bar (STATUS)

Figure 15.4.1.1 Mean Plasma Concentration of Patritumab by Time from Sparse PK Sampling
Pharmacokinetic Analysis Set



-----Lower limit of quantification (<0.1)
Note: Mean Plasma Concentration data are plotted by C1D1 Pre-Infusion, C1D1 End of Infusion, C2D1 Pre-Infusion, C3D1 Pre-Infusion, C3D1 End of Infusion and End of Tr tment.
CxDx = Cycle x Day x
If mean is BLQ, then these are plotted as zero on the linear scale and missing on the semi-log Scale.
Source Data: adam.adpk; Listing 16.2.5.2.1

Figure 15.4.1.2 Mean Plasma Concentration of Patritumab by Time from Intensive PK Sampling
Pharamacokinetic Analysis Set



-----Lower limit of quantification (<0.1)
Note: Mean Plasma Concentration data are plotted by 0, 1(EOI), 3, 4, 5, 6, 24, 48, 168, 336 and 504 hours.
CxDx = Cycle x Day x
If mean is BLQ, then these are plotted as zero on the linear scale and missing on the semi-log scale.
Source Data: adam.adpk; Listing 16.2.5.2.1

The following figures follows Figure 15.4.1.2

Figure 15.4.1.3Mean Plasma Concentration of Cetuximab by Time from Intensive PK Sampling
Pharmacokinetic Analysis Set

Similar as Table 15.4.1.3, will plot data by hours of 0, 3, 4, 5, 6, 7, 24, 48, and 168.

Figure 15.4.1.4Mean Plasma Concentration of Cisplatin by Time from Intensive PK Sampling
Pharmacokinetic Analysis Set

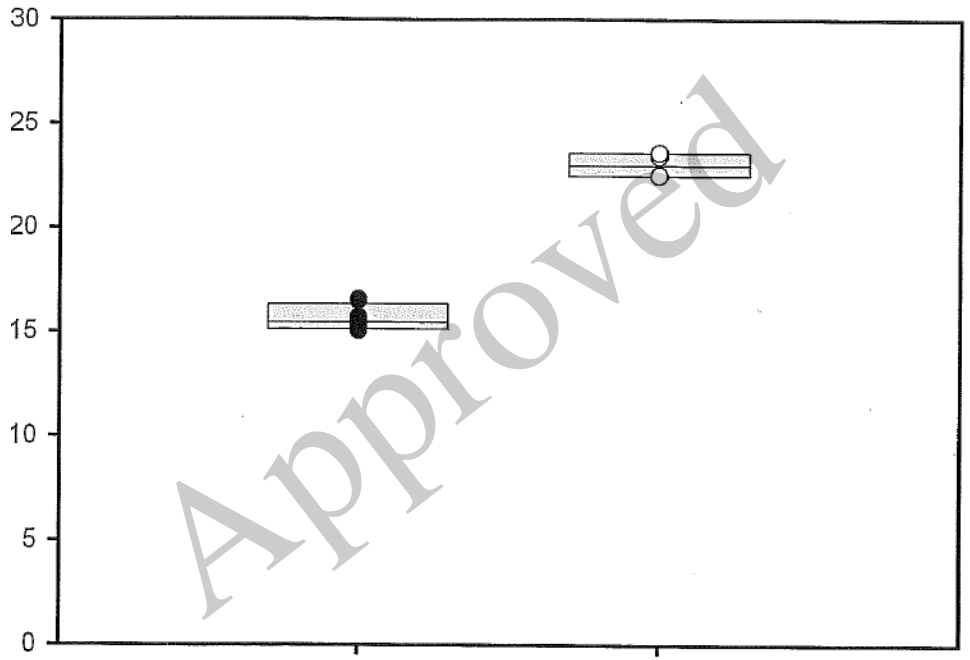
Similar as Table 15.4.1.4, will plot data by hours of 0, 5, 6, 7, 24, and 48.

Figure 15.4.1.5Mean Plasma Concentration of Carboplatin by Time from Intensive PK Sampling
Pharmacokinetic Analysis Set

Similar as Table 15.4.1.5, will plot data by hours of 0, 4.5, 5, 6, 7, 24, and 48.

Figure 15.4.2.1 Boxplot of Patritumab PK Parameters at Cycle 1
Pharmacokinetic Analysis Set

HRG High



Source Data: adam.adpk; Listing 16.2.5.2.1

Programming Note: X-axis only presents one treatment group as Patritumab + cetuximab + cisplatin or carboplatin
Y-axis presents AUC_{last} (ug.day/mL)
Programming Note: continue for HRG Low and Overall on the next page

The following figures follows Figure 15.4.2.1

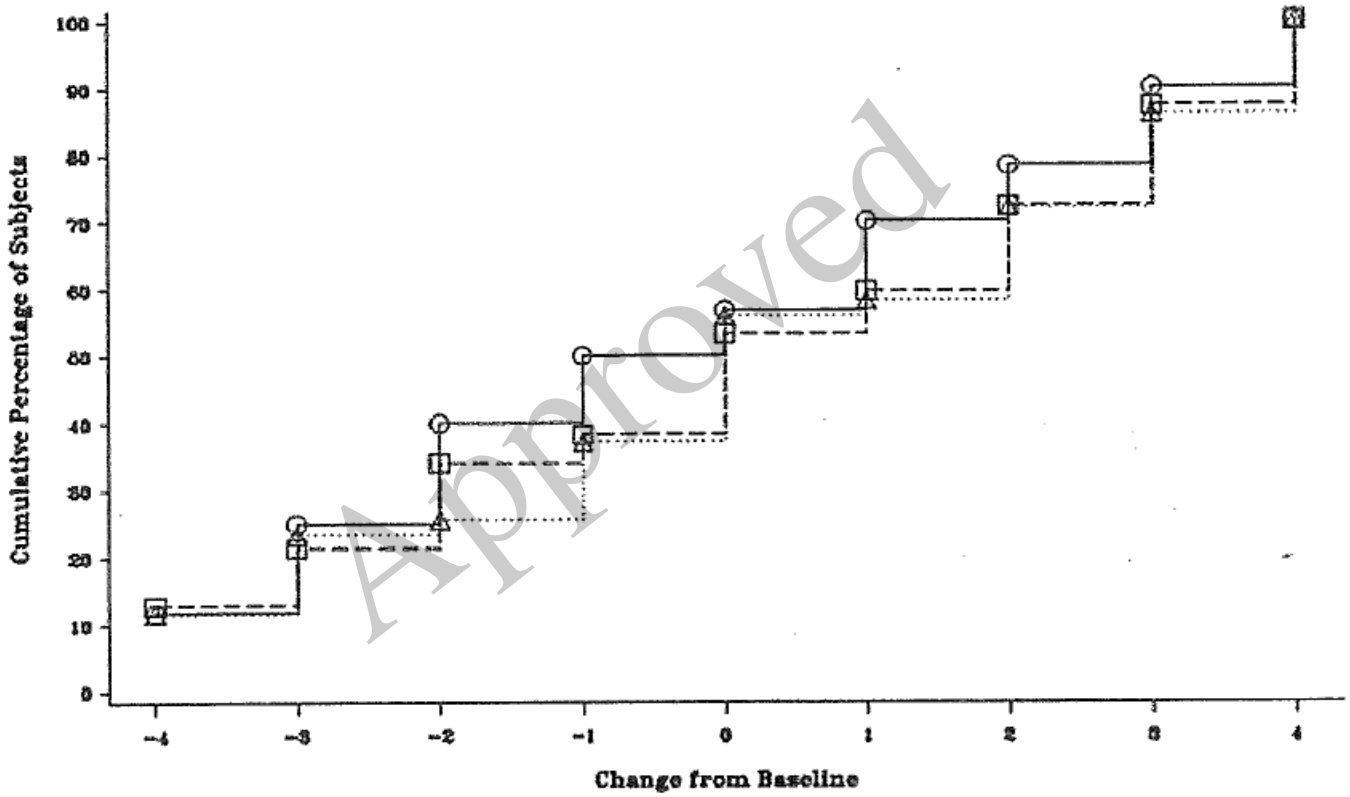
Figure 15.4.2.2 Boxplot of Cetuximab PK Parameters at Cycle 1 by Treatment
Pharmacokinetic Analysis Set

Figure 15.4.2.3 Boxplot of Cisplatin PK Parameters at Cyc e 1 by Treatment
Pharmacokinetic Analysis Set

Figure 15.4.2.4 Boxplot of Carboplatin PK Parameters at Cycle 1 by Treatment
Pharmacokinetic Analys s Set

Figure 15.5.1.1 Plot of Cumulative Distribution Function of Change from Baseline on FACT-H&N HNS Score
FACT-H&N Analysis Set

HRG High

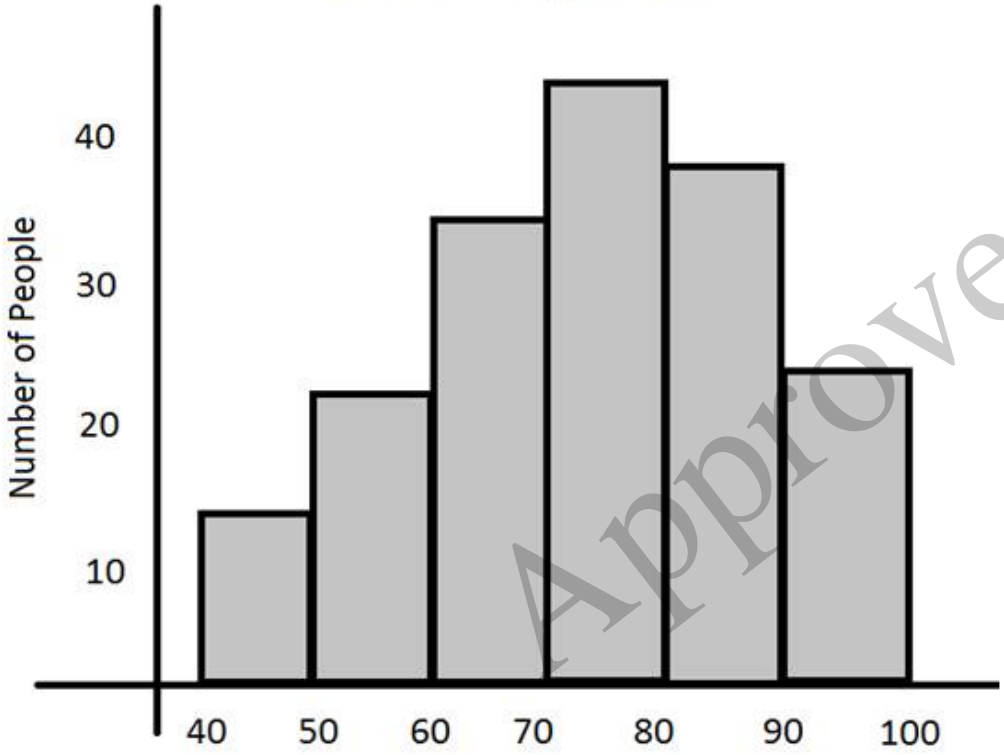


Source Data: adam.adqs; Listing 16.2.9.1, 16.2.9.2
Programming Note: x-axis will be displayed as follows: Cycle 2 Day 1 Change from Baseline; Cycle 3 Day 1 Change from Baseline; Cycle 5 Day 1 Change from Baseline and End-of-Treatment Change from Baseline. X-axis values will range from minimum change to maximum change depending on the data.
Programming Note: continue for HRG Low and Overall on the next page
Display the legend for the two treatment groups: ○ Patritumab + cetuximab + cisplatin or carboplatin
□ Placebo + cetuximab + cisplatin or carboplatin

Figure 15.6.1 Heregulin (HRG) Distribution

Full Analysis Set

HRG High
Treatment: Patritumab + cetuximab + cisplatin or carboplatin



Source Data: adam.adxx
Programming Note: X-axis presents heregulin
Y-axis presents frequency (number of people with the heregulin range)
Programming Note: continue for Placebo + cetuximab + cisplatin or carboplatin and continue for HRG Low and Overall on the next page

Listing 16.2.1.1: Subject Disposition
All Screen Subjects

Subject ID/ Group/Age/ Gender	Screen Fail/ Reason	First Dose Date of Patritumab/ Cetuximab/ Cisplatin/Capboplatin	Last Dose Date (Day) of Patritumab/ Cetuximab/ Cisplatin/Capboplatin	Primary Reason for Discontinuation from Study Treatment	Primary Reason for Discontinuation from Extension Treatment	Follow-up Contact Date	Started New Cancer Treatment
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	No	yyyy-mm-dd/ yyyy-mm-dd/ yyyy-mm-dd	yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)	Completed	xxx xxxxxxx	yyyy-mm-dd (xx)	No
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	No	yyyy-mm-dd/ yyyy-mm-dd/ yyyy-mm-dd	yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)	xxxxxxxxxxx	Did not continue in Ext	yyyy-mm-dd (xx)	Yes – yyyy-mm-dd
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	Yes – xxxxxxxx x						

Source: adam.adsl
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.1.2: Deaths
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	First Dose Date of Patritumab/ Cetuximab/ Cisplatin/Capboplatin	Last Dose Date (Day) of Patritumab/ Cetuximab/ Cisplatin/Capboplatin	Death Date (Day)	Primary Cause of Death
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd/ yyyy-mm-dd/ yyyy-mm-dd	yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)	yyyy-mm-dd (xx)	xxxxxxxxxxxxxxxxxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd/ yyyy-mm-dd/ yyyy-mm-dd	yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)/ yyyy-mm-dd (xx)		
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M				

Source: adam.adsl
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.2.1: Inclusion/Exclusion Criteria
All Screen Subjects

HRG High Subject ID/ Group/Age/ Gender	Inclusion/Exclusion Assessment Date	Failed Inclusion/Exclusion Criteria	If Yes, Specify Criteria [a]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd	No	
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd	Yes	1, 2, x
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd		

Notes: [a] See appended pages of this listing for a complete list of the inclusion and exclusion criteria from Protocol Version 2.0.

Source: adam.adie, Protocol U31287-A-U203 Version 2.0 (27Aug2015)

Programming note: Append next 2 pages to end of this listing.
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.2.1: Inclusion Criteria

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

1

2

…

Source: adam.adie, Protocol U31287-A-U203 Version 2.0 (27Aug2015)

Programming note: list all inclusion criteria from the protocol.

Listing 16.2.2.1: Exclusion Criteria

Subjects who meet any of the following criteria will not be included in the study:

1

2

…

Source: adam.adie, Protocol U31287-A-U203 Version 2.0 (27Aug2015)

Programming note: list all exclusion criteria from the protocol.

Listing 16.2.2.2: Informed Consent
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Study Informed Consent Date (Day)	Consented to Pharmacogenomic Sampling	Sample Taken for Pharmacogenomic/ Date (Day)	Consented to Tumor Tissue Sampling	Sample Taken for Tumor Tissue/ Date (Day)
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd (xx)	Yes	Yes – yyyy-mm-dd (xx)	Yes	Yes – yyyy-mm-dd (xx)
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd (xx)	No			
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M					

Source: adam.adsl, adam.adpg
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.2.3: Protocol Deviation
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Date of Deviation (Day)	Deviation Class	Deviation Text	Source [a]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd (xx)	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	CRF
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	yyyy-mm-dd (xx)	xxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxx xxxxxxx	ICOTRIAL
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M				

Note: [a] ICOTRIAL deviations are obtained from the clinical monitoring database. CRF deviations are derived using CRF data.

Source: adam.addv, ICOTRIAL

Need to confirm if programmed deviations from CRF data is needed.
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.3: Subject Inclusion in Analysis Sets
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Safety Analysis Set	DLT Evaluable Set	Pharmacokinetic Analysis Set
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	Yes	No – Did not receive 80% of cetuximab	Yes
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/M	No – Not Dosed	No – Not Dosed	No

Source: adam.adsl
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.1: Demographic Data
Full Analysis Set

HRG High

Subject ID/Group	Date of Birth	Study Informed Consent Date (Day)	Age (yrs) [a]	Gender	Ethnicity	Race	Height (cm)	Baseline Weight (kg)
xxxxxx/Patritumab+ cetuximab + cisplatin or carboplatin	yyyy-mm-dd	yyyy-mm-dd (xx)	xx	M	Hispanic/Latino	xxxxxxxxxx	xxx.x	xxx.x
xxxxxx/Patritumab+ cetuximab + cisplatin or carboplatin	yyyy-mm-dd	yyyy-mm-dd (xx)	xx	F	Non Hispanic/Non Latino	xxxxxxxxx	xxx.x	xxx.x
xxxxxx/Patritumab+ cetuximab + cisplatin or carboplatin	yyyy-mm-dd	yyyy-mm-dd (xx)	xx	M	Hispanic/Latino	Other: xxxxxxxxx	xxx.x	xxx.x

Notes: [a] Age is calculated as the number of complete years between date of birth and date of informed consent.

Source: adam.adsl
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.2: Pregnancy Test Results
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Visit	Pregnancy Test Done?	Date of Test (Day)	Method	Result
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/F	Screening	Yes	yyyy-mm-dd (xx)	Urine	Negative
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/F	Screening	No			

Source: adam.adlb
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.3: Medical/Surgical History
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Event/Diagnosis	Onset Date (Day)	Continuing
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/F	xxxxxxxxxxxxxxxxxxx	yyyy-mm-dd (xxx)	Yes
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin /xx/F	xxxxxxxxxxxxxxxxxxx	yyyy-mm-dd (xxx)	No

Source: adam.admh
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.4.1: Cancer History for SCCHN
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Cancer Type	Histology	Date of Initial Histologic Diagnosis	Time from Initial Diagnosis to Study Treatment (Months) [a]	Tumor Staging at Study Entry	Grade	Date of Biopsy	Anatomical Location	Type of Biopsy
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin / xx/F	xxxxx	xxxxxxx	yyyy-mm-dd	xxx	IA	Well Differentiated	yyyy-mm-dd	xxxxxxxxxx	FNAB
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	xxxxxxxx	xxxxxxxx	yyyy-mm-dd	xxx	IIB	Mod rat ly Differentiated	yyyy-mm-dd	xxxxxxxxxx	Core Needle
		xxxxxxxxx	yyyy-mm-dd	xxx	Oth r: xxx	Undifferentiated	yyyy-mm-dd	xxxxxxxxxx	Surgery: xxx
		xxxxxxxxxxx	yyyy-mm-dd	xxx	V	Moderately Differentiated	yyyy-mm-dd	xxxxxxxxxx	Excisional

Notes: [a] Time from initial diagnosis to study treatment = (date of initial administration of any study treatment – date of diagnosis + 1)/365.25x12.

Source: adam.admh
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.4.2: Prior Head and Neck Systemic Cancer Therapy
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Intended for	Best Response [a]	Agent Name	Start Date	Stop Date
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin / xx/F	xxxxxxxx	PR	xxxxx	yyyy-mm-dd	yyyy-mm-dd
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin / xx/M	xxxxxxxx	CR	xxxxxxxx	yyyy-mm-dd	yyyy-mm-dd
		SD	xxxxxxx	yyyy-mm-dd	yyyy-mm-dd
		PD	xxxxxx	yyyy-mm-dd	yyyy-mm-dd

Note: [a] CR=Complete Response; PR=Partial Response; SD=Stable Disease; PD=Progressive Disease; NA=Not Applicable

Source: adam.adcm
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.4.3: Prior Radiation Therapy
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Any Prior Radiation Therapy	Indication	Start Date	End Date	Location
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	Yes	xxxxxxxxxxxxxxxx	yyyy-mm-dd	yyyy-mm-dd	xxxxxxxxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	Yes	xxxxxxxxxxxxxxxx	yyyy-mm-dd	yyyy-mm-dd	xxxxxxxxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	No				

Source: adam.adcm
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.5: Prior/Concomitant Medication
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	C: Class W: WHO Drug Term V: Verbatim Name	S: Start Date (Day) E: Stop Date (Day) O: Ongoing	Dose (Units)	Frequency	Indication
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	C: xxxxxxxxxxxxx W: xxxxxxxxxxxxx V: xxxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: O: Yes	xxxxxxx (Other/xxxx)	xxxxxxxxxxxx	xxxxxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	C: xxxxxxxxxxxxx W: xxxxxxxxxxxxx V: xxxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: yyyy-mm-dd (xxx) O: No	xxxxxxx (xxxx)	xxxxxxxxxx	xxxxxxxxxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	C: xxxxxxxxxxxxx W: xxxxxxxxxxxxx V: xxxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: yyyy-mm-dd (xxx) O: No	xxxx xx (xxxx)	xxxxxxxx	xxxxxxxxxxx

Source: adam.adcm
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.4.6: Non-Drug Treatment/Procedures
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Treatment/Procedure	S: Start Date (Day) E: End Date (Day) O: Ongoing	Duration	Indication
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	xxxxxxxxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: yyyy-mm-dd (xxx) O: No:	xxx	xxxxxxxxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	xxxxxxxxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: O: Yes	xxx	xxxxxxxxxx

Source: adam.adcm
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.5.1.1: Investigational Drug Patritumab Administration
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Visit	Date of Infusion (Day)	Start Time/ Stop Time	Dose Level (mg/kg)	Actual Total Dose Administered (mg/kg)	Was IV Completed?	Reason for Change or Interruption
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	Cycle 1 Day 1	yyyy-mm-dd (xx)	hh:mm/hh:mm	xx	xx	No	xxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/M	Cycle 1 Day 1	yyyy-mm-dd (xx)	hh:mm/ hh:mm	xx	xx	Yes	xxx
	Cycle x Day 1	yyyy-mm-dd (xx)	hh:mm/ hh:mm	xx	xx	Yes	xxx

Source: adam.adex
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.5.1.2: Cetuximab, Cisplatin, and Carboplatin Administration
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Visit	Study Drug	Date of Infusion (Day)	Start Time/ Stop Time	Dose Level (unit)	Actual Total Dose Administered (unit)	Was IV Completed?	Reason for Change or Interruption
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	Cycle 1 Day 1	Cetuximab	yyyy-mm-dd (xx)	hh:mm/ hh:mm	xx (mg/m2)	xx (mg/m2)	No	xxx
		Cisplatin	yyyy-mm-dd (xx)	hh:mm/ hh:mm	xx (mg/m2)	xx (mg/m2)	Yes	xxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/M	Cycle 1 Day 1	Cetuximab	yyyy-mm-dd (xx)	hh:mm/ hh:mm	xx (mg m2	xx (mg/m2)	Yes	xxx
		Carboplatin	yyyy-mm-dd (xx)	hh:mm/ hh:mm	xx (mg)	xx (mg)	Yes	xxx

Source: adam.adex
Programming Note: continue for HRG Low and Overall on the next page.

Listing 16.2.5.1.3: Patritumab, Cetuximab, and Cisplatin/Carboplatin Exposure
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Study Drug	Treatment Duration (Weeks) [a]	Treatment Duration (Cycles) [a]	Number of IV Received	Cumulative Dose (unit) [b]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	Patritumab	xx.x	xx.x	xx	xxx (mg/kg)
	Cetuximab	xx.x	xx.x	xx	xxx (mg/m2)
	Cisplatin/Carboplatin	xx.x	xx.x	xx	xxx (mg/m2) / xxx (mg)
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/M					

Notes: [a] Treatment duration (in weeks) for Patritumab and Cisplatin/Carboplatin is calculated as (date of the last dose – date of the first dose + 21)/7.
Treatment duration (in cycles) for Patritumab and Cisplatin/Carboplatin is calculated as (date of the last dose – date of the first dose + 21)/21.
Treatment duration (in weeks) for Cetuximab is calculated as (date of the last dose – date of the first dose + 7)/7.
Treatment duration (in cycles) for Cetuximab is calculated as (date of the last dose – date of the first dose + 7)/21.

[b] Total cumulative dose is the sum of doses taken by a subject across cycles.

Source: adam.adex

Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.5.2.1: Patritumab Pharmacokinetic Sample Collection Time and Results
Pharmacokinetic Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Visit	Patritumab Infusion Date Start Time/ Stop Time (Day)	Nominal Time Point [a]	PK Sample Taken	Date/Time of Sample Collection (Day)	Sample Identification Number	Result (unit)	Excluded from Analysis: Reason if Y	AUC_0-21d/ C_max
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	C1D1	yyyy-mm-dd hh:mm/hh:mm (xx)	Pre-Infusion	Yes	yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	xxx.x/xxxx.x
			1 h	Yes	yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
			3 h	Yes	yyyy-mm-dd hh:mm (xx)	xx xx	xxxxxx	Y:xxxxxxx	
			4 h	No	yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
			5 h		yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
	C1D2	yyyy-mm-dd hh:mm/hh:mm (xx)	24 h		yyyy-mm-dd h :mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy mm-dd hh mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yy y-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F									

Notes: [a] All nominal time points are relative to the end of infusion except for pre-infusion.

Source: adam.adpk

Programming Note: List scheduled times as shown in table 8.1 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.5.2.2: Cetuximab Pharmacokinetic Sample Collection Time and Results
Pharmacokinetic Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Visit	Cetuximab Infusion Date Start Time/ Stop Time (Day)	Nominal Time Point [a]	PK Sample Taken	Date/Time of Sample Collection (Day)	Sample Identification Number	Result (unit)	Excluded from Analysis: Reason if Y	AUC_0-21d/ C_max
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	C1D1	yyyy-mm-dd hh:mm/hh:mm (xx)	Pre-Infusion	Yes	yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	xxx.x/xxxx.x
			3 h	Yes	yyyy-mm-dd hh:mm (xx)	xxxx	xxxxxx	Y:xxxxxxx	
			4 h	Yes	yyyy-mm-dd hh:mm (xx)	xx xx	xxxxxx	N	
			5 h	No	yyyy-mm-dd hh:mm (x)	xxxxx	xxxxxx	N	
	C1D2	yyyy-mm-dd hh:mm/hh:mm (xx)	24 h		yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy-mm dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy-mm dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
	xx	yyyy-mm-dd hh:mm/hh:mm (xx)	xx		yyyy-mm-dd hh:mm (xx)	xxxxx	xxxxxx	N	
xxxxxx/ Placebo+ cetuximab + cisplatin or carboplatin/xx/F									

Notes: [a] All nominal time points are relative to the end of infusion except for pre-infusion.

Source: adam.adpk

Programming Note: List scheduled times as shown in table 8.1 of the protocol.
Programming Note: continue for HRG Low and Overall on the next page.

The following listings follow Table 16.2.5.2.2:

Listing 16.2.5.2.3: Patritumab Pharmacokinetic Sample Collection Time and Results

Listing 16.2.5.2.4: Cetuximab Pharmacokinetic Sample Collection Time and Results

Listing 16.2.6.1.1: Target Tumor Assessment
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Lesion Number	Location	Visit	Assessment Date (Day)	Assessment Method	Longest Diameter (mm) [a]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	1	xxxxxxxxxx	Screening	yyyy-mm-dd (xxx)	Spiral CT Scan	xxx
			Cycle x	yyyy-mm-dd (xxx)	Spiral CT Scan	xxx
	2	Other (xxxxxxxx)	Screening	yyyy-mm-dd (xx)	Spiral CT Scan	xxx
			Cycle x	yyyy-mm-dd (xxx)	Spiral CT Scan	xxx
	SUM LD		Screening	yyyy-mm-dd (xxx)		xxx
			Cycle x	yyyy-mm-dd (xxx)		xxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	x	xxxxxxxxxx	Screening	yyy-mm-dd (xxx)	xxxxxxxxxxxx	xxx
	x	xxxxxxxxxx	Cy le x	yyyy-mm-dd (xxx)	xxxxxxxxxxxx	xxx
	x	xxxxxxxxxx	Cycle x	yyyy-mm-dd (xxx)	xxxxxxxxxxxx	xxx

Notes: [a] Shortest for lymph nodes. SUM LD = Sum of longest diameters.

Source: adam.adtm

Programming note: sort by subject ID, lesion number, and visit.

Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.6.1.2: Non-Target Tumor Assessment
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Lesion Number	Location	Visit	Assessment Date (Day)	Assessment Method	Status
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	1	xxxxxxxxxx	Screening	yyyy-mm-dd (xxx)	Spiral CT Scan	Present
			Cycle x	yyyy-mm-dd (xxx	Spiral CT Scan	Absent
	2	Other (xxxxxxxx)	Screening	yyyy-mm-dd (xxx)	Spiral CT Scan	xxx
			Cycle x	yyyy-mm-dd (xxx)	Spiral CT Scan	xxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/M	x	xxxxxxxxxx	Screening	yyyy-mm-dd (xxx)	xxxxxxxxxxxx	xxx
	x	xxxxxxxxxx	Cycle x	yyyy-mm-dd (xxx)	xxxxxxxxxxxx	xxx
	x	xxxxxxxxxx	Cycle x	yyy-mm-dd (xxx)	xxxxxxxxxxxx	New

Source: adam.adtm

Programming note: sort by subject ID, lesion number, and visit.

Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.6.1.3: Overall Tumor Assessment
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Visit	Tumor Response Assessment Performed?	Date of Overall Response (Day)	Target Lesion Overall Evaluation	Non-Target Lesion Overall Evaluation	Overall Evaluation
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	Cycle x	Yes	yyyy-mm-dd (xxx)	Partial Response	Non-CR/Non-PD	Partial Response
	Cycle x	Yes	yyyy-mm-dd (xxx)	Partial Response	Complete Response	Partial Response
	Cycle x	No				
	Cycle x	Yes	yyyy-mm-dd (xxx)	Stable Disease	Non-CR/Non-PD	Stable Disease

Source: adam.adrs
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.6.2: Progression-Free Survival and Overall Survival
Full Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Randomization Date (Day)	Date of Last Tumor Assessment (Day)	Date of Last Contact When Alive (Day)	Radiographic Progression?/ Date of Progression (Day)	Death?/ Date of Death (Day)	Progression Free Survival (Days) [a]	Overall Survival (Days) [b]	Time to Disease Progression (Days) [c]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	YYYY-MM-DD (xx)	YYYY-MM-DD (xxx)	YYYY-MM-DD (xxx)	No	Yes/YYYY-MM-DD (xxx)	xxx	xxx	xxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M			YYYY-MM-DD (xxx)	No	No	1 (C)	xxx (C)	1 (C)

Notes: (C) = censored observation
[a] PFS is defined as the time from the date of randomization the earlier f 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. Se the SAP for censoring rules.
[b] OS is defined as the time from the randomization date to the d te of death. If there is no death reported for a subject before the cut-off date for OS analysis, OS is censored at the last contact date at which the subject is known to be alive
[c] Time to disease progression is defined as the time from the randomization date to the date of first objective documentation of radiographic disease progression (per RECIST v1.1 as assessed by investigator). See the SAP for censoring rules
Source: adam.adtte
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.6.3: Subjects with Complete Response (CR), Partial Response (PR), or Stable Disease (SD)
Full Analysis Set

HRG High

Subject ID/Group/Age/Gender	Best Overall Response	Date of Earliest Response (Day)	Radiographic Progression?/ Date of Progression (Day)	Date of Last Tumor Assessment (Day)	Duration of Response (Weeks) [a]	Time to Response (Weeks) [b]	Duration of SD (Weeks) [c]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	PR	YYYY-MM-DD (xxx)	Yes/YYYY-MM-DD (xxx)	YYYY-MM-DD (xxx)	xxx	xxx	xxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	CR	YYYY-MM-DD (xxx)	No	YYYY-MM-DD (xxx)	xxx (C)	xxx	xxx (C)
xxxxxx/ Placebo + cetuximab + cisplatin or carboplatin/ xx/M	SD	DDMMMYYYY (xxx)	Yes/ DMMMYYYY (xxx)	DDMMMYYYY (xxx)			xxx

Notes: (C) = censored observation
[a] Duration of response is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of progressive disease (disease progression as assessed based upon tumor measurements and recorded on the CRF page “overall tumor assessment”). See the SAP for censoring rules.
[b] Time to response is defined as the time from the randomization date to the date of the first documentation of objective response (CR or PR).
[c] Duration of SD is defined for subjects whose best response is SD as the time from the date of randomization to the date of the first documentation of progressive disease (disease progression as assessed based upon tumor measurements and recorded on the CRF page “overall tumor assessment”). See the SAP for censoring rules.
Source: adam.adtte

Programming notes:
Sort by best overall response.
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.7.1: Adverse Events
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	TEAE?	S: Class P: Preferred Term V: Verbatim	S: Start Date (Day) E: Stop Date (Day) O: Ongoing	NCI CTCAE Grade	SAE?	DLT?	Causality Pa: Patritumab Ce: Cetuximab Ci: Cisplatin Ca: Carboplatin	Action [a] Pa: Patritumab Ce: Cetuximab Ci: Cisplatin Ca: Carboplatin	Outcome [b]	Other Action [c]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	Yes	S: xxxxxxxxxxxx P: xxxxxxxxxxxx V: xxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: O: Yes	x	Yes	Yes	Related to Pa	Pa: xx Ce: xx	xx	x
	Yes	S: xxxxxxxxxxxx P: xxxxxxxxxxxx V: xxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: O: Yes	x	Yes	Yes	Related to Ci	Pa: xx Ce: xx	xx	x
	Yes	S: xxxxxxxxxxxx P: xxxxxxxxxxxx V: xxxxxxxxxxxx	S: yyyy-mm-dd (xxx) E: yyyy-mm-dd (xxx) O: No	x	No	es	Related to Pa and Ca	Pa: xx Ce: xx	xx	O
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M										

Notes: [a] Action Taken: N = Dose Not Changed, W = Drug Withdrawn, R = Dose Reduced, INT = Drug Interrupted
[b] Outcome: R = Recovered/Resolved, RS = Recovered/Resolved with Sequelae, F =Fatal, NR = Not Recovered/Not Resolved, UNK = Unknown
[c] Other Action: N = None, M = Medication Required, H = Hospitalization or prolongation of hospitalization required, O = Other

Source: adam.adae
Programming Note: continue for HRG Low and Overall on the next page

These Appendices follow Listing 16.2.7.1:

Listing 16.2.7.2: Serious Adverse Events, Including Those Leading to Deaths
Safety Analysis Set

Listing 16.2.7.3: Adverse Events Leading to Study Drug Discontinuation
Safety Analysis Set

Listing 16.2.7.4: Adverse Event Leading to Study Drug Interrupti n or Dose Reduction
Safety Analysis Set

Listing 16.2.7.5: Adverse Events o Interests
Safety Analysi Set

Listing 16.2.8.1.1: Laboratory Data – Hematology
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Lab Name	Parameter (Standard Units)	Visit	Date/Time of Sample (Day)	Result [a]	Normal Limits	Change from Baseline	CTC Grade
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	xxxxxxxxxxx	Test #1 (xxxxx)	Screening	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx-xxxx		
			CxDx	yyyy-mm-dd hh:mm (xx)	xxxx (H)	xxxx-xxxx	xxxx	x
			CxDx	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx-xxxx	xxxx	
			CxDx	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx-xxxx	xxxx	
		Test #2 (xxxxx)	Screening	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx-xxxx		
			CxDx	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx-xxxx	xxxx	
			CxDx	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx-xxxx	xxxx	

Notes: [a] H = Abnormally High, L = Abnormally Low

Source: adam.adlb
Programming Note: continue for HRG Low and Overall on the next page

These Appendices follow Listing 16.2.8.1.1:

Listing 16.2.8.1.2: Laboratory Data – Chemistry
Safety Analysis Set

Listing 16.2.8.1.3: Laboratory Data – Urinalysis
Safety Analysis Set

Programming Notes: Remove Change from baseline and CTC grade columns for urinalysis.

Listing 16.2.8.1.4: Laboratory Data – Coagulat on
Safety Analysis Set

Listing 16.2.8.2.1: Clinically Significant Laboratory Abnormalities or Abnormalities of CTCAE Grade 3 or 4 – Hematology
Safety Analysis Set

Listing 16.2.8.2.2: Clinically Significant Laboratory Abnormalities or Abnormalities of CTCAE Grade 3 or 4 – Chemistry
Safety Analysis Set

Listing 16.2.8.2.3 Subjects with Liver Enzymes (ALT, AST) and Total Bilirubin (TBL) Elevation
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Investigator/ Country/Site	Visit	Date/Time of Sample (Day)	AST (xxx-xxx) [a]	ALT (xxx-xxx) [a]	Total Bilirubin (xxx-xxx) [a]	ALP (xxx-xxx) [a]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	xxxxxxxxxxx	Screening	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx	xxxx-xxxx	xxxx
		CxDx	yyyy-mm-dd hh:mm (xx)	xxxx (H)	xxxx (H)	xxxx-xxxx	xxxx (H)
		CxDx	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx	xxxx-xxxx	xxxx
		CxDx	yyyy-mm-dd hh:mm (xx)	xxxx	xxxx	xxxx-xxxx	xxxx

Notes: [a] H = Abnormally High, L = Abnormally Low

Source: adam.adlb
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.8.3.1: Vital Signs
Safety Analysis Set

HRG High

Subject ID/ Group/Age/ Gender	Visit	Time Point	Date of Vital Sign Assessment (Day)	Weight (kg)	Pulse Rate (beat/min)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Temperature (C)
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	Screening		yyyy-mm-dd (xx)	xxx.x	xxx	xxx	xxx	xxx.x
	C1D1	Pre-Infusion	yyyy-mm-dd (xx)	xxx.x	xxx	xxx	xxx	xxx.x
	C1D1	End of Infusion	yyyy-mm-dd (xx)	xxx.x	xxx	xxx	xxx	xxx.x
	C1D8		yyyy-mm-dd (xx)					
	C1D15		yyyy-mm-dd (xx)	xxx.x	xxx	xxx	xxx	xxx.x
	CxDx		yyyy-mm-dd (xx)	xxx.x	xxx	xxx	xxx	xxx.x
	EOT		yyyy-mm-dd (xx)	xxx.x	xx	xxx	xxx	xxx.x

Source: adam.advs

Programming note: Time point will be missing for every visit except C1D1.
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.8.3.2: 12-Lead ECG
Safety Analysis Set

HRG High

Subject ID/Group/Age/ Sex	Visit	Date of ECG Assessment (Day)	ECG Interpretation	Heart Rate (beats/min)	ECG Intervals (msec)
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	Screening	yyyy-mm-dd (xx)	Normal	xxx	PR: xx RR: xx QRS: xxx QT: xxx QTcB: xxx QTcF: xxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	Screening	yyyy-mm-dd (xx)	Abnormal, not clinically significant	xxx	PR: xx RR: xx QRS: xxx QT: xxx QTcB: xxx QTcF: xxx

QTcB = QTc by Bazett's Correction Formula (msec); QTcF = QTc by Fridericia's Correction Formula (msec)

Source: adam.adeg
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.8.3.3: Physical Examination
Safety Analysis Set

HRG High

Subject ID/ Group/Age/Gender	Visit	Physical Exam Status	Date of Exam (Day)	Body System	Description of Findings
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	Screening	No clinically significant findings	yyyy-mm-dd (xx)	xxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxx
				xxxxxxxxxxxxxxx xxxxxxxx xxxxxx xxxxxxxxx xxxx xxxxx xxxxxxxxx xxxxxxxxxxxxxxx xxxxxxxxxxxxxxx	xxxxxxxxxxxxx xxxxxx xxxxxxxxxxx xxxxxxxxxx xxxxxxxx xxxxxx
	CxDx	Clinically significant changes	yyyy-mm-dd (xx)		
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/M	Screening	No clinically significant findings	yyyy-mm dd (xx)	xxxxxxxxxxxxxxx	
				xxxxxxxxxxxxxxx xxxxxxxxxxxxxxx	
	CxDx	Not Done			

Source: adam.adpe
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.8.3.4: Eastern Cooperative Oncology Group (ECOG) Performance Status
Safety Analysis Set

HRG High

Subject ID/ Group/Age/Gender	Visit	ECOG Assessed?	Date of ECOG Assessment (Day)	ECOG Score [a]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	Screening	Yes	yyyy-mm-dd (xxx)	x
xxxxxx/ Patritumab + cetuximab + cisplatin or carboplatin /xx/M	Screening	Yes	yyyy-mm-dd (xxx)	x
	CxDx	Yes	yyyy-mm-dd (xxx)	x
xxxxxx/ Patritumab + cetuximab + cisplatin or carboplatin/xx/F	Screening	Yes	yyyy-mm-dd (xxx)	x
	CxDx	No	yyyy-mm-dd (xxx)	x

Notes: [a] 0 = Fully active, able to carry on all pre-disease performance without restriction;
1= Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature;
2 = Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours;
3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours;
4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair;
5 = Dead.

Source: adam.adqs
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.8.3.5: Echocardiogram
Safety Analysis Set

HRG High

Subject ID/ Group/Age/Gender	Visit	ECHO or MUGA Scan Completed?	Date Procedure Performed (Day)	Type of Assessment	Left Ventricular Ejection Fraction (LVEF) (%)
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	Screening	Yes	yyyy-mm-dd (xx)	ECHO	xx.x
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/M	Screening	Yes	yyyy-mm-dd (xx)	MUGA	xx.x
	CxDx	No	yyyy-mm-dd (xx)		
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	Screening	Yes	yyyy-mm-dd (xx)		xx.x
	CxDx	Yes	yyyy mm-dd (xx)		xx.x

Source: adam.adeg
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.8.4.1: Human Anti-Humanized Antibody (HAHA)
Safety Analysis Set

HRG High

Subject ID/ Group/Age/Gender	Visit	Time Point	Date/Time of Sample Collection (Day)	Assay Type	Screening Results	Confirmatoy Results	Titer Results	Final Results
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	C1D1	xx	yyyy-mm-dd: hh:mm (xx)	xxxx	Negative			
	CxDx	xx	yyyy-mm-dd: hh:mm (xx)	xxxx	Nega ive			
	CxDx							
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	C1D1		yyyy-mm-dd: hh:mm (xx)	xxxx	Negative			
	CxDx		yyyy-mm-dd: hh:mm (xx)	xxxx	Positive			
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/ xx/F	C1D1		yyyy-mm-dd: hh:mm (xx)	xxxx	Negative			
	CxDx		yyyy-mm-dd: hh:mm (xx)	xxxx	Negative			
	CxDx		yyyy-mm-dd: hh:mm (xx)	xxxx	Negative			

Note: CxDx = Cycle x Day x

Source: adam.adbi
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.8.4.2: Tumor Tissue Sample Collection and Biomarker Results
Safety Analysis Set

HRG High

Subject ID/ Group/Age/Gender	Date of Collection (Day)	Sample ID	Sample Type	Biomarker Test (Standard Unit)	Result
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	yyyy-mm-dd (xxx)	xxxxxx	Fresh Tissue	Test #1 (xxx)	xxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/M	yyyy-mm-dd (xxx)	xxxxxx	Archived	Test #1 xxx)	xxxx
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	yyyy-mm-dd (xxx)	xxxxxx	Archived	Tes #1 xxx)	

Source: adam.adbi

Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.9.1.1: FACT-H&N Item Scores
FACT-H&N Analysis Set

HRG High

Subject ID/Group/ Age/Gender	Visit	Date of Assessment (Study Day)	Scale	Item	Raw Score	Imputed Score [a]
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	C1D1	YYYY-MM-DD (xxx)	HNS	$H\&N_i$	x	
				(i=1..12)	x	x
			EWB	GE1	x	
				GE2	x	x
			FWB	GF1	x	x
				GF2	x	
			PWB	GP1	x	x
				GP2	x	
			SWB	GS1	x	x
				GS2	x	x
	C1D1	YYYY-MM-DD (xxx)	HNS	$H\&N_i$	x	
				H&N2	x	
			EWB	GE1	x	
				GE2	x	
			FWB	GF1	x	x
				GF2	x	x
			…	…		

Notes: EWB=Emotional Well-Being; FWB=Functional Well-Being; PWB=Physical Well-Being; SWB=Social/Family Well-Being; HNS = Head and Neck Additional Concerns Subscale.
[a] If fewer than 50% of the raw score are missing on the subscale the raw score is imputed using the mean of the non-missing items.
Source: adam.adqs
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.9.1.2: FACT-H&N Total and Subscale Scores
FACT-H&N Analysis Set

HRG High

Subject ID/Group/Age/Gender	Visit	Date of Assessment (Study Day)	PWB (# Missing)	SWB (# Missing)	EWB (# Missing)	FWB (# Missing)	HNS Score (# Missing)	FHNSI Score (# Missing)	FACT-H&N
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	C1D1	YYYY-MM-DD (xxx)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx
	CxD1	YYYY-MM-DD (xxx)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx
xxxxxx/ Patritumab + cetuximab + cisplatin or carboplatin /xx/M	C1D1	YYYY-MM-DD (xxx)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx
	C2D1	YYYY-MM-DD (xxx)	xx (x)	x (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx
xxxxxx/ Patritumab + cetuximab + cisplatin or carboplatin/xx/F	C1D1	YYYY-MM-DD (xxx)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx
	C2D1	YYYY-MM-D (xxx)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx
	CxD1								

Notes: EWB=Emotional Well-Being; FWB=Functional Well-Being; PWB=Physical Well-Being; SWB=Social Well-Being; HNS = Head and Neck Additional Concerns Subscale; FHNSI = Head & Neck Symptom Index; FACT-H&N total score = PWB + SWB + EWB + FWB + HNS

Source: adam.adqs
Programming Note: continue for HRG Low and Overall on the next page

Listing 16.2.9.2: EQ-5D Scale Scores
EQ-5D Analysis Set

HRG High

Subject ID/Group/ Age/Gender	Visit	Date of Assessment (Study Day)	Item	Response	Change from Baseline
xxxxxx/ Patritumab+ cetuximab + cisplatin or carboplatin/xx/F	C1D1	YYYY-MM-DD (xxx)	1. Mobility	Not a problem	
			2. Self-care	A modera e problem	x
			3. Usual Activities		
			4.Pain/Discomfort		
			5. Anxiety/Depression		x
			VAS Score		x
			Index Score		
	C1D1	YYYY-MM-DD (xxx)			

Notes: EQ-5D descriptive system is coded 1 - 5, with higher core indicating more severe result.
The VAS score is numbered from 0 to 100, which 100 means the best health you can imagine, 0 means the worst health you can imagine.
Based on the patient's response to each of the 5 dimensions, a 1-digit number expressing the level selected for that dimension will be recorded and combined in a 5-digit number describing the respondent's health state. Each of the 5-digit combinations will be converted to a country-specific index value defining the health state of the patient.

Source: adam.adqs
Programming Note: continue for HRG Low and Overall on the next page