SeattleGenetics

STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNLVA-005
Version:	Version 1 31-May-2019
Protocol Title:	Open-Label Phase 2 Study of Ladiratuzumab Vedotin (LV) for Unresectable Locally Advanced or Metastatic Solid Tumors
Study Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	Ladiratuzumab vedotin
Protocol Number/Amendment:	SGNLVA-005/Original
SAP Version:	Version 1
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The individuals signing below have reviewed and approve this statistical analysis plan.

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ATA	antitherapeutic antibodies
CI	confidence interval
CPI	checkpoint inhibitor
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy-evaluable
EOS	end of study
EOT	end of treatment
FAS	full analysis set
HNSCC	head and neck squamous cell carcinoma
IV	intravenous
LLOQ	lower limit of quantification
LV	ladiratuzumab vedotin
MedDRA	Medical Dictionary for Regulatory Affairs
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
NCA	noncompartmental analysis
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PPoS	predictive probability of success
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SAE	serious adverse event
SD	stable disease
SCLC	small cell lung cancer
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNLVA-005, entitled "Open-Label Phase 2 Study of Ladiratuzumab Vedotin (LV) for Unresectable Locally Advanced or Metastatic Solid Tumors", Original version dated 22Apr2019. Results of the proposed analyses will become the basis of the clinical study report for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final clinical study report (CSR). Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the CSR.

2 STUDY OBJECTIVES

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of LV in subjects with solid tumors. Specific objectives and corresponding endpoints for the study are summarized in Table 2-1.

Table 2-1: Objectives and corresponding endpoints

Primary Objective	Corresponding Primary Endpoint
Evaluate antitumor activity of LV	Investigator-determined confirmed ORR as measured by RECIST v1.1
Secondary Objectives	**Corresponding Secondary Endpoints**
Evaluate the safety and tolerability of LV	Type, incidence, severity, seriousness, and relatedness of AEs
Evaluate stability and control of disease	Investigator-determined DCR as measured by RECIST v1.1
Evaluate durability of response in subjects who respond to LV	Investigator-determined DOR as measured by RECIST v1.1
Evaluate PFS of subjects treated with LV	Investigator-determined PFS as measured by RECIST v1.1
Evaluate survival of subjects treated with LV	OS
Assess PK of LV	Selected PK parameters for LV, total antibody, and MMAE
Assess immunogenicity of LV	Incidence of ATA to LV
Additional Objectives	**Corresponding Additional Endpoints**
Assess biomarkers of biological activity and resistance and predictive biomarkers of response	Relationship between biomarkers in blood and tumor tissue to efficacy, safety, or other biomarker endpoints following treatment with LV

3 STUDY DESIGN

This global, open-label, multicenter trial is designed to assess the activity, safety, and tolerability of LV monotherapy for the treatment of solid tumors. Subjects with the following advanced solid tumors will be enrolled:

Cohort 1: SCLC

Cohort 2: NSCLC-squamous

Cohort 3: NSCLC-nonsquamous

Cohort 4: HNSCC

Cohort 5: esophageal squamous cell carcinoma (esophageal-squamous)

Cohort 6: gastric and gastroesophageal junction (GEJ) adenocarcinoma

Interim futility analyses will be performed separately for each cohort after at least 12 subjects of a given cohort have been treated and are efficacy evaluable post-baseline (**Error! Reference source not found.**). Enrollment to each cohort may be held after 12 subjects for interim futility analysis of the respective cohorts. The Bayesian predictive probability approach will be used to determine the futility criteria. At the time of each interim analysis, the predictive probability of success (PPoS) will be calculated. A PPoS <10% indicates that it is unlikely the objective response rate (ORR) will be better than the response rate of current standard of care at the end of the study given the interim result. Based on efficacy and safety data, together with the PPoS, a cohort may be stopped early by the sponsor.

In all subjects, LV will be administered by IV infusion at a dose of 2.5 mg/kg on Day 1 of each 21-day cycle. Dosing may not exceed 250 mg per infusion. An individual's dose may be modified based upon treatment-related adverse events (AEs). Tumor assessment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) will be performed every 6 weeks for the first 12 months and then every 12 weeks thereafter. Objective responses will be confirmed with repeat scans 4-6 weeks after the first documentation of response.

4 ANALYSIS SETS

4.1 Full Analysis Set (FAS)

The full analysis set (FAS) includes all patients who received any amount of study drug. All efficacy analyses will be based on the FAS.

4.2 Safety Analysis Set

The safety analysis set includes all patients who received any amount of study drug, and thus is equivalent to the FAS. All safety analyses will be based on the safety analysis set.

4.3 Efficacy-Evaluable (EE) Analysis Set

The efficacy evaluable analysis set includes subjects who received any amount of study drug and had at least one post-baseline disease assessment per RECIST v1.1 or had clinical progression per investigator judgment or discontinued from study.

5 STATISTICAL CONSIDERATIONS

5.1 General Principles

In general, all analyses will be presented by cohort and total unless otherwise specified. Descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages per category for categorical variables.

Unless otherwise specified, confidence intervals (CI) will be calculated at 2-sided 90% level.

The 2-sided 90% exact CI using the Clopper-Pearson method will be calculated for the response rates where applicable (e.g., ORR) (Clopper 1934).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 90% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Any analysis not described in this plan will be considered exploratory, and will be documented in the clinical study report as a post hoc analysis or change to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to Section 16 of the CSR.

All statistical Tables, Listings and Figures will be produced using SAS®, version 9.4 or higher. Other statistical software, if used, will be described in the CSR.

5.2 Determination of Sample Size

Up to 180 subjects may be enrolled in the study with up to 30 subjects enrolled in each cohort. In addition, the cohorts may be expanded to enroll additional subjects to better characterize LV activity. A cohort may be expanded to further characterize antitumor activity if the safety profile is acceptable, other efficacy endpoints are comparable to current standard of care, and the confirmed ORR meets cohort-specific criteria. Additional cohorts may also be added in future protocol amendments for additional indications, alternative dosing schedule, biopsy/biomarker analysis, and LV based combination therapy.

The sample size is not based on power calculations for formal hypothesis testing, but is selected to provide a degree of characterization of commonly occurring AEs in the safety profile.

For a sample size of 30 subjects per cohort, assuming confirmed ORR is between 10% and 50%, the 2-sided 90% exact confidence interval (CI) are summarized below:

Confirmed ORR	90% Exact CI (N=30)
10%	(3%, 24%)
20%	(9%, 36%)
30%	(17%, 47%)
40%	(25%, 57%)
50%	(34%, 66%)

This sample size of 30 patients per cohort would additionally provide the following probabilities of observing at least 1 patient having an AE, as summarized below.

True AE Incidence Rate	Probability of Observing at Least One Patient Having an AE (N=30)
5%	79%
10%	96%

5.3 Randomization and Blinding

This is a single arm, open label study. Randomization or blinding will not be performed.

5.4 Data Transformations and Derivations

5.4.1 General

Reported age in years will be used; if not available, age at informed consent in years will be calculated with the SAS® INTCK function (with method specified as "continuous") using informed consent date and birth date.

Time variables based on two dates (e.g., Start Date and End Date) will be calculated as (End Date – Start Date +1 [in days]) unless otherwise specified in the planned analysis section.

Specifically, Study Day will be calculated as (Date–First Dose Date+1) for dates on or after the first dose date. The date of first dose will be Study Day 1. For dates prior to the first dose date, Study Day will be calculated as (Date–First Dose Date). For example, the date before the first dose date will be Study Day -1.

The following unit conversion will be implemented unless otherwise specified:

Months=Days/30.4375

Years=Days/365.25

Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

The end-of-treatment (EOT) date will be the date the EOT visit is performed; if an EOT visit is not performed then the EOT date will be either the end-of-study (EOS) date or 30 days after the last dose of any study drug, whichever is earlier.

5.4.2 Best Response

The determination of antitumor activity will be based on objective response assessments made by the investigator according to the RECIST v1.1 (Eisenhauer 2009). Only response assessments on or prior to start date of any new anticancer therapy will be considered for best response. The patient's best response will be the best demonstrated response to date that has been confirmed, when confirmation is required (i.e. for PR and CR only). The patient's best response will be used in determining the ORR.

A response (CR or PR) will be considered confirmed if the subsequent disease assessment conducted no earlier than 4 weeks after the initial response still shows CR or PR. A patient will have a best response of SD if there is at least one SD assessment (or better) $\geq$5 weeks after the start of treatment and the patient does not qualify for confirmed CR or PR. RECIST v1.1 outlines scenarios for best overall responses when confirmation of CR and PR is required.

5.4.3 Response Assessment Dates

For efficacy assessments, the date of response assessment of CR, PR or SD will be the latest of all radiologic scan dates for the given response assessment. The date of progression per RECIST v1.1 will be the earliest of all radiologic scan dates for the given PD response assessment.

5.5 Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified. Missing AE start date and/or end date will be imputed while calculating duration of events and treatment-emergent status (see Appendix A for imputation details).

For time-to-event endpoints, e.g., duration of response, time to response, PFS, and OS, patients who have no specific event will be censored as specified for each respective endpoint in Section 6.5.

Patients who do not have at least two (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders for analysis of the primary endpoint.

Missing subsequent anticancer treatment start date will be imputed while deriving the time-to-event endpoints as applicable (see Appendix B for imputation details).

For prior therapies end dates, if month and year are present and only day is missing, day may be imputed. The imputed day will be the last day of the month if the prior therapy end date is earlier than the enrollment date based on the available month and year; the imputed day will be the day before enrollment if the prior therapy was stopped within the same month and year as enrollment. If month or year is missing, no imputation will be performed.

For prior therapies start dates, if month and year are present and only day is missing, day may be imputed. The imputed day will be the first day of the month. If month or year is missing, no imputation will be performed.

Unless otherwise specified, if the numeric value of a clinical laboratory test is not available because it is below the lower limit of quantification (LLOQ), "< LLOQ" should be used whenever applicable. In cases where a numeric value is required, e.g., calculating the mean and standard deviation, the LLOQ/2 will be used for the calculation.

5.6 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

5.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned in this study.

5.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroups may include but are not limited to the following:

- Age (18–64, ≥65 years old)
- LIV-1 expression (high, low)
- Prior treatment with CPIs (yes, no)
- Prior treatment with taxanes (yes, no)
- ECOG performance score at baseline (0, 1)
- Number of prior systemic therapies (1, 2, 3, ≥4)
- Time since initial disease diagnosis (<6 month, ≥6 month)
- Time since initial metastatic/locally advanced disease diagnosis (<6 month, ≥ 6 month)
- Time since initial metastatic/locally advanced disease diagnosis (<3 month, ≥ 3 month)
- Time since end of the last prior systemic therapy (<3 month, ≥ 3 month)
- History of brain metastasis (yes, no)
- Liver metastasis at time of enrollment (yes, no)

If the number of patients in some subgroups is not sufficiently large (e.g., <5), the subgroup analysis may not be performed or the small subgroups may be combined if applicable.

5.9 Covariates

No adjustments for covariates are planned in the analyses.

5.10 Timing of Analyses

The primary analysis will be conducted when all treated subjects in a cohort have been followed for at least 6 months or come off study, whichever comes first. Subsequent data cutoff dates may be defined to allow for more precise estimates of time-to-event endpoints.

Interim analysis for futility will be performed separately for each cohort after at least 12 subjects of a given cohort have been treated and are efficacy evaluable post-baseline.

6 PLANNED ANALYSES

6.1 Disposition

Patient disposition will be summarized by cohort and total for all enrolled patients with descriptive statistics. Patients who discontinue study treatment and patients who discontinue the study will be summarized along with reason for discontinuation. The number of patients who signed informed consent and the number and percentage of patients in each analysis set will be summarized.

6.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age at consent, gender, ethnicity, race, baseline height, weight, and ECOG score will be listed and summarized by cohort and total using the FAS. Disease specific characteristics will be listed and summarized by cohort and total using the FAS.

6.3 Protocol Deviations

Important protocol deviations (defined as protocol violations by Seattle Genetics) are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be summarized by category. A list of patients with important protocol deviations will be presented.

6.4 Treatment Administration

Treatment administration will be summarized with descriptive statistics using the safety analysis set. Summaries may include but are not limited to the following:

- Duration of treatment (in weeks), which is defined as time from the first study dose to the earliest of 21 days after the last study dose, EOT visit, death date or start date of subsequent anticancer therapy if applicable.
- Number of cycles per patient

- Number and percentage of patients who were treated at each cycle
- Cumulative doses, which is defined as sum of the actual dose across all cycles.
- Average dose per cycle
- Absolute dose intensity (ADI), which is defined as the actual dose in mg/kg per week that a patient received over the entire treatment period. That is, ADI = Cumulative doses / treatment period in weeks, where treatment period is defined as time from the first study dose to 21 days after the last study dose [(last dose date +21) – first dose date]/7 regardless of death date.
- Relative dose intensity (RDI), which is defined as the ADI divided by the intended dose intensity (IDI). That is, RDI = ADI/IDI × 100, where IDI is defined as the intended dose (i.e., 2 mg/kg regardless of dose reduction in later cycles) in mg/kg per week.
- Number and percentage of patients whose dose was ever modified, which will be summarized by modification type (delay, reduction, unplanned dose adjustment), cycle and overall (i.e., overall drug administrations for a patient). The number and percentage of doses that were modified may also be summarized.

6.5 Efficacy Analyses

All efficacy endpoints will be analyzed by cohort and total using the FAS. In addition, the objective response rate and disease control rate will be analyzed using the EE set.

6.5.1 Primary Endpoint

6.5.1.1 Confirmed Objective Response Rate (ORR)

The primary endpoint of this study is the confirmed ORR per investigator assessment. The confirmed ORR is defined as the proportion of patients who achieve a confirmed CR or PR according to RECIST v1.1 (Eisenhauer 2009). Patients who do not have at least two post-baseline response assessments (initial response and confirmation scan) will be counted as non-responders. Confirmation means a PR is followed by a PR or CR at least 4 weeks later, or a CR is followed by a second CR at least 4 weeks later.

The confirmed ORR of each cohort and its exact 2-sided 90% CI will be calculated.

This endpoint will also be summarized by the subgroups defined in Section 0.

6.5.2 Secondary Endpoints

6.5.2.1 Disease Control Rate (DCR)

DCR is defined as the proportion of patients who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator, or meet the SD criteria at least once after start of study treatment at a minimum interval of 5 weeks. Patients who do not have at least 1

post-baseline response assessment or patients whose response cannot be assessed will be counted as not achieving disease control.

As an exploratory analysis, DCR will also be calculated without requiring confirmation of CR or PR for disease control.

DCR will be estimated for each cohort and its exact 2-sided 90% CIs will be calculated.

6.5.2.2 Duration of Response (DOR)

DOR is defined as the time from the first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD or death due to any cause, whichever comes first. PD includes radiologic evidence of tumor progression and clinical progression per investigator.

Patients who are not evaluable or have a response of SD or better per RECIST v1.1 at the same visit as investigator claim of clinical progression will be counted as disease progression (i.e., an event). The date of progression will be the date of investigator claim of clinical progression or PD date per RECIST v1.1, whichever is earlier.

DOR data will be censored as described below:

- Patients who do not have PD and are still on study at the time of an analysis will be censored at the date of last disease assessment documenting absence of PD.
- Patients who have started a new anticancer treatment prior to documentation of PD will be censored at the date of last disease assessment prior to the start of new treatment.
- Patients who are removed from the study prior to documentation of PD will be censored at the date of last disease assessment documenting absence of PD.

DOR will only be calculated for patients who achieve a confirmed CR or PR.

DOR will be analyzed by cohort using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median DOR and its 2-sided 90% CI will be calculated as appropriate.

Sensitivity analyses will be performed for DOR to evaluate the robustness of treatment effects:

- A sensitivity analysis will be performed by censoring deaths or PD per RECIST v1.1 occurring after two or more missed visits at the last disease assessment;
- Another sensitivity analysis will be performed by counting PD or Death which occurred after start of new anti-cancer as events;
-

6.5.2.3 Progression-Free Survival (PFS)

PFS is defined as the time from the start of study treatment to the first documentation of PD or death due to any cause, whichever comes first.

The same censoring rules as outlined in Section 6.5.2.2 for DOR will be applied to PFS. Patients lacking an evaluation of tumor response after their first dose of study drug will have their event time censored at Day 1.

PFS will be analyzed by cohort using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its 2-sided 90% CI will be calculated as appropriate. The PFS rates at 3 and 6 months, and every 3 months thereafter, will be reported and their 2-sided 90% CIs will be calculated.

Sensitivity analysis of PFS will be performed as described in Section 6.5.2.2 for DOR.

6.5.2.4 Overall Survival (OS)

OS is defined as the time from the start of study treatment to date of death due to any cause. In the absence of death, survival time will be censored at the last date the patient is known to be alive (i.e., date of last contact). Patients lacking data after their first dose of study drug will have their survival time censored at Day 1.

OS will be analyzed by cohort using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its 2-sided 90% CI will be calculated as appropriate. The OS rates at 6 and 12 months, and every 6 months thereafter, will be reported and their 2-sided 90% CIs will be calculated.

6.6 Safety Analyses

All safety analyses will be performed by cohort and total using the safety analysis set.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 22.0 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 5.0 or higher).

Concomitant medications will be coded using WHO Drug Global (version: Mar 2019 B3 format or more recent).

6.6.1 Adverse Events

AEs will be summarized by MedDRA preferred term in descending frequency of occurrence unless otherwise specified. For incidence reporting, if a patient reports more than one AE that was coded to the same system organ class or preferred term, the patient will be counted only once for that specific system organ class or preferred term.

A treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment.

Summaries of AEs will be provided by cohort and total for the following:

- TEAEs
- Grade 3 or higher TEAEs
- TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term and maximum severity. At each system organ class or preferred term, multiple occurrences of events within a patient are counted only once at the highest severity
- AEs related to study drug
- AEs leading to dose delay
- AEs leading to dose reduction
- AEs leading to unplanned dose adjustment
- AEs leading to treatment discontinuation
- AEs leading to death
- Infusion related reactions
- SAEs
- SAEs by system organ class and preferred term
- SAEs related to study drug
- Treatment-emergent Adverse Events of Special Interest (AESI) by system organ class, preferred term and maximum severity
- Treatment-emergent AESI
- Serious AESI

All AEs, SAEs, AEs leading to treatment discontinuation, and AEs leading to death will be listed.

6.6.1.1 Adverse Events of Special Interest (AESI)

Adverse events of peripheral neuropathy are considered AEs of special interest. Other AEs may also be added as AESI, as necessary .

Time to AE onset and time to resolution may be analyzed for treatment-emergent AESI, as appropriate. Patient level time to AE onset and time to resolution will be analyzed by cohort using Kaplan-Meier methodology. Treatment-emergent AESI outcomes will be tabulated. Only patients with treatment-emergent AESI events will be included in these analyses.

Time to onset of treatment-emergent AESI is defined as time from the date of first dose to start date of first treatment emergent AESI.

A treatment-emergent AESI is considered as resolved if the AESI has outcome of recovered/resolved or recovered/resolved with sequelae. For patients with multiple treatment-emergent AESI events, patient level resolution is defined as all treatment-emergent AESI events are resolved as defined above. Patient level time to resolution is defined as time from onset of first treatment-emergent AESI to the time of resolution of all treatment-emergent AESI events (i.e., end date of last resolved AESI event). Patients who do not have resolution for treatment-emergent AESI events will be censored at the date of last follow up.

6.6.2 Clinical Laboratory Parameters

All laboratory results up to the end of treatment visit will be presented in standardized units. Grading of laboratory values will be assigned programmatically per the NCI CTCAE v5.0. The highest post-baseline grade will be presented for each lab test. Shift tables comparing the highest post-baseline to baseline CTCAE grade may be presented.

In addition, clinical laboratory data may be presented graphically for selected lab tests, by scheduled visit.

Laboratory values will be listed with grade per CTCAE and flagged when values are outside the normal reference range.

6.6.3 Deaths

The number of total deaths, deaths that occur within 30 days of last study treatment, and deaths that occur more than 30 days after last study treatment as well as the relationship to disease will be summarized. In addition, cause of death will be displayed in MedDRA preferred term (unless otherwise specified) and summarized. Death information will be listed by patient.

6.6.4 Concomitant Medications

Concomitant medications will be summarized by the World Heath Organization (WHO) drug substance name. The number and percentage of patients taking concomitant medications may be tabulated for the following, but not limited to:

- Granulocyte-Colony Stimulating Factor (G-CSF)

Concomitant medications will be listed by patient.

6.6.5 Other Safety Analyses

6.6.5.1 Vital Signs

Vital sign measurements will be listed by patient for each time point. Summary statistics of vital signs and change from baseline may be tabulated where appropriate.

6.6.5.2 ECOG Performance Status

ECOG performance status will be summarized for each visit. Shifts from baseline to the lowest and highest post-baseline score may be tabulated.

6.6.5.3 ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled and unscheduled ECG, and shifts from baseline may be tabulated.

6.7 Additional Analyses

6.7.1 Pharmacokinetics and Immunogenicity Analyese

LV (ADC), total antibody, and MMAE concentrations will be summarized with descriptive statistics at each PK sampling time point. Selected PK parameters for LV, total antibody, and MMAE will be estimated by noncompartmental analysis and summarized using descriptive statistics. These data may be combined with PK data from other clinical trials with LV for population PK and exploratory exposure-response analyses.

The incidence of ATA will be summarized using the safety analysis set.

6.7.2 Biomarkers

Relationships of biomarker parameters (e.g., baseline values, absolute and relative changes from baseline) to efficacy, safety, and pharmacokinetic parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately in the Biomarker Analysis Plan.

7 INTERIM ANALYSIS

Interim analysis for futility will be performed separately for each cohort after at least 12 subjects of a given cohort have been treated and are efficacy evaluable post-baseline. Enrollment to each cohort may be held after 12 subjects for interim futility analysis of the respective cohorts.

The Bayesian predictive PPoS approach will be used to determine the futility criteria (Lee 2008). At the time of each interim analysis, the PPoS will be calculated. PPoS is the probability of achieving "success" should the cohort be continued to the maximum sample size of 30 given the data observed at interim, and a cohort is considered "success" if the posterior probability that the ORR exceeds the response rate of current standard of care (i.e., 15% for SCLC, 10% for NSCLC-squamous, 15% for NSCLC-nonsquamous, 10% for HNSCC, 10% for esophageal-squamous, and 15% for gastric and GEJ adenocarcinoma) is greater than 90%.

The ORR observed at interim will be counted as a response for the calculation of PPoS. Table 7-1 summarizes the PPoS based on the number of responses observed among the first 12 subjects.

Table 7-1: PPoS based on responses among the first 12 subjects

No. of responses[a] among the first 12 subjects	Predictive Probability of Success					
	SCLC (p_0=15%)	NSCLC-squamous (p_0=10%)	NSCLC-nonsquamous (p_0=15%)	HNSCC (p_0=10%)	Esophageal-squamous (p_0=10%)	gastric or GEJ adenocarcinoma (p_0=15%)
0	0.05%	0.2%	0.05%	0.2%	0.2%	0.05%
1	2%	8%	2%	8%	8%	2%
2	16%	36%	16%	36%	36%	16%
3	45%	73%	45%	73%	73%	45%
4	77%	94%	77%	94%	94%	77%
5	94%	100%	94%	100%	100%	94%

p_0 is the response rate of current standard of care of each cohort
a Including both confirmed and unconfirmed CR or PR observed at interim

If the PPoS is <10% (i.e., ≤1 response among the first 12 subjects), the data indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the cohort given interim results and the cohort could be stopped early due to insufficient activity. On the other hand, if the PPoS is >90%, the data suggests that if the same trend continues, there is a high probability to conclude a "success" at the end of the cohort. The PFS and OS will also be evaluated at the time of the interim analysis. Based on the efficacy and safety data, together with the PPoS, a cohort may be stopped early by the sponsor.

The predictive probability method allows the PPoS be computed at any interim time and provides flexibility in monitoring treatment activity continuously after the initial interim analysis.

In addition to the interim analysis for futility, interim data from the study may be presented at scientific meetings such as the annual meetings of the ASCO and the European Society for Medical Oncology.

8 CHANGES FROM PLANNED ANALYSES

8.1 Changes from the Original Protocol

Not Applicable.

8.2 Changes from the Original SAP

Not Applicable.

9 REFERENCES

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Lee JJ and Liu DD (2008). A predictive probability design for phase II cancer clinical trials. Clin Trials 5: 93-106.

Appendix A IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

The algorithm below should be used to impute adverse event (AE) start dates for which only partial information is known. The algorithm should be applied to every AE record on a record by record basis. AE start dates should be imputed before imputation of AE condition end date in all cases. The AE condition end date should only be used in the imputation of the AE start date if it is a full known date.

Incomplete Start Date: If AE condition end date* is not missing, and the imputed start date is after the end date, the start date will be set to the AE condition end date.

AE day and month are missing

If the year is the same as the year of first dose of any study treatment:
AE start date will be imputed as the first dose date of any study treatment
If the year is before the year of first dose of any study treatment:
AE start date will be imputed as December 31st
If the year is after the year of first dose of any study treatment:
AE start date will be imputed as January 1st

AE month only is missing

Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

If the month/year is the same as the month/year of first dose of any study treatment:
AE start date will be imputed as the first dose date of any study treatment
If the month/year is before the month/year of first dose of any study treatment:
AE start date will be imputed as the last day of the month

If the month/year is after the month/year of first dose of any study treatment:
AE start date will be imputed as the first day of the month

* only use condition end date if known and full end date is available.

Incomplete Stop Date: Within a single record, if the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

If AE outcome is "not recovered/resolved", "unknown", or blank: AE condition end date will not be imputed.

If AE outcome is "recovering/resolving", "recovered/resolved", "recovered/resolved with sequelae", or "fatal" apply the following:

AE day and month are missing

If the year is equal to the year of the last dose date:
AE condition end date will be imputed as the minimum of (last dose date + 30, death date, data extraction date, December 31st of the end date year)
If the year is not equal to the year of the last dose date:

AE condition end date will be imputed as the minimum of (death date, data extraction date, December 31st of the end date year)

AE month only is missing

Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year)

Example

AE Number 4: Condition/Event NAUSEA
First dose date 02APR2012

Prior to imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	UNAPR2012	2	recovering/resolving
2	UNAPR2012	04MAY2012	1	recovered/resolved

Post imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	**30**APR2012	2	recovering/resolving
2	**02**APR2012	04MAY2012	1	recovered/resolved

Appendix B IMPUTATION OF PARTIALLY MISSING SUBSEQUENT ANTICANCER THERAPY START DATE

The algorithm below should be used to impute subsequent anticancer therapy start dates for which only day is missing.

- If the month and year of the start date of subsequent anticancer therapy are the same as the month and year of a response assessment date, and
    - If the response is a PD, subsequent anticancer therapy start date will be imputed as the response assessment date or the day after the last study treatment, whichever is later.
    - If the response is not a PD, subsequent anticancer therapy start date will be imputed as the first day of the month or the day after the last study treatment, whichever is later.
- Else if the month and year of the start date of subsequent anticancer therapy are the same as the month and year of the end date of last study treatment, subsequent anticancer therapy start date will be imputed as the day after the last study treatment end date.
- Else if the start date of subsequent anticancer therapy is later than the end date of last study treatment based on available month and year, subsequent anticancer therapy start date will be imputed as the first day of the month.