SeattleGenetics

STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNLVA-002
Protocol Version:	Amendment 11; 19-Oct-2023
Protocol Title:	Single Arm, Open Label Phase 1b/2 Study of SGN-LIV1A in Combination with Pembrolizumab for First-Line Treatment of Patients with Unresectable Locally-Advanced or Metastatic Triple-Negative Breast Cancer
Study Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

As of 14-Dec-2023, Seagen Inc. became a part of Pfizer Inc.

APPROVAL SIGNATURES

Product:	Ladiratuzumab vedotin(LV; SGN-LIV1A)
SAP Version:	Final
Version Date:	01-May-2024

The individuals signing below have reviewed and approve this statistical analysis plan.

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LIST OF ABBREVIATIONS

ADC	antibody-drug conjugate
AE	adverse event
ATA	antitherapeutic antibodies
CI	confidence interval
CR	complete response
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
iCPD	confirmed progressive disease based on iRECIST guidelines
iDOR	duration of response based on iRECIST guidelines
iPFS	progression-free survival based on iRECIST guidelines
iRECIST	modified RECIST 1.1 for immune-based therapeutics
iUPD	unconfirmed progressive disease based on iRECIST guidelines
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PP	per-protocol
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNLVA-002, entitled "Single Arm, Open Label Phase 1b/2 Study of SGN-LIV1A in Combination with Pembrolizumab for First-Line Treatment of Patients with Unresectable Locally-Advanced or Metastatic Triple-Negative Breast Cancer". 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. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report.

2 OBJECTIVES AND ENDPOINTS

Primary Safety Objectives	Corresponding Endpoint
• Assess the safety and tolerability of the combination of SGN-LIV1A and pembrolizumab in patients with LA/M TNBC • Identify the recommended dose of SGN-LIV1A in combination with pembrolizumab in patients with LA/M TNBC	• Type, incidence, severity, seriousness, and relatedness of AEs • Laboratory abnormalities • Incidence of dose-limiting toxicity (DLT)
Primary Efficacy Objective	**Corresponding Endpoint**
• Evaluate the confirmed ORR of the combination of SGN-LIV1A and pembrolizumab in patients with LA/M TNBC	• Confirmed ORR as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objectives	**Corresponding Endpoints**
• Evaluate the DOR, DCR, PFS, and OS	• DOR as determined by RECIST v1.1 • DCR as determined by RECIST v1.1 • PFS as determined by RECIST v1.1 • OS
Exploratory Efficacy Objectives	**Corresponding Endpoints**

• Evaluate the ORR, DOR, DCR, and PFS according to iRECIST	• ORR as determined by iRECIST • DOR as determined by iRECIST • DCR as determined by iRECIST • PFS as determined by iRECIST
Pharmacokinetic and Immunogenicity Objectives	**Corresponding Endpoints**
• Assess PK and incidence of antitherapeutic antibodies (ATAs) of SGN-LIV1A	• Selected PK parameters for SGN-LIV1A, and MMAE • Incidence of ATAs to SGN-LIV1A
Biomarkers Objectives	**Corresponding Endpoints**
• Evaluate PD-L1 and LIV-1 expression-response relationship • Assess exploratory biomarkers (e.g., in the tumor immune microenvironment or periphery) of study treatment-mediated pharmacodynamic effects	• PD-L1 and LIV-1 expression-response relationship following treatment with SGN-LIV1A and pembrolizumab • Relationship between biomarkers in blood and tumor tissue to efficacy, safety, or other biomarker endpoints following treatment with SGN-LIV1A/pembrolizumab

RECIST = Response Evaluation Criteria in Solid Tumors; iRECIST = immune-related RECIST.

3 STUDY DESIGN

This is a single-arm, open-label, multicenter trial designed to assess the safety and efficacy of LV in combination with pembrolizumab for the treatment of LA/M TNBC. Patients will be enrolled into Part A, Part B, Part C, and Part D sequentially. Patients will enroll in Part B Cohort 1 and Part B Cohort 2 sequentially.

In Part A, patients will receive a dose of LV 2.5 mg/kg as an intravenous (IV) infusion over approximately 30 minutes followed by pembrolizumab 200 mg IV over approximately 30 minutes on Day 1 of each 21-day cycle. In consultation with the sponsor, eligible patients already on treatment prior to Amendment 2, may have their maximum weight cap per infusion increased to 100 kg or remain at 80 kg, if they are receiving benefit (complete response [CR], partial response [PR], or stable disease [SD]). Patients receiving >200 mg LV per infusion are required to be administered prophylactic granulocyte-colony stimulating factor (G-CSF). Dosing may be de-escalated based upon the frequency of dose- limiting- toxicities (DLTs) in Cycle 1.

Part B includes 2 expansion cohorts. Part B Cohort 1 will receive the MAD of LV 2.5 mg/kg. Part B Cohort 2 will receive the dose of LV 2.0 mg/kg. Patients will enroll sequentially into

Cohort 1 followed by Cohort 2. Patients receiving >200 mg LV per infusion are required to be administered prophylactic granulocyte-colony stimulating factor (G-CSF).

In Part C, patients will receive LV 1.0 or 1.25 mg/kg on Day 1, Day 8, and Day 15 in every 21-day cycle, not to exceed 200 mg per infusion, in combination with pembrolizumab administered on Day 1 of every cycle. Part C will have dose escalation and expansion cohorts. Dose escalation in Part C will be conducted using the modified toxicity probability interval (mTPI) method (Ji 2010). At least 2 patients will be enrolled in each dose escalation cohort. The safety monitoring committee (SMC) will evaluate the safety of each dose-level cohort and make dose escalation/de-escalation recommendations using the mTPI decision rules. Only 1 dose-escalation cohort will be open at a time.

The dose-expansion cohorts in Part C will assess the efficacy, safety, and tolerability in a larger number of patients. Dose-expansion cohorts may be opened at any dose level that has cleared DLT evaluation. DLT evaluation will only include data from the dose-escalation cohorts; however, the totality of data from all patients at each dose level will be used to determine the recommended q1wk LV dose.

In Part D, patients will receive LV 1.5 mg/kg administered on Day 1 and Day 8 (off Day 15) of every 21-day cycle, not to exceed 200 mg per infusion, in combination with pembrolizumab administered on Day 1 of every cycle. Ongoing, real-time, continuous review of patient safety and serious adverse events (SAEs) will be conducted by the sponsor's Drug Safety Department. Additionally, the independent safety monitoring committee (ISMC) will ensure periodic safety data review throughout the study.

Under Amendment 2 and later, dosing for patients in Parts A and B is based on patient actual body weight, except for patients weighing >100 kg, where dosing will be based on a 100 kg maximum weight per infusion. For patients in Parts C and D, LV dosing is based on the patient's actual body weight but there will be no weight cap per infusion. An individual's dose may be modified based upon treatment-related adverse events (AEs). In all patients, pembrolizumab 200 mg will be administered by IV infusion approximately 60–90 minutes after administration of LV.

Responses will be assessed by computed tomography (CT) scan and/or magnetic resonance imaging (MRI) scan every 6 weeks (±3 days) for the first 12 months after the first dose of LV and pembrolizumab and every 12 weeks (±7 days) thereafter through the end of the safety follow-up period. No additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time. Objective responses will be confirmed at least 4 weeks after first documentation of response. RECIST v1.1 will be used to score responses for the primary and secondary endpoints, and iRECIST will be used for exploratory endpoints. Investigators will make treatment decisions based on site assessments of scans using iRECIST.

Patients will continue to receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, or study termination by the sponsor.

Pembrolizumab may be administered for a maximum of 35 cycles (approximately 2 years). If LV or pembrolizumab is discontinued, patients may continue to receive the other drug with medical monitor approval. Patients who discontinue study treatment in the absence of disease progression will be followed every 6 weeks for response assessments, physical examinations, and survival until withdrawal of consent, initiation of a new anticancer therapy, death, or study closure, whichever occurs first. After 1 year on study, the frequency of follow-up visits will be reduced to every 12 weeks. All patients, including those with progressive disease (PD), will be followed for survival until the end of the safety follow-up period, death, or study closure, whichever occurs first.

After disease progression or initiation of a new anticancer treatment, survival follow-up will be conducted every 12 weeks (±2 weeks) starting from the last radiographic scan demonstrating disease progression or from initiation of the new anticancer treatment. Survival follow-up will continue until the end of the safety follow-up period, death, or study closure, whichever comes first. Follow-up may be conducted with clinic visits or telephone calls. No further response assessments are required.On a periodic basis, an SMC will monitor the safety of patients participating in the trial. The SMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. An ongoing, real-time review of patient safety and (SAEs) will also be conducted by the sponsor's Drug Safety Department. In addition, an ISMC composed of physicians who are not involved in this study, as well as sponsor representatives, will periodically review cumulative safety data and provide recommendations to the sponsor. Continuous monitoring of the benefit-risk profile will be conducted and continuation of enrollment to the cohort may be altered depending on the benefit-risk profile.

4 ANALYSIS SETS

This section defines each of the analysis sets that will be utilized.

4.1 All Treated Analysis Set

The all treated analysis set will include all patients who receive any amount of SGN-LIV1A or pembrolizumab.The all treated analysis set will be used as the primary dataset for efficacy analysis.

4.2 Safety Analysis Set

The safety analysis set will include all patients who receive any amount of SGN-LIV1A or pembrolizumab. The safety analysis set will be used for all safety and PK analyses. This is also called the all treated patients set for efficacy analyses.

4.3 DLT Evaluable (DE) Analysis Set

The DLT-evaluable (DE) analysis set includes all treated patients in Part A who either (1) experienced a DLT or (2) received at least 75% of intended SGN-LIV1A and pembrolizumab doses and were followed for the full DLT evaluation period. Patients will be replaced for DLT evaluation if, for reasons other than DLT, they are ineligible for DLT evaluation (e.g., pembrolizumab IRR Grade ≥ 3, receipt of prohibited concomitant medication, patient does not meet eligibility criteria), or do not complete the DLT evaluation period.

5 STATISTICAL CONSIDERATIONS

5.1 General Principles

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be summarize continuous variables, Frequencies and percentages will be used to summarize categorical variables. The two-sided 95% exact confidence interval using Clopper-Pearson methodology (Clopper 1934) will be calculated for the response rates where applicable (e.g., ORR).

The median survival time will be estimated using the Kaplan-Meier method; the associated 95% confidence interval (CI) will be calculated based on the complementary log-log transformation (Collett 1994).

Unless otherwise specified, data are to be summarized by dose level and overall. DLT analysis will only include patients in Part A and Part C dose finding part.

Any analysis not described in this plan will be considered exploratory, and will be documented in the clinical study report (CSR) as a post hoc analysis or a 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 the appendix of the CSR. All statistical tables, listings, and figures will be produced using SAS, version 9.3 or more recent. Other statistical software, if used, will be described in the CSR.

5.2 Determination of Sample Size

Approximately 189–211 patients will be enrolled in this study, of which approximately 12–24 patients will be enrolled in Part A, approximately 73 patients will be enrolled in Part B (approximately 48 in Cohort 1 and approximately 25 in Cohort 2), and approximately 64 enrolled in Part C, and approximately 40 patients will be enrolled in Part D..

5.2.1 Part A

Part A will start with 6 patients at 2.5 mg/kg, capped at 80 kg prior to Amendment 2 or 100 kg under Amendment 2 and later. If 2 or more patients experience a DLT, the dose level will be de-escalated to 2.0 mg/kg, capped at 80 kg prior to Amendment 2 or 100 kg for patients treated under Amendment 2 and later. If there are <2 patients experiencing DLTs, the dose level will be expanded to a total of 12 patients. If 4 or more patients experience a DLT among the 12 patients, the dose level will be de-escalated to 2.0 mg/kg, as described above. If <4 patients experience a DLT among the 12 patients, Part B Cohort 1 of the study may be initiated at 2.5 mg/kg, capped as described above.

If the dose level is reduced to 2.0 mg/kg, this dose level will initially enroll 6 patients and the same dose de-escalation algorithm will be used. If further de-escalation is needed, the dose level will be determined by the sponsor in consultation with the SMC.

If the true incidence rate of DLT is 10%, the probability of de-escalation to 2.0 mg/kg is 12%. The probability of de-escalation increases to 96% if the true incidence rate of DLT is 50%.

5.2.2 Part B

Once the MAD has been identified in Part A, Patients will be enrolled in Part B Cohort 1 at the MAD. Approximately 42 LIV-1-positive patients in total will be enrolled at the MAD. Based on the SGNLVA-001 phase 1 study, it is estimated that about 70% of patients are LIV-1-positive. Approximately 60 patients are expected to be enrolled at the MAD, assuming that Part A will enroll 12 patients at the MAD and approximately 48 patients are expected to be enrolled in Part B Cohort 1 at the MAD. Assuming the observed ORR is between 50% and 70%, the widths of 2-sided 95% confidence intervals (CIs) are summarized as below.

Confirmed ORR	Expected width of 95% CI on LIV-1-positive patients (N=42)	Expected width of 95% CI on all patients at the MAD(N=60)
50%	±16%	±13%
60%	±16%	±13%
70%	±15%	±12%

Part B Cohort 2 will enroll approximately 25 patients at 2.0 mg/kg. With the patients in Part A enrolled at 2.0 mg/kg, approximately 30 patients in total will be enrolled at 2.0 mg/kg. Assuming the observed ORR is between 50% to 70%, the widths of 2-sided 95% CIs are summarized as below.

Confirmed ORR	Expected width of 95% CI on all patients at 2.0 mg/kg (N=30)
50%	±18%
60%	±18%
70%	±16%

5.2.3 Part C

In Part C, it is estimated that approximately 4 to 12 patients (assuming evaluation of 2 dose levels) will be treated in dose escalation. Operating characteristics of the dose escalation design, including the average number of patients allocated to each dose across a variety of toxicity scenarios, are presented in the simulation report (**Error! Reference source not found.**).

Up to approximately 64 patients may be enrolled across the dose escalation and expansion cohorts in Part C. In the case that both dose levels go to expansion, approximately 12 patients will be enrolled in each dose level (assuming 2 patients in each of the dose escalation cohort of 1.0 and 1.25 mg/kg and 60 patients in the expansion cohort).

The table below summarizes the 2-sided 95% exact confidence intervals among 62 patients at 1.25 mg/kg (2 in dose escalation and 60 in dose expansion cohort) assuming the observed ORR is between 50% and 70%.

Number of confirmed Objective Response	Confirmed ORR	95% exact CI (N=62)
31	50%	37%, 63%
37	60%	46%, 72%
43	69%	56%, 80%

5.2.4 Part D

Approximately 40 patients will be enrolled in Part D. Ongoing, real-time, continuous review of patient safety and SAEs will be conducted by the sponsor's Drug Safety Department. Additionally, the ISMC will ensure periodic safety data review throughout the study.

Presented in the table below are the 2-sided 95% exact CIs among 40 patients at 1.5 mg/kg assuming the observed ORR is between 50% and 70%.

Number of confirmed Objective Responses	Confirmed ORR(%)	95% exact CI (N=40)
20	50%	34%, 66%
24	60%	43%, 75%
28	70%	53%, 83%

This sample size of 40 patients 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=40)
5%	87%
10%	99%

5.3 Randomization and Blinding

This is a single-arm, open-label study. No randomization will be utilized.

5.4 Data Transformations and Derivations

5.4.1 General

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

Study Day will be calculated as Date – First Dose Date + 1 for dates on or after the first dose date. For dates prior to the first dose date, Study Day will be calculated as Date – First Dose Date. For all calculations of Study Day, the First Dose Date will be the earliest date of treatment administration for SGN-LIV1A or pembrolizumab.

Other 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.

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 EOS date or 30 days after the last dose of any study drug, whichever is earlier.

5.4.2 Response Assessment Dates

At each response assessment time point, scans to evaluate target and non-target lesions can be performed on multiple dates. If the time point response is CR or partial response (PR), then the latest date of all radiologic scans at the given response assessment visit will be the date of response. If the time point response is stable disease (SD), then the earliest date of all radiologic scans at the given response assessment visit will be the date of SD. If the time point response is PD, then the earliest date that PD has been documented will be the date of PD, i.e. the earliest of:

- Date of target lesion assessments when the target lesion response is PD
- Date of non-target lesion assessments when the lesion status is unequivocal progression
- Date of documenting new lesions

5.4.3 Best Response

Primary analysis of response will be based on RECIST Version 1.1.

A patient's best response will be the best demonstrated response to date that has been confirmed. Confirmation is required for PR and CR only. Once a patient achieves a confirmed PR, only evidence of CR will potentially change the patient's confirmed best response. The patient's best response will be used in determining the ORR.

Per RECIST Version 1.1, a response (CR or PR) will be considered confirmed if the following disease assessment (at least 4 weeks after the initial response) still shows response (CR or PR). A patient will have a best response of SD if there is at least one SD assessment (or better) >5 weeks after the start of treatment and the patient does not qualify for CR or PR. The details of best response are provided in 0 and Appendix E.

5.5 Handling of Dropouts and Missing Data

With the exception of the scenarios covered in this section, missing data will not be imputed.

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.

AE dates will be imputed for the purpose of calculating duration of events and treatment-emergent status (see Appendix AAppendix A for imputation details and Appendix B Imputation of Partial Missing Prior Therapy Dates

When calculating time since most recent prior therapy, please following the following algorithm.

The most recent prior therapy date is defined as the latest among all the prior therapies including therapy start and end date. And if prior therapies date are partially missing, please following the following imputation rule. Prior therapy dates will be imputed if both month and year are present and only day is missing.

- For prior therapy start date, impute the first day of the month.
- For prior therapy end date, impute the last day of the month or 1 day before the first dose of study drug, whichever is earlier.

Appendix C for the treatment-emergent definition). Censoring will be described in Section 6 with each planned analysis, as applicable.

Unless otherwise specified, lab values which are recorded or provided as being less than the lower limit of quantification (LLOQ), will be included in figures and summaries as LLOQ/2. For the purpose of grading, lab values reported as less than LLOQ will be imputed as LLOQ.

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, and no formal hypothesis testing will be performed.

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:

- PD-L1 expression

5.9 Covariates

No adjustment for covariates is planned in the analyses.

5.10 Timing of Analyses

The primary analysis will be conducted when all treated patients have come off study. Subsequent cutoff dates may be defined and corresponding database locks may occur to allow for more precise estimates of time-to-event endpoints.

6 PLANNED ANALYSES

6.1 Disposition

Patient disposition will be summarized for all enrolled subjectswith descriptive statistics. Patients who discontinue study treatment and patients who withdraw from the study will be summarized along with reason for discontinuation or withdrawal. The number of patients in each analysis set will be summarized. The reasons for screen failure will also be described, if applicable. The number of patients enrolled at each site will be summarized.

6.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, sex, ethnicity, race, baseline height, weight, and ECOG score will be listed and summarized; summaries will be presented using All Treated analysis set. Disease specific characteristics will also be listed and summarized All Treated analysis set.

6.3 Protocol Deviations

Important protocol deviations (defined as protocol violations by Seagen) 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.

6.4 Prior Therapies

Prior cancer treatment, including types of prior therapies will be summarized using the Safety Analysis Set.

6.5 Treatment Administration

Treatment administration will be summarized for safety analysis set. Summary statistics for duration of therapy and the number of cycles per patient will be presented, as well as the number and percentage of patients who were treated at each cycle and completed each cycle.

6.6 Efficacy Analyses

The primary analysis of efficacy endpoints will be analyzed using the All Treated analysis set. The ORR, DCR, DOR, and PFS will be summarized per RECIST Version 1.1 (Eisenhauer 2009).

6.6.1 Efficacy Endpoints

6.6.1.1 Objective Response Rate (ORR)

ORR is defined as the proportion of patients with confirmed CR or PR according to RECIST Version 1.1. Patients who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders.

The observed ORR and the 95% confidence intervals will be provided using Clopper-Pearson methodology.

The maximum percent reduction (or minimum percent increase if there is no reduction) in the sums of diameters from baseline will be derived for each patient and will be graphically displayed (e.g., using a waterfall plot).

6.6.1.2 Duration of Response (DOR)

Duration of response (DOR) according to RECIST Version 1.1 is defined as the time from first documentation of objective response (that is subsequently confirmed) per investigator to the first documentation of disease progression, or to death due to any cause, whichever comes first. Disease progression includes radiologic evidence of tumor progression and clinical progression per investigator.

Duration of response will only be calculated for the subgroup of patients achieving a confirmed CR or PR. Duration of response will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by expansion cohorts and overall. The

median duration of response and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated for each expansion cohort and overall.

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 the last disease assessment documenting absence of PD;
- Patients who have started a new antitumor treatment (with the exception of palliative radiotherapy on a non-target lesion that is not progressing) prior to documentation of PD will be censored at the date of the last disease assessment prior to start of new therapy;
- Patients who are removed from the study prior to documentation of PD will be censored at the date of the last disease assessment documenting absence of PD.
- Patients who have deaths or PD per RECIST v1.1 occurring after two or more missed visits will be censored at the last disease assessment;

6.6.1.3 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with CR, PR, or SD per RECIST Version 1.1.

The observed DCR and the 95% confidence intervals will be provided for the All Treated analysis setusing Clopper-Pearson methodology, by expansion cohorts and overall.

6.6.1.4 Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from start of study treatment to first documentation of disease progression (PD) based upon the disease assessment per RECIST Version 1.1 or clinical progression, or to death due to any cause, whichever comes first. For patients who are enrolled but fail to receive study treatment, the enrollment date will be used as the starting point in the calculation in PFS. Specifically,

PFS = Date of first documented PD or death – Date of first study treatment +1

The same censoring rules outlined for DOR will be applied to PFS. Patients lacking an evaluation of tumor response at baseline and/or after their first dose will have their event time censored at Day 1.

PFS will be analyzed using the Kaplan-Meier method and Kaplan-Meier plots will be provided. The median PFS and its two-sided 95% confidence intervals (CI) will be calculated using the complementary log-log transformation method (Collett 1994) by expansion cohorts and overall.

6.6.1.5 Overall Survival (OS)

OS is defined as the time from start of study treatment to date of death due to any cause. For patients who are enrolled but fail to receive study treatment, the enrollment dates will be used as the starting point in the calculation in OS. Specifically,

OS = Date of death – Date of first study treatment + 1

In the absence of confirmation of death, OS will be censored at the last date the patient is known to be alive.

Overall survival will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its two-sided 95% confidence intervals (CI) will be calculated using the complementary log-log transformation method (Collett 1994).

6.6.2 Pharmacokinetics and Immunogenicity Endpoints

6.6.2.1 Pharmacokinetics and Immunogenicity Analyese

LV (ADC), total antibody, and MMAE concentrations will be listed 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.

The ATA incidence rate is defined as the proportion of patients that develop SGN-LIV1A ATA at any time during the study.

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

6.7 Safety Analyses

The safety analysis set will be used to summarize all safety endpoints.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher.

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher.

Concomitant medications will be coded using WHO Drug (version: June 2016 or more recent).

6.7.1 Adverse Events

Adverse events 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 drug, through EOT visit or 30 days after last dose date whichever is later or through EOT visit or 90 days after last dose date for SAE. See Appendix C for details

regarding treatment-emergent classification. An overall summary of AEs will be provided. Summaries of AEs will be provided for the following, by preferred term, if not specified otherwise:

- All treatment-emergent AEs
- Treatment-emergent AEs related to SGN-LIV1A
- Treatment-emergent AEs related to both SGN-LIV1A and Pembro
- Treatment-emergent Serious Adverse Events (SAEs)
- Treatment-emergent SAEs related to SGN-LIV1A
- Treatment-emergent SAEs related to both SGN-LIV1A and Pembro
- Treatment-emergent AEs leading to dose delay of SGN-LIV1A
- Treatment-emergent AEs leading to dose reduction of SGN-LIV1A
- Treatment-emergent AEs leading to treatment discontinuation
- Treatment-emergent AEs leading to death
- Infusion-related reactions by preferred term
- DLTs
- Treatment-emergent AEs by system organ class, preferred term and maximum severity.
- Grade 3–5 treatment-emergent AEs
- Treatment-emergent AEs by system organ class and preferred term

All adverse events, adverse events leading to treatment discontinuation, and adverse events leading to death will be listed.

6.7.1.1 Adverse Events of Special Importance(AESI)

Adverse events of peripheral neuropathy may be considered AEs of special importance. Other AEs such as neutropenia may be added to AEs of special importance, as necessary. The definition of adverse events of special importance and search criteria will be maintained in a separate document and will be finalized prior to database lock. AESI will be summarized by MedDRA Preferred Term in descending frequency of occurrence.

6.7.2 Clinical Laboratory Parameters

Grading of laboratory values will be assigned programmatically per the NCI CTCAE v4.03. The highest post-baseline grade will be presented for each lab test.

6.7.3 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug substance name. Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated. Concomitant medications will be listed by patient.

6.7.4 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 identified by descending MedDRA Preferred Term (unless otherwise specified) and summarized. Death information will be listed by patient.

6.7.5 Liver Safety Assessment

Liver safety assessment will be summarized based on the measurements of alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin, and aspartate transaminase (AST).

In addition, subjects with the postbaseline liver function test results that are consistent with the Hy's law criteria will be summarized.

7 INTERIM ANALYSIS

No formal interim analyses are planned. An ongoing real-time review of SAEs will be conducted by Seattle Genetics Pharmacovigilance.

8 CHANGES FROM PLANNED ANALYSES

8.1 Changes from the Original Protocol

Refer to Sec 8.2.

8.2 Changes from the Original SAP

The following changes are mainly due to the scope change from full CSR to abbreviated CSR unless otherwise mentioned.

- iRECIST releated endpoints are not anlyzed.
- Vital signs analyses are not presented.
- All Treated Subjects analysis set is added as the primary analysis set for efficacy analysis, and Efficacy Evaluable Analysis set is removed for CSR as it's intended for during study analysis.
- ITT analysis set is removed as this is not randomized study.
- ECG anlayses are not presented.

- Exploratory analyses for PN like time to onset and resolution/improvement are not performed.
- ECOG status by visit are not summrized.
- Palliative radiotherapy on a non-target lesion that is not progressing is not excluded from the new antitumor treatment when calculating PFS and DOR to be conservative.

9 REFERENCES

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Appendix A Imputation of Partially Unknown Adverse Event Dates

For a pre-existing condition and adverse event (AE) with a partial start or end date, if it can be determined that the event occurred prior to the date of first dose of study treatment, the partial date will not be imputed; Otherwise, the partial date will be imputed using the rules described below. For ease of reading, both pre-existing conditions and AEs will be referred to as AE for the remainder of this document. AE start dates should be imputed before imputation of AE condition end date in all cases.

Incomplete AE Start Date:

AE day only is missing

If the month/year is the same as the month/year of first dose of any study treatment and the onset period and/or onset time indicate that the start of the AE was post-dose:
AE start date will be imputed as the first dose date of any study treatment
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

AE day and month are missing, or month only is missing

If the year is the same as the year of first dose of any study treatment and the onset period and/or onset time indicate that the start of the AE was post-dose:
AE start date will be imputed as the first dose date of any study treatment
If the year is after the year of first dose of any study treatment:
AE start date will be imputed as January 1st

AE day, month and year are missing, or year only is missing

AE start date will be imputed as the first dose date of any study treatment

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

Incomplete AE End 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 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, EOS date)

AE day and month are missing, or month only is 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, EOS date)

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, EOS date)

AE day, month and year are missing, or year only is missing

AE condition end date will not be imputed

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.

Example

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

Prior to imputation

Log line	Start date	Condition end date	Severity	Outcome	Onset
1	UNUNK2011	25APR2012	1	not recovered/resolved	pre-ICF
2	25APR2012	UNAPR2012	2	recovering/resolving	post 1st dose
3	UNAPR2012	04MAY2012	1	recovered/resolved	post 1st dose

Post imputation

Log Line	Start date	Condition end date	Severity	Outcome	Onset
1	**UNUNK**2011	25APR2012	1	not recovered/resolved	pre-ICF
2	25APR2012	**30**APR2012	2	recovering/resolving	post 1st dose
3	**02**APR2012	04MAY2012	1	recovered/resolved	post 1st dose

Appendix B Imputation of Partial Missing Prior Therapy Dates

When calculating time since most recent prior therapy, please following the following algorithm.

The most recent prior therapy date is defined as the latest among all the prior therapies including therapy start and end date. And if prior therapies date are partially missing, please following the following imputation rule. Prior therapy dates will be imputed if both month and year are present and only day is missing.

- For prior therapy start date, impute the first day of the month.
- For prior therapy end date, impute the last day of the month or 1 day before the first dose of study drug, whichever is earlier.

Appendix C Definition of the Term "Treatment-Emergent" with Respect to AE Classification

The algorithm below should be used to determine whether an adverse event (AE) is classified as a treatment-emergent adverse event (TEAE). A TEAE is defined as any AE which worsens in severity during the safety reporting period or is newly occurring at any time, where newly occurring means that the AE was not present at baseline. For ease of reading, both pre-existing conditions and AEs will be referred to as AEs for the remainder of this document. AE dates should be imputed in accordance with the algorithm detailed in Appendix A prior to determination of TEAE classification. Details of the TEAE classification are as follows:

1. For each patient, determine the first dose date, which is the earliest date the patient receives any amount of study drug.
2. **Baseline AEs:** classify an AE record as baseline AE if it satisfies both criteria a and b below:

AE onset satisfies either of i, ii or iii below:

i. Onset date is prior to the first dose date
ii. Onset date is the same as the first dose date, and Onset Period is "started after consent but before the first dose of any study treatment" or Onset Time Relative to Study Treatment is "started before first infusion or before infusion on any dosing day"
iii. Onset Period is "started before the signing of consent" or "started after consent but before the first dose of any study treatment"

AE end date satisfies either of i or ii below:

i. End date is the same as or after the first dose date
ii. End date is missing with outcome equal to

recovering/resolving, or
not recovered/not resolved, or
unknown or missing

3. **Post-baseline AEs:** classify an AE record as post-baseline AE if it meets either of criteria a, b or c below:
   a Onset date is after the first dose date
   b Onset date is the same as the first dose date, and Onset Period is "started after the first dose of any study treatment" or Onset Time Relative to Study Treatment is not "started before first infusion or before infusion on any dosing day"
   c Onset Period is "started after the first dose of any study treatment"
4. **TEAE flag** will be derived as follows:
   a. For all AE records that have an end date prior to the first dose date, assign TEAE flag to 'N'
   b. For all baseline AEs, assign TEAE flag to 'N'
   c. For post-baseline AEs:
      - If the post-baseline AE is a continuing event of a baseline AE (i.e., events with the same AE identifier, where AE identifier is the number before the colon in SDTM AE.AESPID), then compare the post-baseline AE to the most recent baseline AE with the same AE identifier (to be referred to as "baseline AE" below). Assign TEAE flag to "Y" for the applicable post-baseline AE records, if a

post-baseline AE record meets any of the following worsening criteria based on relatedness, seriousness or CTCAE grade:

- If the post-baseline AE is related to treatment, or
- If the post-baseline AE meets the criteria for an SAE and the most recent baseline AE was not an SAE, or
- If the post-baseline AE has a higher CTCAE grade

All subsequent episodes of the same AE should have TEAE flag = 'Y'.

- Otherwise, assign TEAE flag to 'N'
- If the post-baseline AE is not a continuing event of a baseline AE, then assign TEAE flag to 'Y

NOTE: For summaries which include only treatment emergent AEs, include all AEs which have at least one record classified as aTEAE as well as those AEs for which TEAE status could not be determined (e.g., the value of the TEAE variable may be missing if the event cannot be identified as baseline or post-baseline – missing information on the AE CRF should be queried). Only exclude those AEs which were determined to not be treatment emergent for all records.

APPENDIX D RECIST CRITERIA SUMMARY (VERSION 1.1)

Response Evaluation Criteria for Solid Tumors	
Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Measurable lesion	Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm).

From RECIST Version 1.1 (Eisenhauer 2009)

Best overall response when confirmation of CR and PR required		
Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD[b]	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR

PR	SD[b]	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

b In cases where the initial response is followed by SD, it will be considered as confirmed if the SD is later followed by PR or CR. For example, if a patient had PR in first time point, SD in subsequent time point, and PR in the following time point, this PR will be considered as confirmed.

Modified from RECIST Version 1.1 (Eisenhauer 2009)

Appendix E RECIST Response Confirmation Algorithm Details

A response (CR or PR) will be considered confirmed (RSCONFL=Y) if the following disease assessment (at least 4 weeks after the initial response) still shows response (CR or PR).

Note:
Only timepoint responses prior to new anti-cancer therapy are considered.

To classify response throughout the study, if start day of new anti-cancer therapy exists, then set B= start day of new anti-cancer therapy, otherwise B=999999.
Set A=35 days (protocol-specified minimal days for assessment of SD, the earliest day in the window of first scheduled assessment.).

Days A and B define the time windows for the records to be included in the best overall response assessment.

Best Overall Response Algorithm:

Set best overall response to CR if:

- Any record on or before study Day B has AVALC=CR and RSCONFL=Y, where AVALC is the response variable and RSCONFL is a derived variable as a flag for a confirmed responses. The algorithm of the confirmation flag is outlined below in section "Derivation Algorithm for Confirmation Flag (RSCONFL)".

Otherwise set to PR if:

- Any record on or before study Day B has AVALC=PR and RSCONFL=Y.

Otherwise set to SD if:

- Any record between study Day A and B, inclusive, has AVALC=SD; or
- Any record between study Day A and B, inclusive, has AVALC=CR/PR and RSCONFL=N.

Otherwise set to PD if:

- Any record on or before study Day B has AVALC=PD.

Otherwise set to NE.

Derivation Algorithm for Confirmation Flag (RSCONFL)

- For records with AVALC=CR or PR,
  a) Set to Y if CR/PR is confirmed,
  b) Set to N if the next available scan did not confirm the response (e.g. PR followed by PD).
  c) Set to missing if there is no available scan to confirm the response (eg. at interim data cut)

- For all other records (eg. AVALC not CR or PR), leave the value for the variable RSCONFL as missing.

- Confirmation means a PR is followed by a PR or CR (ignoring two NEs or 1SD in between) at least 28 days (4 weeks) later (ie, date of second PR/CR – date of first PR ≥28), or a CR is followed by a second CR (ignoring two NEs in between) at least 28 days later. If there are 2 NEs between 2 responses, the 2 responses need to be within 3 months.

- CR followed by PR should be considered as data issue, and will not be considered a confirmed PR at the time of the previous (initial) CR.

Special considerations for interim data analyses

- A pending PR/CR status will be determined if a response is not confirmed response, and if

  a) the last assessment is CR/PR, or
  b) the last assessment is SD or NE and the second to last is CR/PR, or
  c) the last two assessments were NE/NE, NE/SD or SD/NE, and the third to last is CR/PR.

  Then in the summary tables, the patient will be considered as having CR/PR pending confirmation.

- For a special case at the time of interim data cut, a patient with SD-PR-CR-data cut, be categorized as confirmed PR.