STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNS40-002
Version:	2.0; 18-Jan-2024
Protocol Title:	An Open-label, Phase 2 Basket Study of SEA-CD40 Combination Therapies in Advanced Malignancies
Sponsor:	Seagen, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	SEA-CD40
Protocol Number/Amendment:	SGNS40-002 A03
SAP Version:	2.0
Version Date:	18-Jan-2024
SAP Author	PPD

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

PPD , PhD PPD	Date
PPD , MA PPD	Date
PPD , MD PPD	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CR	complete response
CRF	case report form
CT	computed tomography
DCR	disease control rate
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy-evaluable
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EOT	end of treatment
FAS	full analysis set
HRQoL	health-related quality of life
iCPD	confirmed progressive disease per iRECIST
iCR	immune complete response
IHR	infusion or hypersensitivity reaction
iPR	immune partial response
irAE	immune-related AEs
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
iUPD	immune unconfirmed progressive disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-(L)1	programmed cell death protein 1 (PD-1) or PD-1 ligand 1 (PD-L1)
PFS	progression-free survival
PGI-C	Patient Global Impression of Symptom Change
PGI-S	Patient Global Impression of Symptom Severity
PK	pharmacokinetics
PPoS	predictive probability of success
PR	partial response
PRO	patient-reported outcomes
Q6W	every 6 weeks

RE	Response-evaluable
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	serious adverse event
SD	stable disease
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TPS	tumor proportion score
TTD	time-to-deterioration
ULN	upper limit of normal

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNS40-002, entitled An Open-label, Phase 2 Basket Study of SEA-CD40 Combination Therapies in Advanced Malignancies. 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 STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the antitumor activity of SEA-CD40 combined with other therapies

2.2 Secondary Objectives

- To evaluate the safety and tolerability of SEA-CD40 combined with other therapies
- To evaluate control of disease
- To evaluate durability of response in subjects who respond to study drug(s)
- To evaluate PFS and survival

2.3 Additional Objectives

- To characterize the pharmacokinetics (PK) of SEA CD40 and pembrolizumab and incidence of antidrug antibodies (ADAs) when SEA-CD40 is administered in combination with other therapies
- Cohorts 1, 2, and 3 (Melanoma): To evaluate selected pharmacodynamic parameters of interest for SEA CD40.
- To assess exploratory biomarkers of response, toxicity, and resistance of SEA-CD40 in combination with other therapies
- To evaluate the antitumor activity of SEA-CD40 combined with other therapies per Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST)
- To evaluate patient-reported outcomes of disease/treatment-related symptoms, health-related quality of life (HRQoL), and function

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- Confirmed Objective Response Rate (ORR; confirmed complete response [CR] or partial response [PR]) according to RECIST v1.1 per investigator assessment

3.2 Secondary Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Type, incidence, and severity of laboratory abnormalities
- Frequency of treatment interruptions, dose reductions, and treatment discontinuations due to AEs
- Disease control rate (DCR; confirmed CR, PR, and stable disease [SD]) per investigator assessment
- Duration of response (DOR; duration of confirmed CR or PR) per investigator assessment
- Progression-free survival (PFS) per investigator assessment
- Overall survival (OS)

3.3 Additional Endpoints

- Estimates of selected PK parameters
- Incidence of ADAs
- Cohorts 1, 2, and 3 (Melanoma): Exploratory correlations between QTc and plasma concentrations of SEA-CD40
- Actual and change from baseline values in immune subsets and cytokines in peripheral blood
- Confirmed ORR (immune complete response [iCR] or immune partial response [iPR]) according to iRECIST
- Actual and change from baseline scores on the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ C30)
- Cohorts 4 and 5 (NSCLC): Time-to-deterioration (TTD) in either cough, dyspnea, or chest pain (whichever deteriorates first) as measured by the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC SAQ)
- Cohorts 4 and 5 (NSCLC): Actual and change from baseline values in NSCLC SAQ domains and total scores

4 STUDY DESIGN

This phase 2, global, open-label, multicenter trial is designed to assess the activity, safety, and tolerability of SEA-CD40 in combination with standard of care therapies in subjects with selected solid tumors.

	Tumor type	Study drugs
Cohort 1	Relapsed/refractory melanoma	SEA-CD40 and pembrolizumab
Cohort 2	Uveal melanoma	
Cohort 3	PD-(L)1-naïve melanoma	
Cohort 4	Nonsquamous NSCLC; PD-L1 1-49% TPS	SEA-CD40, carboplatin, pemetrexed, and pembrolizumab
Cohort 5	Nonsquamous NSCLC; PD-L1 <1% TPS	

For Cohorts 1, 2, and 3 (melanoma), initially, up to 15 subjects may enroll in each cohort. Interim safety and efficacy analyses will be performed for each cohort after 15 subjects have received study drug and are efficacy evaluable (EE). Cohorts may continue to enroll up to an additional 25 subjects, for a total of up to approximately 40 subjects in each cohort.

For Cohorts 4 and 5 (NSCLC), initially, 6 total subjects will be enrolled across the 2 cohorts; safety will be assessed after the first treatment cycle. If approved by the SMC, Cohorts 4 and 5 may continue to enroll up to 15 subjects per cohort, followed by continuation to up to 40 total subjects per cohort if appropriate.

Response will be assessed every 6 weeks (Q6W) from the date of first dose for 24 weeks and every 12 weeks thereafter until confirmed disease progression. Diagnostic-quality computed tomography (CT) scans and/or magnetic resonance imaging (MRI) will be performed on the chest and abdomen (and pelvis for Cohorts 1, 2, and 3). The determination of antitumor activity will be based on objective response rate (ORR) assessments as defined by RECIST version 1.1 and by iRECIST. Treatment decisions by the investigator will be based on iRECIST.

The primary analysis of the study will be performed separately for each cohort when all treated subjects in the cohort have been followed for at least 6 months or come off study, whichever comes first. The primary efficacy endpoint of confirmed ORR per RECIST v1.1 will be estimated for each cohort based on the full analysis set (FAS), comprising all subjects who received any amount of study treatment. The point estimate of ORR and 95% exact confidence intervals (CIs) using the Clopper-Pearson method will be provided for each cohort.

Interim efficacy analyses will be performed separately for each cohort after approximately 15 subjects of a given cohort have been treated and are efficacy evaluable. The Bayesian predictive probability of success (PPoS) approach will be used to inform decision-making for continued enrollment. A cohort is considered "successful" if the 90% CI of the response rate at the maximum sample size excludes the background rate. At the time of each interim analysis, the PPoS will be calculated. A PPoS <5% 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 the interim result. Based on efficacy and safety data, together with the PPoS, a cohort may be stopped early by the sponsor. A cohort may also be discontinued at any point at the discretion of the sponsor.

5 ANALYSIS SETS

This section defines each of the analysis sets that will be utilized. The use of each analysis set will be discussed in Section 7.

5.1 Full Analysis Set

The full analysis set (FAS) includes all subjects who received any amount of study drug. The primary analysis set for PFS and OS analyses will be the FAS.

5.2 Safety Analysis Set

The safety analysis set includes all subjects 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.

5.3 Response-Evaluable (RE) Analysis Set

The response evaluable analysis set includes all subjects with measurable disease at baseline who received any amount of study drug and had at least one post-baseline disease assessment per RECIST v1.1 or discontinued study treatment. The primary analysis set for ORR and DCR analyses will be the RE analysis set

5.4 PK Analysis Set

The PK analysis set includes all subjects who received any amount of SEA-CD40 and had at least one PK sample.

5.5 PRO Analysis Set

The PRO analysis set includes all subjects who received any amount of study drug and have at least one PRO assessment. All PRO analyses will be based on the PRO analysis set.

6 STATISTICAL CONSIDERATIONS

6.1 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 95% level.

The 2-sided 95% 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 95% 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.

6.2 Determination of Sample Size

Up to approximately 200 subjects may be enrolled in this study. This includes up to approximately 40 subjects enrolled in each cohort.

For a sample size of 40 subjects per cohort, assuming confirmed ORR is between 30% and 80%, the 2-sided 95% exact confidence interval (CI) are summarized below:

Confirmed ORR	95% Exact CI (N=40)
30%	(17%, 47%)
40%	(25%, 57%)
50%	(34%, 66%)
60%	(43%, 75%)
70%	(53%, 83%)
80%	(64%, 91%)

6.3 Randomization and Blinding

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

6.4 Data Transformations and Derivations

6.4.1 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 (or the decision-making date to end treatment if EOT visit date is not available); if an EOT visit is not performed (and no decision of EOT is made) 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.

6.4.2 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 subject'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 subject'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 subject 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 subject 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.

6.4.3 Response Assessment Dates

For efficacy assessments, if the time point response is CR or 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

6.5 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 and Appendix B for treatment-emergent definition).

For time-to-event endpoints, e.g., duration of response, time to response, PFS, and OS, subjects who have no specific event will be censored as specified for each respective endpoint in Section 7.5.

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

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.

6.6 Multicenter Studies

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

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned in this study.

6.8 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 years, ≥65 years old)
- Categorized weight at baseline (<70, 70–99, and ≥100 kg)
- CD40 expression (<XX, ≥XX)
- History of brain metastasis (yes, no)
- For Cohorts 1 and 3 only: melanoma type (cutaneous vs non-cutaneous)

6.9 Covariates

No adjustments for covariates are planned in the analyses.

6.10 Timing of Analyses

The primary analysis of the study will be performed separately for each cohort when all treated subjects in the cohort have been followed for at least 6 months or come off study, whichever comes first.

Interim efficacy analyses may be performed separately for each cohort after approximately 15 subjects of a given cohort have been treated and are efficacy evaluable.

7 PLANNED ANALYSES

7.1 Disposition

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

7.2 Demographic and Baseline Characteristics

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

7.3 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. A list of subjects with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized with descriptive statistics using the safety analysis set.

Summaries for each study drug administration 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:
    - 42 days after the last study dose for pembrolizumab administration in Cohorts 1, 2, or 3, or 21 days after the last study dose for all other study drug administration
    - EOT visit
    - death date or start date of subsequent anticancer therapy, if applicable.
- Number of cycles per subject
- Number and percentage of subjects who were treated at each cycle
- Cumulative doses
- Average dose per cycle

Summaries for SEA-CD40, carboplatin, and pemetrexed administration may additionally include:

- Absolute dose intensity (ADI), which is defined as the actual dose in mg/kg per week that a subject 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., 10 mg/kg for SEA-CD40 regardless of dose reduction in later cycles) in mg/kg per week (i.e., 10/3 mg/kg/week for SEA-CD40).
- Number and percentage of subjects 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 subject). The number and percentage of doses that were modified may also be summarized.

7.5 Efficacy Analyses

All efficacy endpoints will be analyzed by cohort and total.

7.5.1 Primary Endpoints

7.5.1.1 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 subjects who achieve a confirmed CR or PR according to RECIST v1.1 (Eisenhauer 2009). Subjects 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 95% CI will be calculated.

Up to 5 of the largest measurable lesions will be quantitatively identified at baseline based on lesion diameters (Eisenhauer 2009). The lesions being followed for response assessment will also be quantitatively assessed at each pre-specified time point. A sum of diameters will be calculated at baseline and each assessment visit, and is defined as the sum of all the lesion diameters (longest diameter for non-nodal lesions, short axis for nodal lesions). The change from baseline, as well as the change from the previous response assessment (as applicable), in the sum of diameters will be derived for each assessment visit. 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 subject and will be graphically displayed (e.g., using a waterfall plot).

This endpoint may also be summarized by the subgroups defined in Section 6.8.

Exploratory analysis of ORR may also be conducted using iRECIST guidelines.

7.5.2 Secondary Endpoints

7.5.2.1 Disease Control Rate (DCR)

DCR is defined as the proportion of subjects 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. Subjects who do not have at least 1 post-baseline response assessment or subjects whose response cannot be assessed will be counted as not achieving disease control.

DCR will be estimated for each cohort and its exact 2-sided 95% CIs will be calculated.

7.5.2.2 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.

DOR data will be censored as described below:

- Subjects 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.
- Subjects who started a new anticancer treatment prior to documentation of PD or death will be censored at the date of last disease assessment prior to the start of new treatment.
- Subjects 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.
- Subjects with documented PD or death immediately after 2 or more missed disease assessments will be censored at the date of the last disease assessment prior to the missed visits.

DOR will only be calculated for subjects 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 95% CI will be calculated as appropriate.

7.5.2.3 Progression-Free Survival (PFS)

PFS is defined as the time from the start of study treatment to the first documentation of PD by RECIST v1.1 or death due to any cause, whichever comes first.

The same censoring rules as outlined in Section 7.5.2.2 for DOR will be applied to PFS. Subjects lacking an evaluation of tumor response after their first dose of study drug will have their event time censored at Day 1.

For cohorts with adequate data, 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 95% 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 95% CIs will be calculated.

7.5.2.4 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 subject is known to be alive (i.e., date of last contact).

OS will be analyzed by cohort using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its 2-sided 95% 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 95% CIs will be calculated.

7.6 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 24.0 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).

7.6.1 Adverse Events

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

A treatment-emergent AE is defined as a newly occurring or worsening AE after the first dose of study drug through the end of the safety reporting period. See Appendix B for details regarding treatment-emergent classification. An overall summary of AEs will be provided by cohort and total. Summaries of AEs may also be provided by cohort and total for the following:

- All treatment-emergent AEs
- AEs related to SEA-CD40
- AEs related to pembrolizumab
- AEs related to carboplatin
- AEs related to pemetrexed
- Serious Adverse Events (SAEs)
- SAEs related to SEA-CD40

- SAEs related to pembrolizumab
- SAEs related to carboplatin
- SAEs related to pemetrexed
- AEs leading to dose delay of SEA-CD40
- AEs leading to dose interruption (full dose received) of SEA-CD40
- AEs leading to the dose being stopped early (full dose not received) of SEA-CD40
- AEs leading to dose delay of pembrolizumab
- AEs leading to dose interruption (full dose received) of pembrolizumab
- AEs leading to the dose being stopped early (full dose not received) of pembrolizumab
- AEs leading to dose delay of carboplatin
- AEs leading to dose interruption (full dose received) of carboplatin
- AEs leading to the dose being stopped early (full dose not received) of carboplatin
- AEs leading to dose delay of pemetrexed
- AEs leading to dose interruption (full dose received) of pemetrexed
- AEs leading to the dose being stopped early (full dose not received) of pemetrexed
- AEs leading to treatment discontinuation of any study drug
- AEs leading to death
- AEs that started during infusion
- AEs that started within 24 hours post infusion
- Infusion related reactions by preferred term
- Hypersensitivity reactions by preferred term
- Treatment-emergent AEs by system organ class, preferred term and maximum severity. At each system organ class or preferred term, multiple occurrences of events within a subject are counted only once at the highest severity
- Grade 3–5 treatment-emergent AEs
- Treatment-emergent AEs by system organ class and preferred term

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

Immune-mediated Adverse Events

Immune-mediated AEs will be listed and the incidence will be summarized by preferred term and maximum severity.

7.6.2 Clinical Laboratory Parameters

All laboratory results up to the end of treatment visit will be presented in conventional units. Grading of laboratory values will be assigned programmatically per the NCI CTCAE v5.0. 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.

7.6.3 Concomitant Medications

Concomitant medications may be listed by subject.

7.6.4 Additional Safety Analyses

7.6.4.1 ECOG Performance Status

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

7.6.4.2 Vital Signs

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

7.6.4.3 ECG

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

7.6.5 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 by cohort and total. Death information will be listed by subject.

7.7 Additional Analyses

7.7.1 Pharmacokinetics and Immunogenicity Analyses

SEA-CD40 concentrations will be listed and summarized with descriptive statistics at each PK sampling time point. All PK data will be analyzed by cohort and total using the PK analysis set.

No ADA summaries are planned.

7.7.2 Pharmacodynamic (PD) and Mechanism of Action Biomarkers

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

7.7.3 Patient-Reported Outcome Endpoints

8 NO PRO ANALYSES ARE PLANNED.INTERIM ANALYSIS

Interim efficacy analyses will be performed separately for each cohort after approximately 15 subjects of a given cohort have been treated and are efficacy evaluable post-baseline. The Bayesian predictive probability of success (PPoS) approach will be used to determine the criteria for continuation. A cohort is considered "successful" if the 90% confidence interval

(CI) of the response rate at the maximum sample size excludes the background rate. At the time of each interim analysis, the PPoS will be calculated. A PPoS <5% 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 the interim result. Based on efficacy and safety data, together with the PPoS, a cohort may be stopped early by the sponsor. A cohort may also be discontinued at any point at the discretion of the sponsor. The estimated PPoS based on number of responders observed among the first 15 subjects are presented below.

Number of responders among first 15 subjects	Cohorts 1 and 2 (p_0=4%)	Cohort 3 (p_0=33%)	Cohort 4 (p_0=49%)	Cohort 5 (p_0=32%)
0	0.0044	0.0000	0.0000	0.0000
1	0.1631	0.0000	0.0000	0.0000
2	0.5467	0.0003	0.0000	0.0003
3	0.8743	0.0037	0.0000	0.0037
4	0.9870	0.0236	0.0001	0.0234
5	1.0000	0.0951	0.0010	0.0944
6	1.0000	0.2583	0.0084	0.2570
7	1.0000	0.5025	0.0439	0.5009
8	1.0000	0.7452	0.1509	0.7439
9	1.0000	0.9058	0.3599	0.9051
10	1.0000	0.9760	0.6250	0.9758

The prior distribution is assumed to be beta (0.12, 0.88), beta (0.41, 0.59), beta (0.57, 0.43), and beta (0.4, 0.6), respectively, to approximate the background rate in each disease cohort.

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.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Original Protocol

EE analysis set changed to RE analysis set and used as the primary analysis set for ORR and DCR.

9.2 Changes from the Original SAP

- Updated TEAE definition to align with CRFs
- Added imputation for partially missing subsequent anti-cancer therapy dates
- Updates to reflect current protocol and planned analyses

10 REFERENCES

Clopper, C. J., & Pearson, E. S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 404-413.

Collett D (1994). Interval-censored survival data. Modelling survival data in medical research. Boca Raton, Fla., Chapman & Hall/CRC: 237-251.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., ... & Verweij, J. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer, 45(2), 228-247.

Food and Drug Administration. (2018). Methods to Identify What Is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. https://www.fda.gov/media/116277/download

11 APPENDICES

APPENDIX A: Imputation of Partially Unknown Adverse Event Dates

For an 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. 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:
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:
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 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
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: 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 is newly occurring or worsening in severity, 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 subject, determine the first dose date, which is the earliest date the subject receives any amount of study drug.
2. An AE record from AE page will be classified as a TEAE if it meets the following conditions:
    - Onset period = Started after first dose of any study treatment
    - AE Start Date on or after first dose date of study treatment
    - If subject did not start new anticancer therapy and AESER = "Y", AE Start Date on or before last dose date of any study treatment + 90. Otherwise, AE Start Date on or before last dose date of any study treatment + 30 or EOT visit, whichever is later
3. If the first episode (logline) is marked as TEAE, then all subsequent loglines should also be considered as TEAE, even if the later loglines may start after the earlier of last dose date of any study treatment + 30 days or EOT visit.

NOTE:

1. **For summaries which include only treatment emergent AEs include all AEs which are classified as TEAEs 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.**

Appendix C: Imputation of Partially Missing Subsequent Anticancer Therapy 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.

Signature Page for SGN-CLIN-042104 v1.0

eSignature Approval	PPD Clinical Development 19-Jan-2024 00:16:59 GMT+0000

eSignature Approval	PPD Biostatistics 19-Jan-2024 23:24:55 GMT+0000

eSignature Approval	PPD Biostatistics 22-Jan-2024 16:14:28 GMT+0000

Signature Page for SGN-CLIN-042104 v1.0