SeattleGenetics

STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNBCMA-001
Protocol Title:	A phase 1 study of SEA-BCMA in patients with relapsed or refractory multiple myeloma
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	SEA-BCMA
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The individuals signing below have reviewed and approve this statistical analysis plan.

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LIST OF ABBREVIATIONS

acMMAE	antibody conjugated monomethyl auristatin E
ADC	antibody-drug conjugate
ADI	Absolute dose intensity
AE	adverse event
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
BAP	biomarker analysis plan
CBC	complete blood count
CI	confidence interval
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
DE	DLT-evaluable
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy evaluable
EOS	end of study
EOT	end of treatment
IDI	Intended dose intensity
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRR	infusion-related reaction
IV	intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMAE	monomethyl auristatin E
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PAVA	Pool-Adjacent-Violators Algorithm
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PR	partial response
RDI	Relative dose intensity
RRMM	relapsed or refractory multiple myeloma
q3wk	once every 3 weeks
sCR	stringent complete response
SAE	serious adverse event
SAP	statistical analysis plan

SD	stable disease
SMC	Safety Monitoring Committee
UPC	urine protein to creatinine
UPM	unit probability mass
VGPR	very good partial response

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNBCMA-001, entitled 'A phase 1 study of SEA-BCMA in patients with relapsed or refractory multiple myeloma'. 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 AND CORRESPONDING ENDPOINTS

This study will evaluate the safety and antitumor activity of SEA-BCMA in patients with RRMM. Specific objectives and corresponding endpoints for the study are summarized below in **Error! Reference source not found.**.

Table 1: Objectives and corresponding endpoints

Primary Objectives	Corresponding Primary Endpoint
Evaluate the safety and tolerability of SEA-BCMA monotherapy in subjects with relapsed or refractory multiple myeloma (RRMM)	Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) Type, incidence, and severity of laboratory abnormalities
Identify the maximum tolerated dose (MTD) and/or optimal dose and schedule of SEA-BCMA monotherapy, and in combination with dexamethasone, in subjects with RRMM	Incidence of dose-limiting toxicities (DLTs)
Evaluate the safety and tolerability of SEA-BCMA in combination with SOC therapies in subjects with RRMM	
Secondary Objectives	**Corresponding Secondary Endpoints**
Identify a recommended single-agent dose and schedule of SEA-BCMA	Incidence of DLTs, cumulative safety and activity by dose level and schedule
Assess the pharmacokinetics (PKs) of SEA-BCMA	Maximum serum concentration and area under the serum concentration-time curve
Assess the immunogenicity of SEA-BCMA	Incidence of SEA-BCMA antitherapeutic antibodies (ATA)
Assess the antitumor activity of SEA-BCMA	Best response per the International Myeloma Working Group (IMWG) uniform response criteria (Kumar 2016)
	Objective response rate (ORR)
	Duration of objective response (OR) and complete response (CR)
	Progression-free survival (PFS)
	Overall survival (OS)
Exploratory Objectives	**Corresponding Exploratory Endpoints**

Assess incidence and level of BCMA expression in RRMM and relationship to clinical response to SEA-BCMA	Characterization of BCMA expression on malignant plasma cells
Assess the pharmacodynamic effects and biomarkers of response, toxicity, and resistance to SEA-BCMA	Exploratory biomarkers of SEA-BCMA mediated pharmacodynamic effects
Assess minimal residual disease (MRD) in subjects with very good partial response (VGPR) or better	Rate of MRD clearance
Assess impact of SEA-BCMA in combination with SOC therapies on health-related quality of life (HRQoL) from the subject's perspective.	Descriptive outcomes of qualitative interviews
	Maximum serum concentration and area under the serum concentration-time curve

3 STUDY DESIGN

This is a phase 1, open-label, multicenter, dose-escalation study designed to evaluate the safety, tolerability, and antitumor activity of SEA-BCMA monotherapy and combination in adults with RRMM. The study will be conducted in 4 parts:

Part A: Monotherapy dose-escalation and expansion

Dose-escalation: Up to approximately 25 subjects will be treated with SEA-BCMA monotherapy q2wk to evaluate the safety and tolerability of SEA-BCMA, and to identify the MTD or optimal dose.

Expansion: Up to approximately 20 subjects will be treated with SEA-BCMA monotherapy at dose levels not exceeding the MTD or optimal dose to further characterize the safety and antitumor activity of SEA-BCMA.

Part B: Monotherapy intensive dosing. Up to 20 subjects will be treated at the recommended dose in an expansion cohort testing weekly induction dosing (q1wk) of SEA-BCMA for 8 weeks, followed by q2wk maintenance dosing. This expansion cohort will begin with a 6-subject safety run-in with dose de-escalation permitted.

Part C: Dexamethasone combination therapy cohorts. Up to approximately 60 subjects may be enrolled to evaluate the safety and antitumor activity of SEA-BCMA in combination with dexamethasone.

Cohort 1: The standard dosing combination cohort will combine dexamethasone with SEA-BCMA administered q2wk. This expansion cohort will begin with a 6-subject safety run-in with dose de-escalation permitted. Cohort expansion up to 20 subjects may occur, if permitted after completion of the safety run-in.

Cohort 2: The intensive dosing combination cohort will combine dexamethasone with SEA-BCMA administered q1wk for 8 weeks, followed by q2wk dosing. This expansion cohort will complete a 6-subject safety run-in at 800 mg SEA-BCMA intensive dosing (dose level –1) and, if deemed tolerable, will be followed by a 6-subject run in at 1600 mg SEA-BCMA intensive dosing. Cohort expansion up to a total of 20 subjects may occur in each of up to 2 dose level cohorts, eg, 800 mg and 1600 mg SEA-BCMA dose levels, if permitted after completion of each safety run-in.

Part D: Pomalidomide and dexamethasone combination therapy cohort. Up to 6 DLT evaluable subjects may be enrolled in this safety run-in cohort to evaluate the safety of

SEA-BCMA administered q2wk in combination with pomalidomide and dexamethasone. Part D will be conducted in the US only.

Cohort 1: The standard dosing combination cohort will combine dexamethasone and pomalidomide with SEA-BCMA administered q2wk. This expansion cohort will begin with a 6-subject safety run-in with dose de-escalation permitted.

A Safety Monitoring Committee (SMC) consisting of the study medical monitor, drug safety representative, site investigators, and the study biostatistician will monitor the safety of subjects and make dosing recommendations throughout dose-escalation, dose-expansion, post-remission treatment, and combination therapy treatment. The SMC may recommend investigation of an intermediate dose level or an alternative dosing schedule if warranted by cumulative safety and PK/pharmacodynamic data.

The dose-escalation part of SEA-BCMA monotherapy will be conducted in up to approximately 25 subjects using the modified toxicity probability interval (mTPI) method (Ji 2010) to evaluate safety and tolerability, and to identify the MTD of SEA-BCMA. If the MTD is not reached, safety, PK, pharmacodynamic, and biomarker analyses, as well as preliminary antitumor activity, will be used to determine the optimal dose. De-escalation to a lower dose level may be performed at any time by the sponsor in consultation with the SMC. Intrasubject dose-escalation to a dose level shown to be safe may be permitted in the event that a subject has not experienced a Grade ≥2 adverse event (AE) while on study treatment, has received at least 1 cycle of SEA-BCMA at the current dose level, and achieves stable disease (SD) or better.

4 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 6.

4.1 All Treated Patients Analysis Set

The All Treated Patients set includes all patients who receive any amount of SEA-BCMA. The All Treated Patients set will be used for presentation of safety data and efficacy endpoints.

4.2 DLT Evaluable (DE) Analysis Set

The DLT-evaluable (DE) analysis set will include all treated patients who either (1) experience a DLT, or (2) receive at least 75% of the intended SEA-BCMA dose and are followed for the full DLT evaluation period. The DLT evaluation period is defined as cycle 1 of treatment. For q2wk schedule, cycle 1 includes the first 2 doses of treatment. Patients will be replaced for DLT evaluation if they received prohibited medications (as described in protocol Sections 5.4.2 and 5.4.3), or are deemed inevaluable for clinical reasons by the SMC. Patients on the q2wk dosing schedule who receive only the 1st dose during cycle 1 for reasons other than toxicity may not be DLT-evaluable and will be replaced.

4.3 All Screened Patients Analysis Set

The all screened patients analysis set includes all patients who sign informed consent.

4.4 All Enrolled Patients Analysis Set

The all enrolled patients analysis set includes all patients enrolled in the study. A patient is considered enrolled if he/she has met all criteria for participation in the study and has Seattle Genetics approval as documented in the eCRF.

5 STATISTICAL CONSIDERATIONS

5.1 General Principles

This is a phase 1 dose-escalation study. All analyses will be descriptive; however, confidence intervals may be presented to describe precision of estimates.

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables. The two-sided 95% exact confidence interval using Clopper-Pearson methodology (Collett 1991) 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 summarization will only include patients in the dose escalation part of the study, and will be done by dose level. For all other analyses, patients treated in the dose escalation part of the study may be pooled together with patients treated at the same dose level in the expansion cohorts.

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 output will be produced using SAS®, version 9.3 or more recent. Other statistical software, if used, will be described in the clinical study report.

5.2 Model-based Dose Escalation Rules

The initial dose-escalation portion of the trial will be conducted using the modified toxicity probability interval (mTPI) method (Ji 2010). This part of the study is designed to evaluate the safety and tolerability, and to identify the MTD of SEA-BCMA. The mTPI design uses a Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior

probabilities of 3 intervals that reflect the relative distance between the toxicity rate of each dose level to the target DLT rate. Using a target DLT rate of 25% with a 5% margin, the 3 intervals will be (0, 20%), [20%, 30%] and (30%, 100%), and the corresponding dosing decision rules would be:

1. Escalate if current DLT rate is most likely < 20%
2. Continue if current DLT rate is most likely between 20% and 30%
3. De-escalate if current DLT rate is most likely > 30%

Dose finding decisions are shown in Table 2. E, S, and D represent escalating the dose, staying at the same dose, and de-escalating the dose, respectively. Decision DU means that the current dose level has an unacceptably high toxicity rate and should be excluded from the trial.

Enrollment in this study will occur on a cohort-by-cohort basis. Multiple cohorts may be treated at each dose level, with a maximum of 4 patients treated per cohort. Decisions on dose escalation and subsequent cohort size will be made by the sponsor in consultation with the safety monitoring committee (SMC) after completion of each cohort. Patients in the current cohort must be observed for the full duration of the DLT period before the next cohort of patients is enrolled. In addition, as a precaution, for the first 2 patients in the study there will be a 72-hour observation period before the next patient can be dosed. At doses above Dose Level 1, a 72-hour observation period is required after the first patient in each cohort receives their first dose of SEA-BCMA prior to dosing subsequent patients in the cohort. At least 2 DLT-evaluable (DE) patients will be treated per dose level until the first DLT is observed, then a minimum of 3 DE patients per dose level will be required before escalation to all higher doses. Patients who are considered not evaluable for DLT during Cycle 1 may be replaced. A minimum of 6 DE patients will be observed at the estimated MTD before the MTD or optimal dose is determined. The MTD or optimal dose will be estimated based on data from all patients across all evaluated doses.

De-escalation to a lower dose level may be performed at any time by the sponsor in consultation with the SMC. Intrapatient dose escalation to a dose level shown to be safe may be permitted in the event that a patient tolerates SEA-BCMA and achieves stable disease (SD) or better.

Patients may continue on treatment until progressive disease or unacceptable toxicity, whichever occurs first.

Table 2: Dose-finding spreadsheet for mTPI design

Number of DLTs	Number of DLT-evaluable patients treated at current dose														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E	E	E	E	E	E	E
2	DU	D	D	S	S	S	S	S	S	S	S	S	E	E
3		DU	DU	DU	D	S	S	S	S	S	S	S	S	S
4			DU	DU	DU	DU	DU	D	S	S	S	S	S	S
5				DU	DU	DU	DU	DU	DU	D	S	S	S	S
6					DU	DU	DU	DU	DU	DU	DU	DU	D	S
7						DU	DU	DU	DU	DU	DU	DU	DU	DU
8							DU	DU	DU	DU	DU	DU	DU	DU
9								DU	DU	DU	DU	DU	DU	DU
10									DU	DU	DU	DU	DU	DU
11										DU	DU	DU	DU	DU
12											DU	DU	DU	DU
13												DU	DU	DU
14													DU	DU
15														DU

E = escalate to the next higher dose, S = stay at the current dose, D = de-escalate to the next lower dose, DU = current dose is unacceptably toxic

At the end of the trial when the toxicity outcomes of all the enrolled patients are observed, a dose will be selected as the estimated MTD. The estimation is separated from the design for dose finding. The MTD is selected by performing an isotonic regression that borrows strength cross doses. Let $\hat{p}_i$ be the posterior mean of DLT rate, the pooled adjacent violators algorithm (PAVA) is applied on $\hat{p}_i$ so that the resulting transformed values $\hat{p}_i^*$ increase with the dose levels. That is $\hat{p}_i^* \leq \hat{p}_{i+1}^*$ for all i. The recommended MTD is the dose with a toxicity probability $\hat{p}_i^*$ closest to the target DLT rate 25%, i.e.:

$$\text{Estimated MTD} = \text{argmin } |\hat{p}_i^* - 25\%|.$$

5.3 Determination of Sample Size

Up to approximately 131 subjects are expected to be enrolled in this study. This number is based on the following assumptions:

- Up to approximately 45 subjects will be evaluated in Part A (monotherapy dose-escalation and expansion; q2wk dosing).

  With the mTPI study design, the exact number of subjects needed to complete the dose-escalation portion of the phase 1 study is unknown because it depends on the number of cohorts required to reach MTD and the number of subjects enrolled in each cohort. This number is based on the assumption that approximately 25 subjects will be evaluated in dose-escalation and that approximately 20 subjects will be evaluated in an expansion cohort at the MTD or optimal dose to further define the safety and antitumor activity of SEA-BCMA.

Operating characteristics of the dose-escalation part of the study, including the average number of subjects allocated to each dose across a variety of toxicity scenarios are presented in the simulation report which is in appendix of protocol.

- Up to approximately 20 subjects will be evaluated in Part B, up to 60 subjects will be evaluated in Part C (up to 20 subjects in Cohort 1; up to 20 subjects in each dose level in Cohort 2) and up to 6 subjects will be evaluated in Part D.

No formal hypothesis is planned. The sample size is selected by providing a reasonable estimation precision. Assuming the observed ORR is between 30 to 70%, the 95% binomial exact CIs are summarized below.

ORR	95% CI (N=20)
30%	12%, 54%
40%	19%, 64%
50%	27%, 73%
60%	36%, 81%
70%	46%, 88%

5.4 Randomization and Blinding

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

5.5 Data Transformations and Derivations

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 SEA-BCMA.

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:

$$\text{Months} = \text{Days} / 30.4375$$

$$\text{Years} = \text{Days} / 365.25$$

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.

For efficacy assessments, the date of response will be the latest of all disease evaluations for the given restage assessment. The date of progression will be the earliest of all disease evaluations for the given restage assessment, or the date of investigator claim of clinical progression. Patients who have a response of stable disease or better per IMWG uniform response criteria at the same visit as investigator claim of clinical progression will be counted as clinical progression for determination of best clinical response. An investigator claim of clinical progression is adequate for an assessment of disease progression. For subjects who had C1D22 confirmed response of SD while unconfirmed response as PD and then discontinued treatment without receiving any additional treatment after cycle 1, the best confirmed response will be counted as PD.

5.6 Handling of Dropouts and Missing Data

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

AE dates will be imputed for the purpose of calculating duration of events and treatment-emergent status (see Appendix A for imputation details). 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. For the purpose of grading, lab values reported as less than LLOQ will be imputed as LLOQ.

5.7 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.

5.8 Multiple Comparison/Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed in this phase 1 study.

5.9 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 (<65 vs ≥65 years old)
- BCMA expression levels

5.10 Covariates

This is a phase 1 study. Covariates are not considered for adjustment in the analyses.

5.11 Timing of Analyses

The final analysis for this study will occur after all subjects have completed their treatment and the follow-up period or following study termination by the sponsor.

6 PLANNED ANALYSES

6.1 Disposition

An accounting of study patients by disposition will be tabulated by dose level and total using the All Treated Patients analysis set. Reasons for discontinuation of treatment and study will be summarized.

6.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, gender, ethnicity, race, baseline height, weight, and ECOG score will be listed and summarized; summaries will be presented for each dose level and total using the All Treated Patients analysis set. Disease specific characteristics, including the following measurments at initial diagnosis: M protein, light chain type, ISS stage, chromosomal abnormalities, LDH; refractory or intolerant to selected classes of therapy (PI, IMiD, Anti-CD38 antibody); time from diagnosis; and previous cancer-related treatments will be listed and summarized for each dose level and the total using the All Treated Patients analysis set.

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 by dose level using the All Treated Patients 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. Cumulative dose, absolute dose intensity (ADI) and relative dose intensity (RDI) will be described. The number and percentage of patients whose dose was ever modified will be summarized in tables by modification type, cycle, and overall (i.e. over all drug administrations for a patient); listings may be presented as well.

Duration of treatment (except when calculating exposure) is defined as the time from first dose date to the earliest of :

1. Last cycle day 1 dose date + length of one dosing cycle (i.e., 28),
2. date of death

3. End of study date
4. Analysis data cutoff date if the subject is still on treatment at the time of data cutoff for an analysis.

For the purpose of calculating exposure summaries, duration of treatment is defined as below:

For q2wk schedule: [(last dose date + 14) – first dose date].

For the schedule of q1wk induction for 8 weeks (2 cycles), followed by q2wk dosing:

- If subjects received 2 or less cycles, [(last dose date + 7) – first dose date].
- If subjects received 2 and more cycles, [(last dose date + 14) – first dose date].

Intended Dose Intensity (IDI) is defined as the intended dose of drug (mg) per unit of time. For an initial dose of 100 mg, this is 100 mg/2 weeks = 50 mg/wk with q2wk schedule.

For the schedule of q1wk induction for 8 weeks (2 cycles), followed by q2wk dosing, the IDI is as below.

Initial dose[a]	Total cycles (nc)	Intended total number of doses(nd)	IDI
1600 mg	<=2	4*nc	1600 mg/wk
1600 mg	>2	4*2+ (nc – 2)*2 =2*nc + 4	(1600 * nd) /(4*nc) mg/wk

[a:] the algorithm is similar for other initial dose level.

Absolute Dose Intensity (ADI) is defined as the actual dose (mg) per unit of time that the patient received over the entire treatment period.

Relative dose intensity (RDI) is defined as the absolute dose intensity over the intended dose intensity.

$$RDI = ADI / IDI * 100\%$$

6.5 Efficacy Analyses

All efficacy analyses will be presented using the All Treated patients analysis set, unless otherwise specified, by dose level and total. Analyses may also be performed using the subgroups listed in Section 5.9. Covariates are not considered for adjustment in analyses.

Response assessments, including SPEP/immunofixation, UPEP/immunofixation, SFLC, bone marrow assessments and plasmacytoma evaluation by imaging, as well as overall disease assessment will be listed.

6.5.1 Efficacy Endpoints

6.5.1.1 Objective Response Rate (ORR)

Objective response (OR) rate (ORR) is defined as the proportion of patients with best response sCR, CR, VGPR or PR per investigator. Patients whose disease response cannot be evaluated per IMWG will be considered as non-responder for calculating the ORR in the All Treated Patients analysis set. Patients whose first OR occuers after new antitumor therapy other than study treatment will not be counted as a responder.

The ORR per investigator and its exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991) will be calculated. This endpoint may also be tabulated by the subgroups defined in Section 5.9.

6.5.1.2 Complete Response Rate

Complete response (CR) rate is defined as the proportion of patients with best response sCR or CR per investigator. Patients whose disease response cannot be evaluated per IMWG will be scored as Not Evaluable for calculating the CR rate in the All Treated Patients analysis set. Patients whose first CR occuers after new antitumor therapy other than study treatment will not be counted as a CR when calculating CR rate.

The CR rate and its exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991) will be calculated. This endpoint may also be tabulated by the subgroups defined in Section 5.9.

6.5.1.3 Duration of Response

Duration of response is defined as the time from first documentation of objective response (sCR, CR, VGPR, or PR) to the first documentation of disease progression (PD) or to death due to any cause, whichever comes first. Disease progression includes radiologic evidence of tumor progression and/or clinical progression per investigator. Duration of response for patients who don't have additional response assessments after documentation of objective response will be censored as 1 day.

Duration of response data will be censored as described below:

- Patients who do not have disease progression 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 progressive disease.
- Patients who have started an antitumor treatment other than the study treatment prior to documentation of disease progression 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 disease progression will be censored at the date of the last disease assessment documenting absence of progressive disease.

Duration of response will only be calculated for the subgroup of patients achieving a sCR, CR, VGPR or PR. Duration of response will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. 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 total.

6.5.1.4 Progression Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from the start of study treatment to the first documentation of disease progression (PD) based upon the disease assessment per IMWG 2014 criteria or clinical progression, or to death due to any cause, whichever comes first. Specifically,

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

Patients who don't have post-treatment response assessments or death will be censored on the treatment start date(i.e., PFS is censored as 1 day). The same censoring rules outlined in Section 6.5.1.3 for the DOR will be applied to PFS.

PFS will be analyzed using the Kaplan-Meier methods 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).

The analysis of PFS may be performed for each of the subgroups specified in Section 5.9.

6.5.1.5 Overall Survival (OS)

Overall survival is defined as the time from the start of study treatment to date of death due to any cause. 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. If the last recorded date where a patient is known to be alive is the date of first dose of study treatment, survival time will be censored on the treatment start date (i.e., OS duration of 1 day).

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).

ATA incidence will be summarized by dose level and total for all treated patients.

6.6 Safety Analyses

The All Treated Patients analysis set will be used to summarize all safety endpoints, by dose level and total.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1 or higher).

Laboratory values and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

Concomitant medications will be coded using WHO Drug (version: June 2017 or more recent).

6.6.1 Adverse Events

Adverse events will be summarized by MedDRA preferred term in descending frequency of occurrence unless otherwise specified. For incidence reporting, if a 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 is defined as a newly occurring or worsening AE after the first dose of SEA-BCMA. An overall summary of AEs will be provided by dose level and total. Summaries of AEs will also be provided by dose level and total for the following, by preferred term, if not specified otherwise:

- All treatment-emergent AEs
- AEs related to SEA-BCMA
- Serious Adverse Events (SAEs)
- SAEs related to SEA-BCMA
- AEs leading to dose elimination of SEA-BCMA
- AEs leading to dose delay of SEA-BCMA
- AEs leading to dose interruption of SEA-BCMA
- AEs leading to dose reduction of SEA-BCMA
- AEs leading to treatment discontinuation
- AEs leading to death
- Infusion related reactions by preferred term
- Adverse Events considered as DLT
- 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.

6.6.1.1 Adverse Events of Special Importance

Adverse events of infusion related reactions(IRRs) and associated symptoms may be considered AEs of special importance.

6.6.2 Dose-Limiting Toxicity

The observed number and proportion of patients experiencing a DLT will be reported for the dose escalation part of the study. At each dose level, model-based estimates of the probability of DLT will be presented along with the corresponding 95% credible intervals.

6.6.3 Clinical Laboratory Parameters

Clinical laboratory data will be summarized for selected lab tests, by dose level and scheduled visit. Summary statistics may be tabulated where appropriate. The worst post baseline grade will be presented by dose level and total for each lab test.

Laboratory results and NCI CTCAE grades for hematology, and serum chemistry will be presented in data listings. All laboratory data through the end of treatment visit will be presented in standardized units.

6.6.4 Concomitant Medications

Concomitant medications will be listed by patient.

6.6.5 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 dose level and total. In addition, cause of death will be identified by descending MedDRA preferred term (unless otherwise specified) and summarized by dose level and total. Death information will be listed by patient.

6.6.6 ECOG Performance Status

Shifts from baseline to the best and worst post-baseline score will be tabulated.

6.7 Pharmacokinetics and Immunogenicity Endpoints

6.7.1 Pharmacokinetics

PK concentration will be summarized with descriptive statistics or plotted at each PK sampling time point using the All Treated Patients analysis set. The following PK parameters will be determined where data allow and will be summarized using All Treated Patients analysis set.

- Area under the curve (AUC)
- Concentration at the end of infusion (C_{eoi}) or maximum observed concentration (C_{max})
- Trough concentration (C_{trough})
- Terminal or apparent terminal half-life ($t_{1/2}$)
- Systemic clearance and volume of distribution at steady state

- Accumulation ratio

6.7.2 Antitherapeutic Antibody (ATA) Incidence Rate

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

7 INTERIM ANALYSIS

No other formal statistical interim analyses are planned. Data will be evaluated after each dose level to determine DLTs and inform dose-escalation decisions. The SMC will monitor the trial for safety and DLTs on an ongoing basis. The process for SMC decisions and the roles and responsibilities of the SMC will be detailed in a separate document.

8 CHANGES FROM PLANNED ANALYSES

8.1 Changes from the Original Protocol

Efficacy-Evaluable Analysis Set was not used in the final CSR analysis.

8.2 Changes from the Original SAP

Efficacy-Evaluable Analysis Set, PK Analysis set were not used in the final CSR analysis.

The following Subgroups will not be explored.

- Cytogenetic risk group (high, intermediate, normal)
- Refractory to prior therapies (refractory to IMiD and PI vs not; refractory to IMiD and PI and anti-CD38 anitbody vs not)
- Number of prior therapies (<5 vs ≥5)
- Baseline beta-2 microglobulin (<3.5 vs ≥3.5)
- ISS stage at initial diagnosis (1, 2, 3)
- MRD-negative CR rate and its exact two-sided 95% confidence interval will also be presented.

MRD negative CR, and duration of CR is not summarized.

Exploratory analyses which will be covered by Biomarker Analysis Plan are removed.

IRR by cycle analysis is removed.

ECG summary analysis is removed.

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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 first dose of any study treatment, the partial date will not be imputed; otherwise, the AE partial date will be imputed using the rules described below.

a **A. AE occurred prior to the first dose of any study treatment**, i.e., satisfies either i or ii below:

i. Onset date is prior to the first dose date

ii. (Onset date is completely missing or the same as the first dose date) and (Onset Period is "started before the signing of consent" or "started after consent but before the first dose of any study treatment")

5. **B. AE occurred after the first dose of any study treatment**, i.e., satisfies either i or ii below:

i. Onset date is after the first dose date

ii. (Onset date is completely missing or the same as the first dose date) and (Onset Period is "started after first dose of any study treatment" or missing)

b Note: compare AE onset date with the first dose date on the common precision only for all the date comparisons described in A and B above; e.g., "2019" is considered greater than "2018-xx-xx"; "2019-03" is considered equal to "2019-03-xx". Issue a WARNING to the log when (onset date is completely missing or the same as the first dose date) and Onset Period is missing.

For AE occurred after the first dose of any study treatment (see B. above) only:

- Impute incomplete AE start date as the followings:
  - **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
- Impute incomplete AE end date as the followings when AE outcome is "recovering/resolving", "recovered/resolved", "recovered/resolved with sequelae", or "fatal":
  - **AE day only is missing:** AE end date will be imputed as the minimum of (last day of the AE end date month/year, death date, data extraction date, 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 end date will be imputed as the minimum of (December 31st of the AE end date year, last dose date + 30, death date, data extraction date, EOS date); if the year is not equal to the year of the last dose date, AE end date will be imputed as the minimum of (December 31st of the AE end date year, death date, data extraction date, EOS date)
  - **AE day, month and year are missing, or year only is missing:** AE condition end date will not be imputed

NOTE: if the subject did not receive any dose of the study treatment, do not impute any AE of the subject

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eSignature Approval	PPD Biostatistics 25-Aug-2023 19:03:55 GMT+0000

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