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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7389-M001-218
Study Protocol Title:	An Open-Label Single-Arm Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination with Pembrolizumab in Subjects with Metastatic Triple Negative Breast Cancer (mTNBC)
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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC Level 1	anatomical therapeutic chemical class
ATC Level 3	Pharmacological class
$AUC_{(0-t)}$	area under the concentration-time curve from zero time (pre-dose) to the time of last quantifiable concentration
$AUC_{(0-inf)}$	area under the concentration-time curve from zero time (pre-dose) extrapolated to infinite time
ß -hCG	beta-human chorionic gonadotropin
BLQ	Below the limit of quantification
BMI	body mass index
BOR	best overall response
BSA	body surface area
BUN	blood urea nitrogen
CBR	clinical benefit rate
CI	confidence interval
CL	total clearance
C_{max}	maximum observed concentration
CR	complete response
CRF	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
C1D1	Cycle 1 Day 1

Abbreviation	Term
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
ER	estrogen
FDA	US food and drug administration
FAS	Full Analysis Set
HER-2	human epidermal growth factor receptor 2
irAE	immune-related adverse events
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
IV	Intravenous
LDH	Lactate Dehydrogenase
LLT	lower level term
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRT	mean residence time
mTNBC	metastatic triple-negative breast cancer
NCA	Non-compartmental analysis
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate

Abbreviation	Term
OS	overall survival
PK/PD	Pharmacokinetic/pharmacodynamics
PD	progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PP	predictive probability
PR	Partial Response
PT	preferred term
Q1	first quantile
Q3	third quantile
RBC	red blood cell
RDI	relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors (version 1.1)
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SD	standard deviation
SMQ	Standardized MedDRA Queries
SOC	system organ class
$t_{1/2}$	terminal elimination phase half-life
T4	thyroxine
TEAE	treatment-emergent adverse event
t_{max}	time at which the highest drug concentration occurs
t_{last}	the time of the last measurable (positive) concentration.

Abbreviation	Term
TSH	thyroid stimulating hormone,
TTR	time to response
ULN	upper limit normal
UNK	unknown response
Vz	volume of distribution at terminal phase
WBC	white blood cells
WHO DD	WHO Drug Dictionary

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze the efficacy and safety variables and report results for Eisai Protocol E7389-M001-218, An Open-Label Single-Arm Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination with Pembrolizumab in Subjects with Metastatic Triple Negative Breast Cancer (mTNBC). The focus of this SAP is for the planned primary, secondary and exploratory efficacy and safety analyses during the interim monitoring and at the final analysis in the study. The analysis details for Pharmacokinetic, Pharmacodynamics, Pharmacogenomics, and Biomarker analyses are not described herein this SAP. Separate analysis plans will be completed for these specific analysis variables and attached to the final SAP and clinical study report.

Reference materials for this statistical analysis plan (SAP) include the protocol amendment 04 of E7389-M001-218 (dated 2019-05-29) and Case Report Forms (CRF, Version, 2017-2-21). If the protocol or case report forms are amended or updated then appropriate adjustments to the SAP may be made if they are related to the planned analyses.

The SAP described hereafter is an *a priori* plan. This is an open label study and the SAP will be finalized and approved before database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

4.1 Study Objectives

In subjects with mTNBC previously treated with 0 (Stratum1) or 1 to 2 (Stratum 2) lines of systemic anticancer therapy in the metastatic setting and currently treated with eribulin mesylate in combination with pembrolizumab:

4.1.1 Primary Objective

- For the Phase 1b part – to determine safety and tolerability of eribulin mesylate in combination with pembrolizumab in all subjects (ie, Stratum 1 and 2).
- For the Phase 2 part – to evaluate objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by independent imaging review (IIR) in all subjects.
- For the Phase 2 part – to evaluate ORR per RECIST 1.1 by IIR in Stratum 2 subjects and compare with the historical response rate of pembrolizumab monotherapy of 10%.

4.1.2 Secondary Objectives

- For the Phase 2 part, in all subjects and separately in Stratum 2 subjects, to evaluate Progression-Free Survival (PFS) per RECIST 1.1 by IIR.
- To evaluate Overall Survival (OS).
- To evaluate Duration of Response (DOR) per RECIST 1.1 by IIR.
- To evaluate Clinical Benefit Rate (CBR) per RECIST 1.1 by IIR.

- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by investigator review.
- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by IIR and OS outcome by PD-L1 (programmed death receptor-ligand 1) expression.
- To evaluate the safety and tolerability of the combination.

4.1.3 Exploratory Objectives

- To evaluate time to response (TTR) per RECIST 1.1 by IIR in all subjects and separately in Stratum 2 subjects.
- To evaluate exposure-response relationship in all subjects.
- To explore potential effects of pembrolizumab co-administration on the pharmacokinetics (PK) of eribulin mesylate in all subjects.
- To explore efficacy outcomes (ORR, PFS, DOR, and CBR) per immune-related RECIST 1.1 (irRECIST) by IIR and investigator review for all subjects and separately in Stratum 2 subjects.

4.2 Overall Study Design and Plan

This is an open-label, single-arm, multicenter, Phase 1b/2 study of eribulin mesylate in combination with pembrolizumab in subjects with metastatic triple-negative breast cancer previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Subjects may have received prior neo/adjuvant chemotherapy.

The Phase 1b part includes 1 initial safety run-in cohort in which at least 6 subjects will receive eribulin mesylate 1.4 mg/m^2 intravenously (IV) on Days 1 and 8 of a 21-day cycle and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle (dose level 1). Dose-limiting toxicity (DLT) will be assessed in the first cycle. Dose level 1 can be selected as the recommended Phase 2 dose (RP2D) if no more than 1 subject has a DLT. Otherwise, eribulin mesylate dose will be lowered from 1.4 mg/m^2 to 1.1 mg/m^2 on Days 1 and 8 of a 21-day cycle (dose level 0). If no more than 1 out of 6 subjects at dose level 0 has a DLT, the Phase 2 part will proceed with dose level 0. Approximately 12 subjects may be enrolled in the Phase 1b part of the study.

Under protocol amendment 1, 107 subjects (including subjects in Phase 1b who are on RP2D level) were enrolled in 2 strata and received the same combination treatment at the RP2D level. The strata include no prior systemic anticancer therapy in the metastatic setting (Stratum 1) and previously treated with 1 to 2 lines of systemic anticancer therapy in the metastatic setting (Stratum 2). Bayesian predictive probability (PP) of response rate was used to monitor the response rate after postbaseline tumor assessments for at least 38 subjects were available. The study could be stopped early for efficacy or futility if PP crosses the prespecified boundary. Hence, efficacy conclusion of the primary efficacy endpoint of ORR could be made on the basis of the predictive probability prior to the full enrollment of 100 evaluable subjects in the study .

There is clinical interest to have a more precise estimation of the efficacy data for Stratum 2. Therefore, per protocol amendment 3, additional subjects will be added to Stratum 2 in order to include a total of 80 evaluable subjects in Stratum 2 for final analysis. As a result, approximately 150 subjects in total (145 evaluable with 80 in Stratum 2) will be enrolled. Per protocol amendment 4, additional subjects will be added to Stratum 2 in order to include a total of at least 100 evaluable subjects in Stratum 2 for final analysis.

5 DETERMINATION OF SAMPLE SIZE

A total of approximately 170 subjects (165 evaluable with 80 in Stratum 2) will be enrolled.

Under protocol amendment 1, 107 subjects including at least 6 from the Phase 1b part were enrolled in the study. Enrollment was into 2 strata, which included first-line (Stratum 1) versus second- and third-line (Stratum 2) subjects. Bayesian predictive probability was used to monitor the study after response data from the first 38 subjects were available. Sample size calculation was carried out assuming the historical response rate of 0.2. Using simulation, the model parameters (θ_L=0.025, θ_U =0.99, and θ_T=0.95) were calibrated such that the frequentist 1-sided Type I error was 0.0326 when the tumor response rate in the combination regimen was 0.2 (under frequentist's null hypothesis H_0), and the power was 0.9278 when the response rate was 0.35 (under frequentist's alternative hypothesis H_a). The expected numbers of subjects needed to reach the decisions were 56 and 61 when p=0.2 (under H_0) and 0.35 (under H_a), respectively. A vague beta prior distribution for response rate, p, was specified in PP calculation; that is, p~beta (0.2, 0.8). PP was updated for every 3 new subjects in the simulations, which mimics the group sequential decision making in a real trial setting. Without Bayesian interim monitoring, the Type I error was estimated as 0.0358, and power was estimated as 0.9418 in demonstrating posterior probability P(p>0.2|data) ≥0.95. Five thousand simulations were run to estimate these design characteristics.

Per protocol amendment 3, additional subjects will be enrolled to ensure 80 evaluable subjects in Stratum 2. Using binomial exact test, the power is 0.92 with 80 evaluable subjects to demonstrate statistical significance at 1-sided alpha of 0.025 for the assumptions of H_0: ORR=0.10 vs. Ha: ORR=0.25. With 80 subjects, the 95% confidence interval for ORR from binomial distribution will be 0.160-0.359 if the observed ORR is 0.25.

Per protocol amendment 4, additional subjects will be added to Stratum 2 in order to include a total of at least 100 evaluable subjects in Stratum 2 for final analysis.

6 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

6.1 Study Endpoints

RECIST 1.1 criteria will be used in the evaluation of tumor status for the primary, secondary and exploratory endpoints, irRECIST criteria will be used in the evaluation of tumor status for one of the exploratory endpoints. Tumor response data obtained per RECIST 1.1 by IIR will be utilized in the main analysis of ORR, PFS and DOR. In addition, tumor assessment data assessed per RECIST1.1 by investigator review and per irRECIST by IIR and by investigator review will be considered as secondary or exploratory (CTCAE, 2009).

6.1.1 Primary Endpoint

Objective Response Rate (ORR) - defined as the proportion of subjects who had best overall response (BOR) of Complete Response (CR) or Partial Response (PR).

6.1.2 Secondary Endpoints

The secondary efficacy endpoints are as follows:

- **Progression-Free Survival (PFS)** - defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first.
- **Overall Survival (OS)** – defined as the time from the date of first dose of study drug until date of death from any cause.
- **Duration of Response (DOR)** – defined as the time from the date that a confirmed objective response is first documented to the date of PD or death due to any cause for those subjects with a confirmed PR or CR.
- **Clinical Benefit Rate (CBR)** – defined as the proportion of subjects who had BOR of CR, PR, or durable SD (≥24 weeks).
- Estimates of ORR, PFS, OS and DOR in the PD-L1 Positive Set.

6.1.3 Exploratory Endpoints

- **Time to Response (TTR)** – defined as the time from the first dose date to the date that the confirmed objective response is first documented for subjects who had BOR of CR or PR based on RECIST 1.1.
- **ORR, BOR, PFS, DOR, CBR and DCR** using irRECIST

6.2 Study Subjects

6.2.1 Definitions of Analysis Sets

The DLT Evaluable Set includes subjects in Phase 1b who complete the first treatment cycle (i.e., take at least 2 doses of eribulin mesylate with no more than one dose reduction and at least 1 dose of

pembrolizumab). Subjects in phase 2 who had a DLT event will be considered evaluable for the dose-limiting toxicity as well. It is the analysis set for DLT evaluation in the Phase 1b part.

The Full Analysis Set (FAS) (Safety Analysis Set) includes all subjects who received any amount of either study drug. This is the analysis set for safety analyses and analyses of PFS and OS.

The Evaluable Analysis Set (EAS) (subset of Full Analysis Set) includes all subjects treated at RP2D level who have both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued early or death. It is the analysis set for efficacy analyses.

The PD-L1 Positive Set (subset of Evaluable Analysis Set) includes evaluable subjects whose PD-L1 expression level is above the threshold that is to be specified prior to the final analysis. Key primary and secondary efficacy endpoints (i.e., ORR, PFS, OS, and DOR) will be summarized in this analysis set.

6.2.2 Subject Disposition

The number (percentage) of enrolled and treated subjects will be summarized as well as subjects who discontinued single drug and subjects who discontinued the combination treatment and reasons for discontinuation. Survival status at the last follow-up visit before data cutoff date will be summarized as well. In addition, the number (percentage) of subjects who remain in each phase at data cutoff date (i.e. treatment phase) will be summarized.

Subject disposition will be summarized by stratum and combined.

6.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock for the primary analysis of ORR.

Major protocol deviations will be summarized and listed by each category. All protocol deviations identified according to study entry criteria and during treatment will be listed.

6.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS will be summarized by stratum and combined using descriptive statistics. The derivation of baseline is given in Section 8.

Continuous variables include age, weight, vital signs, height, BMI, and BSA; categorical variables include sex, age group, race, ethnicity, PD-L1 status, pregnancy test status at baseline, ECOG status and enrollment strata. In addition, disease characteristics including time from original breast cancer diagnosis to first study dose, age at original histological/cytological diagnosis, time from MBC diagnosis to first study dose, histology/cytology of the primary tumor, HER-2 status, estrogen (ER) status, progesterone status, lesions baseline, tumor staging at study entry, baseline metastases, and baseline lactate dehydrogenase (LDH) level will be summarized.

6.2.5 Medical History

The number (percentage) of subjects reporting a history of any medical condition, as recorded on the CRF, will be summarized by stratum and overall. A subject data listing of medical and surgical history will be provided. Medical History will be coded using MedDRA (version 22.0) and summaries completed by System Organ Class and Preferred term.

6.2.6 Prior and Concomitant Therapy

All investigator terms (verbatim terms) for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD, version WHODDMAR18_HD_B2) drug codes. The number (percentage) of subjects who took prior or concomitant medications will be summarized on the FAS by Anatomical Therapeutic Chemical (ATC Level 1) class, Pharmacological (ATC Level 3) Class and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days (90 days if given for adverse events) after the subject's last dose. A listing of prior and concomitant medications will be included in the clinical study report for this protocol.

6.2.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates will review treatment compliance during investigational site visits and at the completion of the study. Treatment compliance will not be summarized since the data will not be entered in the clinical database. However, dose modifications (i.e., reduction/delay/omission) for eribulin will be summarized in Section 6.6.2.

6.3 Data Analysis General Considerations

All efficacy analyses will be summarized in the appropriate analysis set defined in Section 6.2.1 with available data in the clinical database at the data cutoff, by stratum and combined.

6.3.1 Pooling of Centers

Data from all centers will be pooled in the analysis. No adjustment of center effect is planned in the models for the primary, secondary and exploratory endpoints.

6.3.2 Adjustments for Covariates

No adjustments for covariates are planned for primary and secondary analyses in the study. Baseline factors may be used in the model as covariates as supportive analyses for endpoints.

6.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustments will be made in the exploratory trial. A two-sided alpha of 0.05 will be used in the frequentist tests unless otherwise specified.

6.3.4 Examination of Subgroups

The summaries for primary efficacy endpoint, ORR, and key secondary efficacy endpoints, PFS and OS, will be provided by the following subgroups. Test statistics (i.e. ORR and corresponding 95% CI, median and 95% CI for PFS and OS) for each category will be presented.

- stratification factor (Stratum 1 vs. 2)
- PD-L1 expression (positive vs. negative)
- age group (<50 vs. ≥50 Years)
- race (White, Non-White)
- baseline Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1)
- with vs. without bone involvement
- with vs. without liver involvement
- with vs. without lung involvement
- with vs. without brain involvement
- histology type of breast tumor (Ductal Adenocarcinoma vs. Lobular Adenocarcinoma)
- Site of disease (visceral vs. non-visceral only)
- time from original diagnosis to the first study dose (<2 yrs vs. ≥ 2 yrs)
- time from metastatic disease to the first study dose (<3 mos vs. ≥ 3 mos)
- number of organs involved (≤2 vs. >2)
- baseline LDH level (≤1.5xULN vs. >1.5 ULN; ≤2xULN vs.>2ULN)

Additional subgroup analyses may also be conducted after all study data have been examined to better provide an understanding the treatment responses, if deemed necessary.

6.3.5 Handling of Missing Data, Drop-outs, and Outliers

At the time of primary analysis, if death or disease progression is not observed from a subject, corresponding censoring rules for OS and PFS will be followed. They are defined in Section 8.

Potential outlier values will be investigated. They will be analyzed as is in the locked database.

6.3.6 Other Considerations

Not applicable.

6.4 Efficacy Analyses

Approximately 165 evaluable subjects on RP2D will be enrolled in the study, including phase 1b and 2. Subjects enrolled in phase 1b and treated on RP2D level will be pooled with subjects in phase 2 for efficacy analysis. The analysis methods described in Section 6.4 will be applied to the Evaluable Analysis Set (EAS) unless otherwise stated.

6.4.1 Primary Efficacy Analyses

6.4.1.1 ORR in All Subjects

Bayesian predictive probability (PP) design was used in original study design (Yin, 2012). Under original design, in the combined Stratum 1 and 2 subjects, the ORR value per RECIST 1.1 by IIR was assumed to be 0.20 for the historical control (see Table 1 footnote a in protocol amendment 04) and the ORR in this trial was expected to be 0.35. Under protocol amendment 1, approximately 100 evaluable subjects were expected to be enrolled. Bayesian PP was used to monitor the response rate after postbaseline tumor assessments of at least 38 subjects were available. The calculation of PP was based on the goal of claiming superiority of the combination therapy at the end of the study if

$$P(p>0.2|data)\geq 0.95 \qquad (1)$$

where p was the response rate of the combination therapy, 0.2 was the response rate of historical control based on single agents pembrolizumab and eribulin in recent trials (Table 1 in Protocol Amendment 4), 0.95 was the prespecified target probability (θ_T), and P(p>0.2|data) is the posterior probability. On the basis of the accumulated data up to time of data monitor in the study, the probabilities of all possible future outcomes that lead to equation (1) at the end of the study would be added in order to obtain the predictive probability as given in (2) below. Therefore, early decision of study termination prior to reaching approximately 100 evaluable subjects was possible for claiming the combination therapy is promising when PP is above a prespecified upper threshold (θ_U) or for claiming futility when PP is below a prespecified lower threshold (θ_L). The upper and lower cutoff probabilities for decision-making, θ_U and θ_L, were set as 0.99 and 0.025. Under the predictive monitoring, the study proceeded as follows:

- If PP> θ_U(=0.99), stop the study and claim the combination therapy promising
- If PP< θ_L(=0.025), stop the study and claim the combination therapy not promising
- Otherwise, continue the study until the number of evaluable subjects reaches to 100

The Bayesian stopping boundaries are included in Appendix 13.1.

After completion of enrollment under protocol amendment 1, Bayesian PP is no longer used for continuous monitoring of efficacy and futility as the study will not be stopped early for either efficacy or futility.

Details of Bayesian Approach

Objective Response Rate (p) will be compared to a historical control rate (p_0) of 0.2 via Bayesian posterior probability:

$$\Pr(p>p_0=0.2|data)\geq \theta_T \quad (1)$$

where a pre-specified target probability (θ_T) is set at 0.95. Without any interim analysis, the trial requires the posterior probability of p>0.2 to be at least 0.95 at the end of the trial in order to demonstrate the superiority of combination therapy over historical control.

Since interim monitoring is implemented in the trial, Bayesian predictive probability (PP) is calculated when there are 38 patients in the Interim Analysis Set (definition in interim analysis section) to evaluate how likely the trial would complete its full enrollment. Specifically, on the basis of the accumulated data up to the time of data monitor in the trial, PP is calculated by adding the probabilities of all possible future outcomes that lead to equation (1).

Suppose a maximum number of accrued subjects is set as N_{max} and assume the number of responders X among the current n subjects follows a binomial(n, p) distribution, the posterior distribution p|x~beta(a+x, b+n-x) where a (=0.2) and b (=0.8) are parameters in the prior beta distribution, p~beta(a,b). Let Y be the number of ORR in the potential m=N_{max} - n future subjects, Y ~beta-binomial (m, a+x, b+n-x). When Y=i, the posterior distribution of p|(X=x,Y=i)~beta(a+x+i, b+N_{max}-x-i). The PP can then be calculated as follows,

$$\begin{aligned} PP &= E\{I[\Pr(p > 0.2 \mid x, Y)] \geq 0.95 \mid x\} \\ &= \sum_{i=0}^{m} \Pr(Y = i \mid x)\, I\{\Pr(p > 0.2 \mid x, Y = i) > 0.95\} \end{aligned} \quad (2)$$

Where I[A]=1 if A is true and I[A]=0 if A is false. PP characterizes the future trial conclusion given the strength of the currently observed data.

Therefore, early decision of trial termination is possible for efficacy when PP is above a pre-specified upper threshold (θ_U) or for futility when PP is below a pre-specified lower threshold (θ_L). In the current trial, the upper (θ_U) and lower (θ_L) cutoff probabilities for decision making are set as 0.99 and 0.025. Under the predictive monitoring, the trial proceeds as follows:

- If PP> θ_U(=0.99), stop the trial and claim the combo promising
- If PP< θ_L(=0.025), stop the trial and claim the combo not promising
- Otherwise, continue the trial until the number of evaluable subjects reaches 100

The Bayesian stopping boundaries are included in Appendix 13.1. During the trial, PP will be calculated with updated response information till the boundary is crossed. In case continuous PP monitoring is not conducted because of operational and logistic reasons (e.g. delayed TA assessments and fast enrollment) or it is decided to take the trial to full enrollment even θ_U is crossed in order to gather more efficacy data, posterior probability in equation (1) will be evaluated to determine the efficacy of the combination regimen after the tumor response status has been collected from the last evaluable subjects. That is, to claim efficacy if $Pr(p>0.2|data) \geq 0.95$. A two-sided 95% credible interval of ORR based on posterior distribution of p will be constructed to aid the interpretation of the results.

Final Analysis

In the evaluable subjects in Stratum 1 and 2 combined, Bayesian posterior probability in equation (1) will be evaluated to determine the efficacy of the combination regimen after the tumor response status has been collected from the last evaluable subjects. That is, to claim efficacy if $P(p>0.2|data) \geq 0.95$. A 2-sided 95% credible interval of ORR in the evaluable subjects will be constructed to aid the interpretation of the results.

Sensitivity Analysis

Sensitivity analyses of ORR for the evaluable subjects in Stratum 1 and 2 combined will be performed using frequentist approach. The hypotheses for the test of ORR are as follows:

$$H_0: p=0.2$$

$$H_1: p>0.2$$

Assuming number of ORR follows a binomial (N_{max}, p) distribution, the binomial exact test will be used in hypothesis testing. A 2-sided Clopper-Pearson 95% CI will also be constructed.

6.4.1.2 ORR in Stratum 2

Under protocol amendment 3, in Stratum 2 subjects, the hypotheses for ORR per RECIST by IIR are updated to be H_0: ORR=0.10 vs. Ha: ORR=0.25, based on the most recent pembrolizumab monotherapy trial (Table 1 in protocol amendment 4). Therefore, additional subjects will be enrolled to ensure 80 evaluable subjects in Stratum 2 to provide >90% power for the comparison of H_0: ORR=0.10 vs. Ha: ORR=0.25 at 1-sided alpha value of 0.025.

Under Protocol Amendment 4, additional subjects will be enrolled to ensure 100 evaluable subjects in Stratum 2 to obtain more precise estimate of ORR.

Final Analysis

In the evaluable Stratum 2 subjects, a binomial exact test will be used to test the estimated ORR per RECIST 1.1 by IIR versus a historical response rate of 10% at 1-sided alpha value of 0.025. A 2-sided Clopper–Pearson 95% CI of ORR will be constructed for calculating exact binomial intervals.

6.4.2 Secondary Efficacy Analyses

PFS, OS and DOR

Progression-Free Survival (PFS), Overall Survival (OS) and Duration of Response (DOR) will be analyzed using Kaplan-Meier product-limit estimates. Median PFS and OS and the survival rate of PFS (at 6, 9 and 12 months) and OS (at 6, 12 and 18 months), probability of DOR ≥ 6, 9 and 12 months will be presented with two-sided 95% CIs, if they can be estimated from the model. Censoring rules and data handling are described for each variable in Section 8 of this SAP.

The probability of PFS, OS and DOR will be plotted over time. The median, first and third quartiles from Kaplan-Meier estimation for PFS, OS and DOR will be provided with 95% CIs if estimable.

Clinical Benefit Rate

A 2-sided Clopper–Pearson 95% CI will be constructed for calculating exact binomial intervals.

6.4.3 Other Efficacy Analyses

The analysis of time to response (TTR) will follow the analysis of PFS. The analysis will be performed in the subjects with confirmed PR/CR by RECIST1.1.

In addition to RECIST1.1 by IIR, tumor assessment data (i.e., ORR, PFS, DOR, and CBR) will be assessed per RECIST1.1 by investigator review and per irRECIST by IIR and investigator review in the sensitivity analysis.

All efficacy analyses will be performed in overall subjects and also for each stratum.

Efficacy outcomes will be further evaluated in the PD-L1 Positive Set. The clinical utility of PD-L1 as a predictive marker in mTNBC subjects who receive eribulin mesylate and pembrolizumab combination treatment will be assessed.

6.5 Pharmacokinetic, Pharmacodynamic and Pharmacogenomic Analysis

6.5.1 Pharmacokinetic Analyses

Plasma concentration versus time data will be analyzed using a population PK approach to estimate population PK parameters. Scatter plots of dose normalized plasma concentration and associated tabulations will be generated by actual sample collection time and for each PK sample collection visit. A separate Population PK data analysis plan will be developed that will describe selection of

appropriate PK structural model, estimation of model parameters and related variability, covariate testing on model parameters as appropriate.

Individual eribulin PK parameters for phase 1b will be, but not limited to $t_{1/2}$, t_{max}, C_{max}, $AUC_{(0-t)}$, t_{last}, $AUC_{(0-inf)}$, , CL, V_z will be calculated based on Cycle 1 Day 1 (C1D1).

6.5.2 Pharmacodynamic Analyses

The effect of soluble biomarkers will be summarized. The analyses will be detailed in a separate analysis plan.

6.5.3 Pharmacokinetic / Pharmacodynamic Analyses

Exploratory/graphical analyses will be conducted for PK/PD evaluations with data from Phase 1b and Phase 2, and be followed by model based analyses. These analyses will be detailed in a separate data analysis plan to be handled by Modeling&Simulation group.

6.5.4 Pharmacogenomic and Biomarker Analyses

Pharmacogenomic and biomarker analyses will be performed and reported separately. Details of these analyses will be described in a separate analysis plan.

6.6 Safety Analyses

All safety analyses will be performed in the Safety Analysis Set. The incidence of treatment-emergent adverse events (TEAEs, Section 6.6.3) and SAEs will be summarized. Laboratory test results, vital signs and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, and maximum for continuous variables; and n [%] for categorical variables. Abnormal values will be flagged.

Safety information will be summarized by stratum and combined.

6.6.1 RP2D and Dose-limiting Toxicity in Phase1b

The Phase 1b study will include at least 1 safety run-in cohort in which 6 mTNBC subjects who receive eribulin mesylate 1.4 mg/m^2 on Days 1 and 8 and pembrolizumab 200 mg on Day 1 of a 21-day cycle (dose level 1). Subjects will be observed for dose-limiting toxicity (DLT) in the first cycle. The purpose of the safety run-in cohort(s) is to study safety of the 2-drug combination. The Phase 2 part will proceed with dose level 1 when no more than 1 subject has a DLT. Otherwise, a lower eribulin mesylate dose of 1.1 mg/m^2 and pembrolizumab 200 mg will be evaluated in another cohort of 6 subjects. If no more than 1 subject has a DLT in the first cycle, the Phase 2 part will proceed with dose level 0 as the RP2D. Otherwise, alternative doses (eribulin mesylate 0.7 mg/m^2) will be explored prior to the start of the Phase 2 part.

6.6.2 Extent of Exposure

The number of cycles/dose taken on treatment, the number of subjects requiring dose reductions, dose delays, and dose omissions(dose omission were determined by number of study drug not administered as pre-specified from the study drug exposure CRF) for eribulin, and the number of administration of pembrolizumab will be summarized. One cycle is defined as 21 days of treatment. Specifically:

- The number of cycles received and the number of doses taken will be summarized for eribulin with descriptive statistics. Subject is considered received one cycle if the subject received at least one doses on either day 1 or day 8 of a cycle. Also the number of administration of pembrolizumab will be summarized with descriptive statistics.

- The duration of treatment (weeks) by each study drug and overall will be summarized with descriptive statistics. It will be calculated as (date of last infusion with administrated positive dose – date of first infusion + 1)/7 for each drug. It will be calculated as (date of last infusion with administrated positive dose of study drugs – date of first infusion of study drugs + 1)/7 for overall.

- For eribulin, the number of subjects with dose reductions, dose omissions and dose delays will be summarized by counts and percentages according to study medication data. In addition, frequency of dose reductions, dose omissions and dose delays will be summarized by categories (0, 1, and ≥2).

- Total dose of eribulin (two definitions: mg and mg/m^2) per subject will be computed as the sum of all of the doses received during study.

- Average dose intensity per subject (mg/m^2/week for eribulin) and relative dose intensity per subject (percent of total dose received relative to total planned dose (including the missed doses)) will be summarized by descriptive statistics for eribulin.

  Average dose intensity (mg/m^2/week) for eribulin = total dose (mg/m^2)/ duration of treatment in weeks.

  Relative dose intensity (RDI)(%) for eribulin= total dose (mg/m^2)/ total planned dose(mg/m^2).

Total dose (mg/m^2), average dose intensity and relative dose intensity will be calculate based on BSA at each visit. If BSA is missing, the last BSA before missing will be carried forward as the BSA for the visit.

Subject data listings will be provided for all dosing records, and for the summary statistics calculated above.

6.6.3 Adverse Events

All Adverse Events (AE) will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical

terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 22.0) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

The incidence of TEAEs will be summarized descriptively. A TEAE is defined as an AE that emerged during treatment or up to 30 days (90 days for SAEs and /or events of clinical interest) following last dose of study drug, having been absent at pretreatment (Baseline) or

- Reemerged during treatment or up to 30 days (90 days for SAEs and /or events of clinical interest) following last dose of study drug, having been present at pretreatment (Baseline) but stopped before treatment, or

- Worsened in severity during treatment or up to 30 days (90 days for SAEs and /or events of clinical interest) following last dose of study drug relative to the pretreatment state, when the AE was continuing.

Per protocol amendment 1, Events of clinical interest (ECI) for this trial include: an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2× ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

We used the following AE PT terms to identify ECI above:

- ALT increased
- AST increased
- Blood bilirubin increased
- Blood alkaline phosphatase increased

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

An overview table, including the incidence of and the number of subjects with TEAEs, TEAEs with grade 3 or above, serious adverse events (SAEs), deaths, and TEAEs that led to death, treatment discontinuation, dose reduction, or dose interruption will be provided.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. TEAEs by preferred term, and CTCAE Grade will be summarized in descending frequency order.

The number (percentage) of subjects with treatment-related TEAEs including Eribulin, Pembrolizumab, both Eribulin and Pembrolizumab will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be possibly or probably related to study treatment or with missing assessment of the causal relationship.

The number (percentage) of subjects with TEAEs leading to death, TEAEs with grade 3 or above, SAEs, TEAEs leading to discontinuation from study drugs, TEAEs leading to study drug dose reduction of eribulin and TEAEs leading to study drug interruption of study drugs will be summarized by MedDRA SOC and PT in separate tables. Separate subject data listings of all AEs, all AEs leading to death, treatment-related AE, grade 3 or above AEs, SAEs, and AEs leading to discontinuation from study drug will be provided.

6.6.4 Treatment-Emergent Adverse Events of Special Interest

Potential immune-related adverse events (irAE) are the primary events of clinical interest (ECIs) in addition to the adverse event specific to eribulin (peripheral neuropathy and neutropenia, etc). The listings of ECI potentially related to Pembrolizumab, Eribulin or both are documented in separate files.

Standardized MedDRA Queries (SMQ) of treatment-emergent ECI will be summarized by MedDRA preferred term and CTCAE grade.

6.6.5 Laboratory Values

Clinical laboratory tests to be performed, including hematology, chemistry and urinalysis are summarized in Table 1.

Laboratory results will be standardized and summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Table 1, the actual value and the change from baseline to each postbaseline visit and to off treatment visit (end of treatment defined as the last value within 30 days of the last study dose) will be summarized by visit using descriptive statistics.

Laboratory parameters will be categorized according to CTCAE v4.03 grades. Shift tables of laboratory values by CTCAE grade from baseline to worst grade will be provided. Percentages will be based on the number of subjects with non-missing baseline and relevant postbaseline results.

Table 1. Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC
Clinical Chemistry	
Electrolytes	Sodium, potassium, chloride, calcium, magnesium
Liver Function Tests	ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin
Renal Function	BUN, serum creatinine
Thyroid Function	TSH, T4[a]
Serum pregnancy	Serum β-hCG
Other	LDH, total protein, glucose (fasting[b])
Urinalysis	Glucose, ketones, pH, protein, RBCs, WBCs, specific gravity

ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cells

a: Thyroid function will be assessed at the Screening Visit and then every 2 cycles (starting at C2) throughout the study.

b: Fasting glucose at Screen, only

6.6.6 Vital Signs

Descriptive statistics for vital signs parameters (i.e., diastolic and systolic BP, resting pulse rate, respiratory rate, temperature) and changes from baseline will be presented by visit and dosing cohort.

6.6.7 Electrocardiograms

ECG findings (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) at baseline and unscheduled visit will be summarized.

In addition, the number (percentage) of subjects with at least one postbaseline abnormal ECG result in QTc Fridericia values during the treatment period will be summarized. Clinically abnormal ECG results in Fridericia values will be categorized as follows:

Change from baseline in QTc interval:

- At least one postbaseline increase of >30 ms
- At least one postbaseline increase of >60 ms
- At least one postbaseline value of >450 ms

- At least one postbaseline value of >480 ms
- At least one postbaseline value of >500 ms

6.6.8 Other Safety Analyses

ECOG performance status will be summarized descriptively by visit and by shift from baseline to worst postbaseline.

6.7 Other Analyses

No other analysis is planned.

6.8 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

7 INTERIM ANALYSES

The Interim Analysis Set includes all subjects treated at RP2D level who have either completed two post-baseline tumor assessments or discontinued early. The planned interim analysis will be performed when there are 38 such subjects. If the number of subjects in the Interim Analysis Data Set is not exactly 38 at the time of the interim analysis, the Bayesian stopping boundaries will be adjusted based upon the current information (Appendix 13.1)

Interim decisions can be made on the basis of the expected response rate at the end of the study, which compromises the current information with the future sample size via predictive probability approach. The Bayesian design can continuously update the predictive probability of the study outcome, such that early termination of a study is possible for either superiority or futility. The pre-specified Bayesian stopping boundaries are included in Appendix 13.1.

The study statistician will work with the clinical study managers and data managers to define the datasets for the interim analysis. The study statistician will assess the impact of any issues such as unsolved data queries, missing data or data entry delays on the interim results.

If the protocol needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

Baseline

Baseline is defined as the non-missing value most recently collected before the first dose of any study drug.

In the analyses of ORR, CBR and DCR, subjects without baseline or postbaseline tumor assessment will be considered as non-responders and will be included in the denominator when calculating ORR, CBR and DCR. Non-responders will be excluded in the analysis of DOR.

Study Day 1

Study Day 1 is defined as the day of the first dose of any study drug administrated.

By-visit analysis

All by-visit analyses will be performed using assessment at corresponding scheduled visits recorded in the eCRF (not including unscheduled).

The unscheduled visits will be included in the analyses that involve definition of worst post-baseline assessment.

Definition of BOR by RECIST 1.1

The definition of BOR by RECIST 1.1 will follow Appendix 3 in protocol. In particular,

- Tumor assessments after any new anti-caner therapy, including the palliative radiotherapy, will be deleted in defining BOR.
- Tumor assessment after PD defined by RECIST 1.1 will be deleted in defining BOR.
- The following BOR responses are defined based on the timepoint-level response
  - Complete Response (CR): A BOR of CR requires two timepoint assessments of CR, with the second at least 4 weeks after the initial CR. An intervening timepoint assessment of PR, SD, or PD prevents confirmation. BOR of CR cannot be preceded by PD.
  - Partial Response (PR): A BOR of PR requires a first assessment of PR and a second assessment of PR (or CR) at least 4 weeks after the initial PR. An intervening timepoint assessment of PD prevents confirmation. BOR of PR cannot be preceded by PD.
  - Stable Disease (SD): A BOR of SD is assessed if the criteria for BOR of CR~~,~~ *or* PR are not met and if, in addition, an assessment of SD (or better) has been documented at least once $\geq$ 8 weeks from the first dose of study treatment.
  - Progressive Disease (PD): A BOR of PD is defined by any timepoint assessment of PD with no prior BOR qualifying as SD, PR, or CR.
  - Not evaluable (NE): A BOR of NE refers to subjects with either no postbaseline tumor assessment(s) or with postbaseline tumor assessment(s) that are not evaluable [i.e., due to insufficient data for assessment of response per applied response criteria RECIST 1.1 or an early SD with duration < 8 weeks].
  - Unknown response (UNK): A BOR of UNK refers to subjects with no baseline tumor assessment

Definition of BOR by irRECIST

- Investigator Review

Subjects who experience PD defined by RECIST1.1 will have a confirmation scan at least 4 weeks apart to confirm PD (irPD). Subjects may continue receiving study treatment while waiting for confirmation of irPD if they are clinically stable. If a subject discontinued study treatment without confirmation of irPD, the subject will be counted as irPD.

Tumor assessments after any new anti-caner therapy, including the palliative radiotherapy, will be deleted in defining BOR. The overall time point tumor response data collected via both the CRF of the irRECIST and the CRF of the RECIST 1.1 will be used. Simply add prefix 'ir' to CR/PR/SD/PD/NE from RECIST 1.1 and follow the definition of BOR per RECIST 1.1 to define BOR per irRECIST (irCR/irPR/irSD/irPD/irNE). Table 2 describes the scenarios of PD by RECIST 1.1 followed by different confirmation scans.

Table 2. BOR by irRECIST for Scenarios with PD (defined by RECIST 1.1) Followed by Subsequent Scans

Timepoint 1 Overall Response	Timepoint 2 (≥ 4 weeks since Timepoint 1) Overall Response	BOR by irRECIST
PD	CR [a]	If subject has been followed for ≥4 weeks and CR is confirmed, BOR is irCR. If CR not confirmed, then follow same rule as BOR by definition of RECIST 1.1.
PD	PR [a]	If subject has been followed for ≥4 weeks and PR is confirmed, BOR is irPR. If PR not confirmed, then follow same rule as BOR by definition of RECIST 1.1.
PD	SD [b]	irSD
PD	PD [c]	irPD
PD	NE	irPD
PD		irPD, if no confirmation scan.

[a] The subject should be followed for ≥ 4 weeks to confirm the CR/PR.

[b] The subject is on the study treatment and followed for further tumor assessments.

[c] PD is confirmed. The subjects should be discontinued from the study treatment, and no further tumor response assessments will be performed.

Other exploratory endpoints using irRECIST: ORR, PFS, DOR, CBR and DCR will be derived similarly as those using RECIST1.1; but the derivation will be based on irCR, irPR, irSD and irNE instead of CR, PR, SD and NE.

- Independent Imaging Review

  BOR by irRECIST for IIR data will follow the same principle as above except tumor assessments by mRECIST 1.1(modified RECIST 1.1) criteria for the time points up to PD are used.

Censoring rule for OS

Subjects who are lost to follow-up or withdrawal from study will be censored at the last date the subject was known to be alive, and subjects who remained alive will be censored at the time of data cutoff.

Censoring rule for PFS by RECIST 1.1

The PFS derivation rules in this SAP follow the sensitivity of analyses described in Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)".

Definition of Progression Date: Progression date is assigned to the first time at which radiological progression can be declared.

For progression based on a new lesion, the progression date is the date of the initial detection of the new lesion, if there were multiple new lesions detected, then the earliest date of initial detection will be used.

Table 3 shows the primary censoring rules for the derivation of PFS based upon investigator's tumor assessment.

Censoring rule for irPFS by irRECIST

Definition of progression date by irRECIST (i.e., irPD):

- For the subjects who experience PD by RECIST 1.1 and then confirmed by irPD (> or <28 days) or not confirmed due to any reasons, the first documented PD date by RECIST 1.1 is the date of irPD.

- For the subjects who experience PD by RECIST1.1 and then followed by irCR/irPR/irSD, the first documented progression date is the date of first irPD defined by irRECIST.

- If the subject had new lesion earlier than overall timepoint response of PD in irRECIST, the date of new lesion is not counted as irPD date. (this is different from PD by RECIST 1.1 for which, as soon as subject developed new lesions, subject is considered as PD and PD date is the date of new lesion).

Censoring rule will be same as RECIST1.1 except that for the second rule in Table 3.

"Date of first radiologic PD assessment" means the irPD Date determined as above.

Duration of Response

Duration of Response (DOR) – defined as the time from the date that a confirmed objective response is first documented to the date of PD or death due to any cause for those subjects with a confirmed PR or CR. For subjects who did not experience PD or death by the end of data cut off, the date of last adequate radiologic assessment before missing tumor assessments or new anti-cancer therapy will be used as censoring date.

BOR, PFS and DOR will be defined separately for IIR data and for investigator reviewed data following the same rules.

Table 3. Censoring Rules for Analysis of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or post-baseline tumor assessments	Date of the first dose	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off	Date of last adequate radiologic assessment prior to or on date of data cut-off	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after two or more missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.
New anticancer treatment includes palliative radiotherapy. Any tumor assessments after new anticancer treatment started will be removed in the definition of PFS.

** More than two missed visits is defined if the duration between the last tumor assessment (including NE) and death or PD is longer than 126 days (18 weeks) or 168 days (e.g. 24 weeks) for subjects on the every 9 or 12 week scanning schedule in this study:

The priority of the censoring rules is as follows:

1. If the subject had PD or death, the following sequence will be applied:
    - If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of the first dose. However, if the subject did not have baseline tumor assessment and died within 126 days (18 weeks) after the first dose and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
    - If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
    - If a subject missed two assessments before PD or death (No. 7), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criteria, the earliest

censoring date will be used.

- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

Rules for missing dates:

In case of dates missing in adverse event and concomitant medication collection following rules will be followed.

- **Adverse Events**

  Adverse Events with incomplete start dates will be considered treatment emergent if:

  a. Day and month are missing and the year is equal to or after the year of the first dose date;

  b. Day is missing, and the year is after the year of the first dose;

  c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;

  d. Year is missing; or

  e. Complete date is missing.

- **Concomitant Medications**

  Medications will be considered concomitant if:

  a. Day and month are missing and the year is equal to or after the year of the first dose date;

  b. Day is missing, and the year is after the year of the first dose;

  c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date; or

  d. Year is missing; or complete date is missing.

Pharmacokinetics/Pharmacodynamic Data Handling

- **Lower Limit of Quantification of Eribulin Plasma Concentration**

The Lower Limit of Quantification (LLOQ) of eribulin plasma concentration is 0.200 ng/mL.

- **Below Limit of Quantification Handling for Calculation of Pharmacokinetic Parameters**

While calculating PK parameters in Phoenix/WinNonlin, BLQ values will be handled according to the NCA-MNL.

- **BLQ Handling for Developing Concentration-Time Profiles**

When developing individual concentration-time profiles, BLQ values will be handled according to the NCA-MNL.

- **Handling of Anomalous Concentration Values**

The handling of anomalous concentration values will follow the guidance in the NCA-MNL.

- **General Rules for Presentation of Drug Concentrations and PK Parameters**

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD, and CV) will have 3 significant digits. For t_{max} and t_{lag}, raw values and median have fixed 2 decimal places.

Table 4. General Rules for Presentation of Drug Concentrations and PK Parameters

Typical variable	Standard Unit (depends on compound)	N	Digit rule	Raw Minimum Maximum	Mean Median	SD	Geometric Mean	CV (%)
E2027 concentration	ng/mL	X	Significant digits	3	3	3	-	-
C_{max}, C_{min}	ng/mL	X	Significant digits	3	3	3	3	3
t_{max}, t_{lag}[a]	h	X	Fixed decimal places	2	2	-	-	-
λ_z	1/h	X	Significant digits	3	3	3	3	3
$t_{1/2}$	h	X	Significant digits	3	3	3	3	3
AUC	ng·h/mL	X	Significant digits	3	3	3	3	3
$\%AUC_{ex}$	%	X	Significant digits	3	3	3	3	3
CL	L/h	X	Significant digits	3	3	3	3	3
V_d	L	X	Significant	3	3	3	3	3

Typical variable	Standard Unit (depends on compound)	N	Digit rule	Raw Minimum Maximum	Mean Median	SD	Geometric Mean	CV (%)
			digits					
MRT	h	X	Significant digits	3	3	3	3	3

a: Mean, SD, geometric mean and CV will not be calculated for t_{max} and t_{lag}.
CV(%) = sqrt(exp[SD^2 of log transformed data]-1)×100

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.3 or higher, and/or other validated statistical software as required. Non-compartmental analysis (NCA) will be performed using Phoenix 64 WinNonLin (version 7.0 or later).

11 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11 .pdf.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Washington, DC: United States Food and Drug Administration, 2007.

Yin, G.S. Clinical trial design: Bayesian and frequentist adaptive methods. Wiley: Hoboken, New Jersey 2012.

NCA-MNL: 302-104.01-MNL: Non-compartmental pharmacokinetic analysis, June 2018.

13 APPENDICES

13.1 Bayesian Stopping Boundaries

N	LB	UB	N	LB	UB	N	LB	UB
38	6	16	60	12	22	82	19	27
39	6	16	61	12	22	83	19	27
40	6	17	62	12	23	84	19	27
41	7	17	63	13	23	85	20	27
42	7	17	64	13	23	86	20	27
43	7	18	65	13	23	87	20	28
44	7	18	66	14	23	88	21	28
45	8	18	67	14	24	89	21	28
46	8	18	68	14	24	90	22	28
47	8	19	69	14	24	91	22	28
48	9	19	70	15	24	92	22	28
49	9	19	71	15	25	93	23	28
50	9	20	72	15	25	94	23	28
51	9	20	73	16	25	95	24	28
52	10	20	74	16	25	96	24	28
53	10	20	75	16	25	97	25	28
54	10	21	76	17	26	98	25	28
55	10	21	77	17	26	99	26	28
56	11	21	78	17	26	100	27	28
57	11	21	79	18	26			
58	11	22	80	18	26			
59	12	22	81	18	27			

Footnote:

N=number of subjects included in the predictive probability calculation;
LB=lower bound (futility boundary crossed if # objective response ≤LB);
UB=upper bound (efficacy boundary crossed if # objective response ≥UB).

SIGNATURE PAGE

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Signature PPD 08 OCT 2019
Date

Oncology Business Group, Eisai Inc.

Approval:

Signature PPD 10/8/2019
Date

Oncology Business Group, Eisai Inc.

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