ET-D-031-14

Non-interventional, multicenter, prospective, European study to describe the effectiveness of trabectedin + PLD in the treatment of relapsed ovarian cancer (ROC) patients by previous usage of an antiangiogenic drug

Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

Non-interventional, multicenter, prospective, European study to describe the effectiveness of trabectedin + PLD in the treatment of relapsed ovarian cancer (ROC) patients by previous usage of an antiangiogenic drug

Protocol Number ET-D-031-14

Version:	**Version 3.0**
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TABLE OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
BSA	Body Surface Area
CR	Complete Response
DCR	Disease Control Rate
DM	Data Management
DMP	Data Management Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
IC	Informed Consent
KM	Kaplan-Meier
LOCB	Last Observation Carried Backwards
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall Survival
PLD	pegylated Liposomal Doxorubicin
PD	Progression of Disease
PFS	Progression-Free Survival
PR	Partial Response
PS	Performance Status
RECIST	Response Evaluation Criteria In Solid Tumors
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SmPC	Summary of Product Characteristics
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides details of statistical analyses outlined within PharmaMar Protocol ET-D-031-14 Version 4 – Amendment 2, dated 18 September 2018. The scope of this plan includes the final analyses that are planned and will be executed by Mapi, an ICON Plc company. Results from these proposed analyses will become the basis of the clinical study report.

2. OBJECTIVES

Primary Objective

To assess the progression-free survival (PFS) according to investigator criteria in relapsed ovarian cancer patients treated with trabectedin + pegylated liposomal doxorubicin (PLD) according to standard local clinical practice following approved Summary of Product Characteristics (SmPC) indication and dose, overall and by previous usage of antiangiogenic drug.

Secondary Objectives

The secondary objectives (overall and by previous usage of antiangiogenic drug) will be to:

1. Determine the response rates (complete response [CR] + partial response [PR]), and disease control rate (DCR; CR + PR + stable disease [SD])

2. Determine overall survival (OS)

3. Determine evolution of the patient's performance status (PS)

4. Evaluate treatment duration and number of cycles, treatment exposure, and time to next treatment

5. Evaluate the safety of the combination of trabectedin + PLD

3. STUDY OVERVIEW

3.1 Study Design

This is a non-interventional, prospective, multicenter study including at least 300 patients from approximately 70 sites from Germany, Italy, Spain, France, and Belgium, with platinum-sensitive relapsed ovarian cancer for whom trabectedin + PLD is administered according to standard local clinical practice following approved SmPC indication and dose. There is no involvement with any treatment decisions for the patients included in the study.

To be enrolled in this study, the patients must meet all inclusion criteria and have none of the exclusion criteria. The reason(s) for not enrolling a patient in the study (patient declined, no reply, patient not fulfilling the selection criteria) are recorded in a patient qualification log at each site. This enables subsequent assessment of potential selection bias necessary for quality assurance of the data collected.

The study will begin with the enrollment of the first patient. The individual patient study duration will be up to 13 months (12-month Observation Period + 1-month Follow-up Period). Patients treated during the entire observation period will have a visit at month 12 and a follow up visit 1 month after. Patients ending treatment before the end of the 12 months observation period will, in addition to the 1 month after follow up visit, have an additional visit at month 12.

Trabectedin is administered every 3 weeks as a 3-hour infusion at a dose of 1.1 mg/m2, immediately after PLD at 30 mg/m2. There is no predefined limit as to the number of cycles of treatment with trabectedin. Treatment may continue as long as the treating physician feels there is benefit, even in the presence of apparent progression of disease.

3.2 Sample Size

At least 300 patients are to be selected. With this number it is judged that PFS after treatment with trabectedin + PLD will be estimated with sufficient accuracy.

4. STUDY ENDPOINTS

Further detail and definitions of the endpoints can be found in Section 5. The primary endpoint is determination of PFS as reported by the investigator. The secondary endpoints are:

1. Response rate (CR or PR)
2. Disease control rate (CR or PR or SD)
3. Overall survival
4. Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO PS)
5. Treatment duration (number of cycles)
6. Treatment exposure
7. Time to next treatment
9. Safety assessment (adverse events (AE)s and serious adverse events (SAE)s, including adverse drug reactions and serious adverse drug reactions)

5. DEFINITIONS

5.1 General

Study Day 1

Will be defined as the first day with trabectedin + PLD administration therapy.

Baseline Tumor Imaging

The patient's baseline tumor imaging will be considered the imaging performed prior to the initial trabectedin + PLD administration (Day 1) or the earliest imaging study following Day 1.

5.2 Treatment Exposure

Treatment Duration

Duration of treatment as total number of weeks on trabectedin and/or PLD will be calculated as follows:

$$\left(\frac{lastdosedate - firstdosedate + 21days}{7} \right)$$

Treatment duration should not, however, go beyond date of death or the start date of a subsequent anti-cancer treatment.

Cycle

Cycle duration will be calculated as the time from the administration of trabectedin and/or PLD for the given cycle to the day before the administration of the subsequent cycle. The last cycle duration for a patient will be set to 21 days (but no later than death or start of subsequent anti-cancer treatment).

Dose Intensity

Weekly dose intensity (mg/week) is calculated as:

Cumulative dose received / Total number of weeks on drug (treatment duration)

Relative Weekly Dose Intensity

Relative weekly dose intensity = (Reported weekly dose intensity / Expected weekly dose intensity) x 100

Derived Body Surface Area (BSA)

BSA will be calculated by the following Mosteller formula to:

$$\text{BSA } (m^2) = \sqrt{(height(cm)Xweight(kg))/3600}$$

5.3 Effectiveness

Overall Best Response

Overall best response for a patient is the best-observed disease response based on all response assessments available for each patient up to reported PD and prior to any subsequent anticancer therapy. The assessments of SD must occur at least once on or after day 42 to be considered for best response.

Objective Response (OR)

Objective response is defined as a best tumor response assessment of either complete response or partial response. Patients who prematurely discontinue without a tumor assessment will be considered non-responders.

Disease Control (DC)

Disease control is defined as a best tumor response assessment of CR, PR, or SD. Patients without a post-baseline tumor disease assessment will be considered to not have disease control.

Thus, for all patients:

If overall best tumor response = CR, PR or SD then: DC=1

Otherwise: DC=0

Progression-free Survival (PFS)

Time (in months) from day 1 to the earliest date of disease progression as reported by the investigator or death, regardless of cause, (whichever is first). Patients with no reported disease progression and alive will be censored at last contact date/last date known alive.

PFS = (date of progressive disease or death - date of day 1) / 30.4375

All tumor assessment dates will be based on the actual imaging dates reported by the investigator.

Overall Survival

Overall survival time is calculated as the number of days from day 1 to death (date of death - date of first dose). Time to death will be summarized in months. Patients who have not died (no record of death) or are lost to follow up will be censored at the date of last contact/last date known alive.

5.4 Safety

Adverse Events

All AEs (serious and non-serious, related and not related) reported from Day 1 of study treatment to 30 days post last dose of study treatment.

6. ANALYSIS DATASETS

6.1 Full Analysis Set

The full analysis set (FAS) will consist of all the patients enrolled into the study and who have at least one administration of trabectedin. The FAS will be the primary analysis set for the safety analyses and analyses assessing effectiveness.

7. INTERIM ANALYSIS

An interim analysis after 50% (i.e., ~150 patients) of the recruitment will be performed in order to obtain a first approach of the results.

8. DATA SCREENING AND ACCEPTANCE

Edit checks to clean the data are to be described in the data validation plan as part of the data management plan (DMP). Data management (DM) for this study will provide clean raw data for the planned analysis (interim and final).

8.1 Data Handling and Electronic Transfer of Data

All data for this study will be received from data management as SAS datasets for the analysis and as described in the Data Transfer Plan.

Data coding will be applied as agreed:

Data type	Coded, Yes or No?
AEs	Yes
Prior Anticancer Therapy (Baseline Visit)	Yes
Medical History	No
Conmeds	Yes
Surgery	No
Subsequent anticancer drugs	Yes

8.2 Handling of Missing and Incomplete Data

If dates are missing or incomplete for adverse events, concomitant medication data, deaths or prior anticancer therapies, algorithms as defined in Section 12.1 will be used. Dates of assessment for reported tumor response assessment are expected to be complete. If there are any missing or partial missing dates in this data field, the study statistician will be informed.

8.3 Detection of Bias

The reason for non-participation in the study (patient declined, no reply, patient not fulfilling the inclusion criteria, or presence of any exclusion criterion) will be recorded in a patient qualification log at each site. This will enable subsequent assessment of potential non-participation (selection) bias necessary for quality assurance of the data collected. Given the variation of clinical practice not only across, but also within countries, a good geographical representation of patients with relapsed ovarian cancer will be attempted

by targeting study centers spread across the regions of each of the countries. This variation in clinical practices will contribute to more representative results for each country as well as across this European region.

8.4 Distributional Characteristics

The assumptions behind each statistical method will be assessed. If the assumptions are not met, these will be described and further analyses may be carried out using data transformations and/or alternative analytical methods. The use of transformations or alternative methods will be fully described in the final study report.

9. STATISTICAL METHODS OF ANALYSIS

9.1 General Principles

All analysis will be based on the FAS and will be presented overall and by previous antiangiogenic usage (yes/no).

Appropriate descriptive statistics will be produced for each parameter. For continuous data the mean, standard deviation, median, minimum and maximum will be presented. For categorical data, the frequency and percentage in each category will be presented. The data will be analyzed using the normal approximation and its 95% CI. However, in analyses where sample size is considered to be too low, the exact binomial estimator and its 95% CI will be calculated. Time-to-event endpoints (PFS and OS) and their fixed-time estimations will be analyzed using the Kaplan-Meier (KM) method.

Any p-values presented will be descriptive in nature and the significance level selected will be 5%.

Statistical analyses will be conducted using SAS version 9.4 or later for Windows, and/or any other applicable software suitable for the planned statistical analyses.

9.2 Patient Accountability

A summary of the number and percentage of patients enrolled by country and site will be produced.

Data with reasons for non-participation in the study (patient declined, no reply, patient not fulfilling the inclusion criteria, or the presence of any exclusion criterion) collected and recorded in the patient qualification log at each site will be summarized upon data availability.

Patient disposition over the course of the study and summaries for inclusion/exclusion criteria will be provided. The disposition summaries will include the number of patients enrolled, number of patients who did not received any trabectedin, and the number of patients included in the FAS. The number of trabectedin cycles received before IC was provided and for those patients, time from first dose of trabectedin to IC will be presented.

Reasons for treatment discontinuation will be summarized along with reasons for not completing the study as reported by the investigators.

Survival status at end of study, including number of deaths along with cause of death, will be summarized. Number of deaths along with cause of death within 30 days of last dose of trabectedin will also be presented.

9.3 Demographic and Baseline Characteristics

Summary statistics for each of the following demographic and baseline characteristics will be tabulated based on the FAS:

- Age as continuous and categorical : <65, [65, 75) and ≥75 years
- ECOG/WHO performance status
- BRCA-1/2 status
- Baseline weight, height, investigator reported BSA and derived BSA
- Time since initial ovarian cancer diagnosis, tumor grade and histology at initial tumor diagnosis
- Time since relapsed ovarian cancer diagnosis
- Prior tumor therapies, including surgery, and radiotherapy
- Occurrence of physical examination abnormalities and body systems in which abnormalities were found

- Anti-tumor treatment (chemo and non-chemo) including bevacizumab usage, PD reported during or after bevacizumab, number of regimens received, best response reported for the latest regimen received prior to trabectedin, time since latest regimen last dose taken, time since latest regimen reported PD and recurrence
- Medical history: co-morbidities
- Baseline imaging

9.4 Effectiveness Analyses

9.4.1 Analyses of Effectiveness Primary Endpoint

The primary endpoint for this study is PFS. Summaries of the primary endpoint will be based on the FAS. KM estimates and 95% CIs will be calculated based on estimated variance for log-log transformation of the estimate. KM time to event curves will also be presented.

9.4.2 Analyses of Effectiveness Secondary Endpoints

Objective Response

Objective response is defined as a best tumor response of complete or partial response as reported by the investigator in the overall response evaluation. Patients without an assessment of disease response will be treated as non-responders.

Descriptive statistics will be provided for best overall tumor response. The number and percentage of patients within each category of best response (CR, PR, SD, PD, and not evaluable (NE) (including reported in the electronic case report form (CRF) as not evaluable) and not done (including not assessed, not reported, and not done) will be presented. The proportion will be estimated by dividing the number of patients within each category of response by the number of patients available in the full analysis set. Each patient will be counted within only one response group, with the best response during the study (from the start of the treatment until the end of study treatment or PD, whichever occurs first), as reported by the investigator. No confirmation of response requirement will be applied for this analysis. Objective response rate (CR + PR) and two-sided exact binomial 95% confidence intervals will be presented. Additionally, descriptive

statistics for objective response will be presented stratified on BRCA 1/2 status (positive, negative, unknown).

Disease Control

The disease control will be reported along with two-sided exact binomial 95% confidence intervals.

Overall Survival

OS will be descriptively analyzed as done for the primary endpoint PFS.

9.4.3 Analyses of Effectiveness Other Endpoints

Symptomatic Response

Symptomatic response will be summarized for the treatment period including 30 days post last trabectedin administration.

9.4.4 Analyses of Other Endpoints

ECOG

ECOG/WHO performance status scores will be summarized at baseline, worst/best scores under treatment, and scores at end of treatment. The change in scores from baseline to best/worst and end of treatment scores will also be summarized presenting categories: <0 (indicating an improvement), 0-2, >2-4, and >4 (indicating worst deterioration).

Treatments

The recommended dosage for trabectedin in relapsed ovarian cancer is 1.1 mg/m^2 administered as a 3-hour infusion every 3 weeks (3h_q3w), immediately after infusion of 30 mg/m^2 PLD. There is no predefined limit as to the number of cycles of treatment with trabectedin. Treatment may continue as long as the treating physician feels there is benefit, even in the presence of apparent progression of disease. To minimize the risk of PLD infusion reactions, PLD infusion should be in accordance with the SmPC. Any

trabectedin dose modifications and/or change in dosing interval should be in accordance with the SmPC and the treating clinician's best clinical judgment.

Patients must receive corticosteroids (e.g., 20 mg dexamethasone iv) 30 minutes prior to PLD (in combination therapy) or Yondelis (in monotherapy); not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

1.

Trabectedin administration history will be summarized presenting the number of previous cycles received prior to IC. Descriptive statistics will be calculated for total number of cycles started or infusions received, trabectedin administration setting (inpatient/ outpatient), trabectedin administered dose per infusion (mg), cycle duration (days), trabectedin treatment duration will be presented as number of weeks on trabectedin treatment. Cumulative dose administered, dose intensity (mg)/week, relative weekly dose intensity (%), and total dose of trabectedin administered (mg) per cycles will also be presented. The number and percentage of patients with modifications (including dose missed, reductions, dose delays, or doses withheld) from the investigator reported schedule will be summarized by type of dose modification and reason for the dose modification. The number of dose missed/reductions/interruptions/delays per patient will also be summarized.

Data for trabectedin administration setting (inpatient/ outpatient) and dose modifications is not collected for drug taken prior to IC. For this reason summaries will include appropriate footnotes clarifying this.

Finally, proportion of patients treated with < 6 cycles and >= 6 cycles stratified on BRCA 1/2 status (positive, negative, unknown), will also be quantified.

2.

PLD administration history will be summarized presenting the number of previous cycles received prior to IC. Descriptive statistics will be calculated for total number of cycles started or infusions received, PLD administration setting (inpatient/outpatient), PLD administered dose per infusion (mg), PLD treatment duration will be presented as number of weeks on PLD treatment. Cumulative dose administered, dose intensity (mg)

/week, relative weekly dose intensity (%), and total dose of PLD administered (mg) per cycles will also be presented. The number and percentage of patients with modifications (including dose missed, reductions, dose delays, or doses withheld) from the investigator reported schedule will be summarized by type of dose modification and reason for the dose modification. The number of dose missed/reductions/interruptions/delays per patient will also be summarized.

Data for PLD administration setting (inpatient/ outpatient) and dose modifications is not collected for drug taken prior to IC. For this reason summaries will include appropriate footnotes clarifying this.

Finally, proportion of patients treated with < 6 cycles and >= 6 cycles stratified on BRCA 1/2 status (positive, negative, unknown), will also be quantified.

3.

Number of patients receiving trabectedin + PLD, trabectedin alone, and PLD alone will be summarized.

4.

Exposure to subsequent anticancer drugs will be described. Time from last dose of trabectedin to first anticancer treatment received, overall type of therapy, setting (single, combo) and number of cycles, and best response for the next anticancer therapy post trabectedin will be described.

9.5 Safety Analyses

9.5.1 Adverse Events

A solicited reporting system of AEs (serious and non-serious, related and not related) was used during this study, from the beginning of trabectedin + PLD treatment. Whenever possible the investigator recorded the diagnosis, classified each adverse event in regards of seriousness and causal relationship to study drugs (trabectedin + PLD), and reported severity (grade).

AEs will be coded in the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 or higher by system organ class and a preferred term. Each event will be graded according to medical record documentation as 1 = mild, 2 = moderate, 3 = severe, 4 = disabling or life threatening consequences, and 5 = death.

The descriptive summaries presenting treatment emergent AEs will include AEs reported from Day 1 of study treatment to 30 days post last dose of study treatment. AE summaries will use the patient's maximum severity reported for each system organ class and preferred term. The corresponding summaries will be presented for AEs and SAEs grade 3 or higher.

Patient incidence of adverse drug reactions (ADR) related to trabectedin and related to PLD, respectively, will be tabulated by system organ class, preferred term and severity grade for all drug reactions and serious drug reactions. The corresponding summaries will be presented for ADRs and SADRs grade 3 or higher. ADR's relationship to treatment reported as unknown will be assumed to be related to both trabectedin and PLD.

In addition, and complementing the summaries above, AEs, SAEs, ADRs and SADRs will also be summarized by preferred term only, and in descending order of frequency.

A summary table will also be produced summarizing all event summaries and will include, AEs, SAEs, ADRs, SADRs, those leading to treatment discontinuation, and fatal events on study.

9.5.2 Concomitant Medication

The number and percentage of patients receiving each reported medication will be summarized as data is available.

9.5.3 Laboratory Test Results

Laboratory tests will be collected when available, at initiation of treatment and during the observation period. During the follow up period those laboratory tests associated with AEs and SAEs will to be collected when available. Laboratory tests will be reported based on the treating clinician's usual practice procedures.

The number and percentage of patients with clinically significant results will be summarized.

9.5.4 Physical Examination

Physical examination data is collected at baseline and subsequent cycles, during the observation period.

Weight, height and BSA will be summarized, values at baseline, values and change from baseline to end of observation period (last dose of study treatment administration plus 30 days) will be presented. Additionally, the maximum and minimum observed post-baseline values will be summarized along with the change from baseline to the maximum and minimum observed value.

BSA may be summarized as reported by the investigator and as calculated from the weight and height data.

9.5.5 Exposure to Subsequent Surgery

The number and percentage of patients reporting subsequent surgery for ovarian cancer will be summarized along with the time from last dose of trabectedin to first post-surgery, the type of surgical procedure and anatomical site reported has been collected as free text which does not enable for statistical processing as data will not be coded for this study.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no significant changes to the protocol-specified analyses.

11. LIST OF PLANNED TABLES AND FIGURES

Table shells corresponding to this SAP will be documented separately. The shells document will contain the details regarding the content and layout of the tables and graphs to serve as requirement documentation for statistical programming.

Unless otherwise specified, the following outputs will be produced subject to study design and the availability of data, overall and by previous antiangiogenic usage.

11.1 Planned Tables

Category	Table Title
Disposition	Summary of Enrollment by Country and Site
Disposition	Reasons for Non-participation
Disposition	Summary of Inclusion and Exclusion Criteria
Disposition	Patient Disposition
Demographics and Baseline	Demographics and Baseline Characteristics
Demographics and Baseline	Medical History
Demographics and Baseline	Prior Anticancer Therapy
Demographics and Baseline	Baseline Imaging
Effectiveness - Primary Endpoint	Progression-free Survival
Effectiveness - Secondary Endpoint	Best Tumor Response
Effectiveness - Secondary Endpoint	Overall Survival
Effectiveness	Summary of Symptomatic Response
Other Secondary Endpoints	Summary of ECOG Performance Status
Treatments - Secondary Endpoints	Exposure to Trabectedin
Treatments - Secondary Endpoints	Trabectedin Dose Modification
Treatments - Secondary Endpoints	Exposure to PLD
Treatments - Secondary Endpoints	PLD Dose Modification
Treatments - Secondary Endpoints	Subsequent Anticancer Therapy after Stopping Trabectedin
Safety	Overall Summary of Patient Incidence of Treatment-Emergent Adverse Events
Safety	Overall Summary of Patient Incidence of

Category	Table Title
	Treatment-Emergent Adverse Drug Reactions
Safety	Treatment-Emergent Adverse Events
Safety	Treatment-Emergent Adverse Drug Reactions Related to Trabectedin
Safety	Treatment-Emergent Adverse Drug Reactions Related to PLD
Safety	Treatment-Emergent Serious Adverse Events
Safety	Treatment-Emergent Serious Adverse Drug Reactions Related to Trabectedin
Safety	Treatment-Emergent Serious Adverse Drug Reactions Related to PLD
Safety	Treatment-Emergent Adverse Events Grade 3 or Higher
Safety	Treatment-Emergent Grade 3 or Higher Adverse Drug Reactions Related to Trabectedin
Safety	Treatment-Emergent Grade 3 or Higher Adverse Drug Reactions Related to PLD
Safety	Treatment-Emergent Serious Adverse Events Grade 3 or Higher
Safety	Treatment-Emergent Grade 3 or Higher Serious Adverse Drug Reactions Related to Trabectedin
Safety	Treatment-Emergent Grade 3 or Higher Serious Adverse Drug Reactions Related to PLD
Safety	Treatment-Emergent Adverse Events in Descending Order of Frequency
Safety	Treatment-Emergent Adverse Drug Reactions Related to Trabectedin in Descending Order of

Category	Table Title
	Frequency
Safety	Treatment-Emergent Adverse Drug Reactions Related to PLD in Descending Order of Frequency
Safety	Treatment-Emergent Serious Adverse Events in Descending Order of Frequency
Safety	Treatment-Emergent Serious Adverse Drug Reactions Related to Trabectedin in Descending Order of Frequency
Safety	Treatment-Emergent Serious Adverse Drug Reactions Related to PLD in Descending Order of Frequency
Safety	Treatment-Emergent Grade 3 or Higher Adverse Events in Descending Order of Frequency
Safety	Treatment-Emergent Grade 3 or Higher Adverse Drug Reactions Related to Trabectedin in Descending Order of Frequency
Safety	Treatment-Emergent Grade 3 or Higher Adverse Drug Reactions Related to PLD in Descending Order of Frequency
Safety	Treatment-Emergent Grade 3 or Higher Serious Adverse Events in Descending Order of Frequency
Safety	Treatment-Emergent Grade 3 or Higher Serious Adverse Drug Reactions Related to Trabectedin in Descending Order of Frequency
Safety	Treatment-Emergent Grade 3 or Higher Serious Adverse Drug Reactions Related to PLD in Descending Order of Frequency
Safety – Conmeds	Concomitant Medications

Category	Table Title
Safety – Labs	Summary of Hemoglobin
Safety – Labs	Summary of Absolute Neutrophil Count (ANC)
Safety – Labs	Summary of Platelet Count
Safety – Labs	Summary of Serum Creatinine
Safety – Labs	Summary of Total Bilirubin
Safety – Labs	Summary of Total Alkaline Phosphatase
Safety – Labs	Summary of Aspartate Aminotransferase (AST)
Safety – Labs	Summary of Alanine Aminotransferase (ALT)
Safety – Labs	Summary of Creatine Phosphokinase (CPK)
Safety – Labs	Summary of Albumin
Safety – Labs	Clinically Significant Laboratory Tests
Safety – Physical Examination	Physical Examination – Weight (kg)
Safety – Physical Examination	Physical Examination – Investigator Reported Body Surface Area (m^2)
Safety – Physical Examination	Physical Examination – Calculated Body Surface Area (m2)
Safety	Exposure to Subsequent Surgery

11.2 Planned Figures

Category	Graph Title
Effectiveness	Kaplan-Meier Plot of Progression-free Survival Time
Effectiveness	Kaplan-Meier Plot of Overall Survival Time

12. APPENDICES

12.1 Handling of Dates, Incomplete Dates and Missing Dates

Dates for the following variables will be imputed using the algorithm described below:

- Adverse events
- Concomitant medications

Imputation rules for partial or missing AE/concomitant medication *start dates*:

Start Date		Stop Date: Complete: *yyyymmdd*		Stop Date: Partial: *yyyymm*		Stop Date: Partial: *yyyy*		Stop Date: Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing AE/concomitant medication *stop dates*:

1. Initial imputation
    a. For partial stop date mmyyyy, impute the last of the month.
    b. For partial stop date yyyy, impute December 31 of the year.
    c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.

3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie. set the stop date as missing).

- Deaths

Imputation rules for partial or missing *death dates*:

1. If death year and month are available but day is missing:
   - If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
   - If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
   - If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is totally missing, do not impute.

Imputation rules for partial or missing *stop dates for prior radiotherapy*:

1. Initial imputation
   a. For partial stop date mmyyyy, impute the last of the month.
   b. For partial stop date yyyy, impute December 31 of the year.
   c. For completely missing stop date, do not impute. Raise date issue to Statistician.
2. If the stop date imputation leads to a stop date that is on or after the first dose date of trabectedin administration, then impute the stop date as the day prior Day 1.

Imputation rules for partial or missing *start cycle dates of prior chemo*:

Start Date	Stop Date

		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	2	2	2	n/a	2	2
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	3	3	3	n/a	3	3
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	4	4	1	4	1	5

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

5 = do not impute

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing *prior chemo date of last cycle*:

1. Initial imputation
    a. For partial stop date mmyyyy, impute the last of the month.
    b. For partial stop date yyyy, impute December 31 of the year.
    c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date or after first dose date of trabectedin, then impute the stop date as the death date or first dose date of trabectedin whichever is earlier.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie. set the stop date as missing) and inform the Statistician.

Imputation rules for partial or missing *prior surgery and prior radiotherapy dates*:

Apply imputations, if needed,

a. For partial date mmyyyy, impute the first of the month.
b. For partial date yyyy, impute Jan 1st of the year.
c. For completely missing, do not impute.

Exclude from table any data with imputed date of medical history or surgery with a year after first dose date year and inform Statistician of any data in medical history or surgery with a date reported after first dose date.

Imputation rules for partial or missing *medical history dates*:
If year of diagnosis is missing impute with year of day 1 of trabectedin.

12.2 Handling of MissingTotal Dose Received

In the event of total dose data reported as unknown for a cycle prior to IC, of either trabectedin or PLD, then imputation of total dose will be performed. If the total dose is missing the value will be imputed using last observation carried forward (LOCF) and last observation carried backwards (LOCB) as necessary.