STATISTICAL ANALYSIS PLAN

Protocol XPORT-MEL-033

A PHASE 2 OPEN-LABEL MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SELINEXOR IN COMBINATION WITH PEMBROLIZUMAB IN RECURRENT ADVANCED MELANOMA

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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DOCUMENT HISTORY

Version	Date	Author(s)	Brief Summary of Changes
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TABLE OF CONTENTS

TABLES INCLUDED IN THE TEXT

Section Page

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
BSA	body surface area
CI	confidence interval
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
HR	hazard ratio
iCPD	immune confirmed progressive disease
iCR	immune complete response
IDMC	independent data monitoring committee
INR	international normalization ratio
iORR	immune objective response rate
iPFS	immune progression-free survival
iPR	immune partial response
iRECIST	immunotherapy Response Evaluation Criteria in Solid Tumors
iUPD	immune unconfirmed progressive disease
mITT	modified intent-to-treat

Abbreviation	Definition
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SI	international system of units
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
WBC	white blood cell
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. OVERVIEW AND INVESTIGATIONAL PLAN

1.1. Study Design

XPORT-MEL-033 is an open-label, multicenter, Phase 2 study to evaluate the safety and efficacy of selinexor in combination with pembrolizumab in patients with recurrent advanced melanoma. This includes patients with histologically confirmed diagnosis of locally advanced unresectable stage III or metastatic stage IV melanoma not amenable to local therapy. Patients must have confirmed PD per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer 2009) on or within 12 weeks of the last dose of anti-PD-1/L1 monotherapy or combination therapy (including relatlimab or other anti-LAG-3 mAb) per Society for Immunotherapy in Cancer Guidelines (Kluger, 2020).

Approximately 40 patients will be enrolled at up to 20 sites in the United States into one of the following 2 arms:

- Primary resistance to initial checkpoint inhibitor (CPI) therapy (Arm A): Selinexor 80 mg orally (PO) QW+ Pembrolizumab 400 mg IV once every six weeks (Q6W)
- Acquired resistance to initial CPI therapy (Arm B): Selinexor 80 mg PO QW + Pembrolizumab 400 mg IV Q6W

Patients in Arm A (primary resistance) must have disease progression after receiving at least 6 weeks of prior anti-PD-1/L1 mAb with the best response as PD, or SD<6 months. (Patients with a PR or CR who have disease progression within 6 months will be considered to have primary resistance in this study.)

Patients in Arm B must have disease progression after receiving at least 6 months of prior anti-PD-1/L1 mAb with the best response as CR, PR, or SD>6 months. (Patients who have disease progression after neoadjuvant or adjuvant therapy, will be considered to have secondary resistance in this study.)

1.2. Study Objectives

1.2.1. Primary Objective

- To evaluate objective response rate (ORR) per RECIST v1.1 response criteria

1.2.2. Secondary Objectives

- To evaluate progression-free survival (PFS) per RECIST v1.1 response criteria
- To evaluate overall survival (OS)
- To evaluate rates of complete response (CR) per RECIST v1.1 response criteria
- To evaluate duration of response (DOR) per RECIST v1.1 response criteria
- To evaluate disease control rate (DCR) per RECIST v1.1 response criteria
- To evaluate the safety and tolerability of pembrolizumab and selinexor combination regimen

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1.3. Study Endpoints

1.3.1. Primary Endpoint

- ORR, defined as proportion of patients who achieved a CR or partial response (PR) per RECIST v1.1

1.3.2. Secondary Endpoints

- PFS, defined as time from date of first treatment to the date of first documented progressive disease (PD) or death due to any cause, whichever occurs first. Responses are assessed per RECIST 1.1.
- OS, defined as time to death, from the date of first treatment.
- Complete response rate (CRR), defined as proportion of patients who achieved a CR per RECIST 1.1.
- DOR, defined as the duration of time from first occurrence of response ≥PR until the first date of PD or death due to any cause, whichever occurs first. Responses are assessed per RECIST 1.1.
- DCR, defined as the percentage of patients who have achieved CR, PR or SD for a minimum of 12 weeks. Responses are assessed per RECIST 1.1.
- Safety and tolerability of study treatment will be evaluated based on AE reports, vital signs, clinical laboratory results, and physical examination findings, by the occurrence, nature, and severity of AEs as categorized by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

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1.5. Interim Analysis

Interim analyses will be conducted according to the Simon's two-stage designs specified in Section 1.4.

1.6. Modifications to the Statistical Section of the Protocol

Not applicable. The current SAP is based on Protocol v3.0.

1.7. Changes in the Statistical Analysis Plan

Not applicable. This is the original version of the SAP.

2. GENERAL STATISTICAL METHODS AND DATA HANDLING

This SAP outlines the methods to be used in the analysis of clinical data in order to answer the study objectives. Endpoints and methods to be used in the analysis of PK data or predictive biomarkers are not included in this document.

2.1. General Considerations

This is an open-label, multicenter, Phase 2 study. All summary statistics will be computed and displayed among the corresponding analysis population, and by each scheduled assessment time point whenever applicable. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. Graphical displays will be provided as appropriate.

2.2. Missing Data Handling

In general, missing baselines will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data will be summarized using counts (n) and percentages (%). The denominator will be the analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data will be summarized based on observed data only. The number of observed data will be presented.

2.2.1. Handling of Computation of Treatment Duration if Study Treatment End Date is Missing

For the calculation of treatment duration, the date of the last dose of study treatment is equal to the date of last non-zero study treatment dosing reported on study treatment dosing form. The last dose intake should be clearly identified on the electronic case report form (eCRF) dosing page and should not be approximated by the last returned package date.

2.2.2. Handling of Missing/Partial Dates for Adverse Events or Concomitant Medications

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date does not indicate whether the AE started prior to or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent.

These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings. In data listings, an ongoing flag will be identified from the eCRF AE page.

Refer to Karyopharm Biostatistics and Statistical Programming Rule Book v2.0 for details on imputation methods.

2.2.3. Handling of Missing or Partial Birth Date for Calculation of Age

Refer to Karyopharm Biostatistics and Statistical Programming Rule Book v2.0 for details on imputation methods.

2.2.4. Handling of AEs When Date and Time of First Dose of Study Treatment Are Missing

When the date and time of the first dose of study treatment are missing, all AEs that occurred on or after signing the informed consent should be considered as TEAEs. The exposure duration should be kept as missing.

2.2.5. Handling of Missing Assessment of Relationship of AEs to Study Treatment

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment in the frequency tables is considered as related.

2.3. Study Treatment Dosing Date

Study treatment dosing date is the actual dosing date on which a patient received study treatment (selinexor or pembrolizumab), as recorded on the study drug exposure eCRF.

The date of first study treatment is defined as the earliest date of non-zero dose of the study treatment. The date of last study treatment is defined as the latest date of non-zero dose of the study treatment.

2.4. Study Day Calculation

Based on the study protocol, study Day 1 is the first study treatment dosing date. The day before Day 1 is considered Day -1, there is no Day 0.

A patient is considered as treated in a cycle if the patient received any non-zero dose of study treatment in that cycle.

Study day for a given assessment is defined as

- the assessment date – the date of first study treatment + 1 if the assessment date is on or after Day 1, or
- the assessment date – the date of first study treatment if the assessment date is before Day 1.

2.5. Baseline Measurement

In general, the baseline value is defined as latest value prior to the first dose of study treatment. In the case an assessment is performed on the same date as the first dose, but it is impossible to determine the evaluation time relative to the time of taking the first dose, the evaluation time will be assumed to be following the protocol-defined schedule.

2.6. Visit Windows

For safety data that are summarized/plotted by time points, non-missing assessments from all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using a

windowing scheme. Analysis visit windows are defined in Table 2-1 and Table 2-2. If there are 2 or more assessments mapped to the same analysis visit for a patient, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments mapped to the same analysis visit with the same distance from the target visit day, then select the latest one for the analysis.

Table 2-1 Visit Windows for Clinical Laboratory Tests

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
C1D15	Day 15	Day 2 to 21
C1D29	Day 29	Day 22 to 35
C2D1	Day 43	Day 36 to 49
C2D15	Day 57	Day 50 to 63
C2D29	Day 71	Day 64 to 77
C3D1	Day 85	Day 78 to 91
...		
(every 14 days)		
NOTE: Day 1 is the start date of first selinexor or pembrolizumab dose. The visit window is Target Date – 7 days to Target Date + 6 days for post-baseline visits, except for C1D15 analysis visit. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-2 Visit Windows for Vital Signs

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
C2D1	Day 43	Day 2 to 63
C3D1	Day 85	Day 64 to 105
C4D1	Day 127	Day 106 to 147
...		
(every 42 days)		
NOTE: Day 1 is the start date of first selinexor or pembrolizumab dose. The visit window is Target Date – 21 days to Target Date + 20 days for post-baseline visits, except for C2D1 analysis visit. Analysis visit and visit window may change for certain parameters depending on the data availability.		

2.7. Subgroups

The following subgroup analyses on selected efficacy endpoints will be conducted:

- Age
- Sex
- Race
- Ethnicity
- Baseline ECOG

2.8. Pooling of Centers for Statistical Analyses

All participating centers in the study will be pooled together for analysis.

2.9. Computing and Coding Standards

Activities will be performed using the tools summarized in the table below:

Table 2-3 Computing and Coding Standards

Table, listing, and figure production	SAS Version 9.4 or higher
Coding	
AEs	MedDRA Version 23.0 or higher
Medical Histories	MedDRA Version 23.0 or higher
Prior and Concomitant Medications	WHO DDE Version September 2019 or higher
Grading	
AEs	CTCAE Version 5.0
Labs	CTCAE Version 5.0

3. PATIENT INFORMATION

3.1. Disposition of Patients and Analysis Populations

Patient disposition will be summarized in each of the following categories:

- Patients who received at least one dose of study treatment (partial or complete)
- End of treatment:
  - Patients who were still on treatment
  - Patients who discontinued treatment and primary reason for treatment discontinuation
- Survival follow-up status
  - Patients who discontinued treatment and entered survival follow-up
- End of study:
  - Patients who discontinued treatment and were still on study
  - Patients who discontinued from the study and the primary reasons for study discontinuation

3.1.1. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will consist of all patients who receive at least one dose of any study treatment. This population will be used for primary analyses of efficacy.

3.1.2. Efficacy Evaluable Population

The efficacy evaluable (EE) population will consist of all mITT patients who have at least one post-baseline disease response assessment. This population will be used for supportive analyses of efficacy.

3.1.3. Safety Population

The safety population will consist of all enrolled patients who have received at least one dose of both study treatments. Patients will be analyzed according to treatment received.

3.2. Demographics, Medical History, and Baseline Characteristics

Demographic, medical history and baseline characteristics will be summarized among the mITT population, as well as the safety population if needed. P-values on demographic, medical history and baseline characteristic data will not be calculated.

3.2.1. Demographic

Demographic data will be summarized by treatment arm, as well as overall, and will include race, ethnicity (Hispanic origin), and age at time of enrollment.

3.2.2. Prior Antineoplastic Therapy

3.2.2.1. Prior Antineoplastic Therapy - Systemic Therapy

Prior antineoplastic regimen will be summarized by treatment arm and overall for the safety population.

The following variables will also be summarized:

- Number of lines of prior antineoplastic regimen
- Type of prior antineoplastic regimen
- Best response to most recent antineoplastic therapy
- Duration of the most recent prior antineoplastic therapy
- Days since discontinuation of most recent systemic therapy, which will be calculated as date of enrollment - end date of the most recent systemic therapy + 1

3.2.2.2. Prior Antineoplastic Therapy - Radiation

Prior radiation therapy will be summarized by treatment arm, as well as overall, and will include the following variables:

- Number of patients who received any prior antineoplastic radiotherapy
- Number of prior antineoplastic radiotherapy

3.2.2.3. Prior Antineoplastic Therapy - Surgery

Prior antineoplastic surgery will be summarized by treatment arm, as well as overall, and will include the following variables:

- Number of patients who received any prior antineoplastic surgery
- Number of prior antineoplastic surgeries
- Procedure of prior antineoplastic surgeries
- Type of resection of prior antineoplastic surgeries
- Duration from most recent prior antineoplastic surgery to enrollment

3.2.3. Medical History

Medical history other than melanoma will be summarized in the mITT population by MedDRA system organ class (SOC) and preferred term (PT) using the number and percentage of patients who have at least one occurrence of a SOC and PT. The summary will be sorted by alphabetic order in SOC, and further by decreasing frequency of PT within each SOC. When more than one PT has the same frequency, the order of presentation will be alphabetic in PTs.

3.2.4. Disease History

Melanoma disease history will be summarized by treatment arm, as well as overall, and will include the following variables:

- Time since initial diagnosis to first dose
- Stage of initial melanoma diagnosis
- Stage of current melanoma diagnosis
- Time to disease recurrence on anti-PD-1/L1 therapy, defined as disease progress/relapse date – therapy start date + 1. Number of patients progressed/relapsed during or after the therapy will be provided.

3.2.5. Baseline Characteristics

Baseline characteristics will be summarized by treatment arm, as well as overall, and will include the following variables:

- Baseline age (years), height (cm), weight (kg), body surface area (m2), and body mass index (BMI, kg/m2)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status

3.3. Prior and Concomitant Medications and Procedures

Prior medications are any treatments received by the patient prior to the first dose of study treatment. Prior medications can be discontinued before first dose of study treatment or can be ongoing during treatment period.

Concomitant medications are any treatments received by the patient concomitantly with study treatment, from first dose of study treatment to last dose of study treatment + 30 days during the treatment period.

Concomitant medication consists of any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations. Patients may continue their baseline medication(s). Concomitant medications include all medications used to mitigate AEs such as nausea, for supportive care, to treat or prevent infection, or to maintain the use of selinexor in this study. All concomitant medication(s) must be reported on the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable. Concomitant medication will be summarized for the safety population, unless otherwise specified.

All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE). Concomitant medications will be summarized according to the WHO DDE by the ATC level 2 (therapeutic level), level 4 (generic level) and standard name.

Note that a medication can be classified as both a prior medication and a concomitant medication. The use of prior and concomitant medications and procedures may also be provided in a data listing.

Please refer to Section 2 for details on data handling rules related to computation, dates, imputation for missing dates.

3.4. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and compliance will be summarized in the safety population.

3.4.1. Extent of Study Treatment Exposure

The extent of exposure for the study treatment (selinexor or pembrolizumab) during treatment period will be assessed using the following variables:

- Number of study treatment doses received
- Duration of study treatment exposure
- Average dose received per week
- Number and percentage of patients with a dose reduction
- Number and percentage of patients with a dose interruption
- Number and percentage of patients with missed dose

Duration of study treatment exposure is defined as the *date of last study treatment - date of first study treatment + 1*, regardless of unplanned intermittent discontinuation.

3.4.2. Treatment Compliance

Study treatment compliance will be summarized descriptively as a quantitative variable, calculated as

$$\frac{\text{number of study treatment doses taken}}{\text{number of study treatment doses scheduled}} \times 100\%.$$

A study treatment dose is considered scheduled if selinexor or pembrolizumab is scheduled. Note that the number of scheduled study treatment doses does not include doses missed due to treatment interruption or other reasons not related to patient choice. The number and percentage of patients with study treatment compliance ≥ 70% will be provided.

4. EFFICACY

4.1. General Considerations

Efficacy analysis will be conducted using the mITT population. The PP population will be used for supportive analyses of efficacy.

4.2. Primary Efficacy Endpoints

4.2.1. ORR

ORR is defined as the proportion of patients who achieve CR or PR per RECIST v1.1.

The primary efficacy endpoint of ORR will be analyzed for each arm separately on the mITT population which consists of all enrolled patients who received any study treatment. Estimated ORR with 95% exact confidence interval (CI) will be summarized for each arm.

4.3. Secondary Efficacy Endpoints

4.3.1. Definition of Secondary Efficacy Endpoints

Table 4-1 are the secondary efficacy endpoints:

Table 4-1 Efficacy Endpoints and Definitions

Endpoint	Definition
Secondary Endpoints	
Progression-free survival (PFS)	Duration of time from date of first study treatment until the first date that PD assessed by RECIST 1.1 is objectively documented or death due to any cause. Refer to Table 4-2 for details on PFS outcome status (PFS event vs. censored) and censoring definitions.
Overall survival (OS)	Duration from the date of first study treatment until death due to any cause. If death event did not occur during the follow-up period, the patient is censored at the date of discontinuation from the study (i.e. withdrawal of consent), or date of last participating visit (e.g., a telephone contact with patient status being alive) on or before database cutoff date, whichever occurs first.
Complete response rate (CRR)	Proportion of patients who achieved a CR per RECIST 1.1
Duration of response (DOR)	Duration of time from first meeting CR or PR measurement criteria (whichever occurs first) until the first date that PD recurrence is objectively

	documented or death due to any cause. Responses are assessed per RECIST 1.1. Refer to Table 4-2 or details on the outcome and censoring definitions.
Disease control rate (DCR)	Proportion of patients who have a response of CR, PR, or SD ≥ 12 weeks. Responses are assessed per RECIST 1.1.

4.3.2. Analyses of Secondary Efficacy Endpoints

Analysis of secondary efficacy endpoints will be performed on the mITT population, unless otherwise stated.

4.3.2.1. Analyses of Binary Secondary Endpoints

Binary secondary endpoints of CRR and DCR will be calculated by point estimate with a 95% exact confidence interval (CI) using the exact method.

4.3.2.2. Analyses of Time to Event Secondary Endpoints

For each time to event secondary endpoint (PFS, OS and DOR), the number of patients with events, number of patients censored, estimates and 95% CI for the median of event time will be presented by treatment group.

Time-to-event will be plotted for each treatment group using the Kaplan-Meier method. The plot will include the number of patients at risk for each treatment group over time.

Table 4-2 PFS and DOR Outcome and Censoring Definitions

#	Situation	Date of event or censoring	Outcome
1	No baseline disease assessment	Date of first treatment	Censored
2	No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of first treatment	Censored
3	Documented PD without missing 2 or more consecutive assessments	Date of PD	Event
4	Death before documented PD and without missing 2 or more consecutive assessments	Date of death	Event
5	No documented PD or death on or before • Database cut • Withdrawal of informed consent • Lost to follow-up • Date of discontinuation from treatment + 30 days • Two or more consecutive missing assessments and the disease assessment result after the gap is PD[1] • Start of new antineoplastic therapy, whichever occurs first	Date of last adequate disease assessment prior to the events listed in the left column	Censored

1. If disease assessment results after 2 or more consecutive missing assessments were not PD, the disease assessment gap will be ignored.

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5. SAFETY

All safety analyses will be reported by the actual treatment arm patients received and overall, among patients in the safety population.

Safety analyses will be based on the reported AEs and other safety information, such as clinical laboratory assessments including hematology and serum chemistry, vital signs, and physical examination.

The observation period will be divided into the following periods:

- The pre-treatment period is defined as the time from the signed informed consent date up to first dose of study treatment.
- The treatment period is defined as the time from first dose of study treatment to last dose of study treatment + 30 days inclusive, or start of new anti-neoplastic therapy exclusive, whichever occurs first.
- The post-treatment period is defined as the time beyond the treatment period.

All safety analyses will be performed using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., enrolled but did not receive any dose of study treatment, partial or complete) will be listed separately.
- The baseline value is the last available value before the first dose of study treatment.
- The analyses of the safety variables will be descriptive, and no systematic statistical testing is planned.

5.1. Adverse Events

An AE is defined as any undesired medical occurrence in a patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study treatment, whether or not related to the study treatment.

All AEs (including serious adverse events [SAEs]) will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA).

The severity of all AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) grading scale. The severity of the AE is different from the seriousness of the AE. For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” “severe”, “life-threatening” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.
- Life-threatening.

5.1.1. Definitions of Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), and Treatment-Emergent Treatment-Related Adverse Events (TRAEs)

5.1.1.1. Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events (TEAEs) are defined as any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment, i.e., from the date of first study treatment up to the date of last study treatment + 30 days inclusive (or the day before initiation of a new anti-neoplastic treatment, whichever occurs first). Additionally, TEAEs also include any event that developed post the treatment period but was assessed by the Investigator as related to study treatment.

5.1.1.2. Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence, at any dose, that:

- Results in death
- Is life-threatening

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Other medically important conditions: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

SAE needs to be clearly documented on the patient's AE form. SAEs that occur at any time between the signing of the ICF up to the first dose of study treatment, must be reported (in addition to SAEs that occur after the first dose of study treatment).

5.1.1.3. Treatment-emergent Treatment-Related Adverse Events (TRAEs)

A TRAE is any TEAE that is assessed by the Investigator as related to study treatment.

5.1.2. Analysis Methods

The primary focus of AE reporting are TEAEs.

If an AE date/time of onset (occurrence or worsening) is incomplete, an imputation algorithm will be used to determine the AE as treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is not treatment emergent. Details on classification of AEs with missing or partial onset dates are provided in Section 2.2.2.

AE summaries will include number (n) and percentage (%) of patients who have experienced an AE. The denominator for computation of percentages is the number of patients in the corresponding treatment arm.

Unless otherwise specified, sorting order will follow the alphabetic order in SOC, and further by decreasing frequency of PTs within each SOC. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

5.1.2.1. Analysis of TEAEs

An TEAE overview summary table will be provided, which will include the number of patients with at least one of the following adverse events:

- TEAEs
- Grade 3/4 TEAEs
- Serious TEAEs
- TEAEs leading to dose modifications of study treatment
    - TEAEs leading to dose reduction of study treatment
    - TEAEs leading to dose interruption of study treatment
- TEAEs leading to study treatment discontinuation
- TEAEs leading to death
- TRAE
- Serious TRAEs
- TRAEs leading to dose modifications of study treatment
    - TRAEs leading to dose reduction of study treatment
    - TRAEs leading to dose interruption of study treatment
- TRAEs leading to study treatment discontinuation
- TRAEs leading to death

TEAEs will be summarized by primary SOC and PT and will include the following categories:

- All TEAEs
- TEAEs related to study treatment
- All TEAEs, by maximum grade
- TEAEs related to study treatment, by maximum grade
- Grade 3 or higher TEAEs

- Grade 3 or higher TEAEs related to study treatment
- TEAEs leading to dose modification of study treatment

The most commonly reported (at least 10% of all patients) TEAEs will be presented by PT only and will include the following categories:

- The most commonly reported TEAEs
- The most commonly reported TEAEs related to study treatment

5.1.2.2. Analysis of SAEs

Treatment-emergent SAEs will be summarized by primary SOC and PT and will include the following categories:

- All treatment-emergent SAEs
- All treatment-emergent treatment-related SAEs
- Treatment-emergent SAEs leading to dose modifications of study treatment
- Treatment-emergent SAEs leading to study treatment discontinuation
- All treatment-emergent SAEs leading to death

All SAE will be provided in a data listing.

5.2. Death

The following summaries on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (AEs with CTCAE Grade of 5 or outcome as fatal on the AE report page as reported by the Investigator), by primary SOC and PT
- TEAEs leading to death and are related to study treatment, by primary SOC and PT
- Listing of all death events
- Listing of all TEAEs leading to death

5.3. Laboratory Safety Variables

5.3.1. Definitions

Clinical laboratory data consists of blood analysis, including hematology, and serum chemistry. Clinical laboratory values in conventional units will be converted using the international system of units (SI).

The laboratory parameters will be classified as follows:

- Hematology tests including hemoglobin, hematocrit, white blood cell (WBC) count, and platelet count
- Serum chemistry tests including sodium, creatinine, ALT, potassium, glucose, AST, chloride, calcium, alkaline phosphatase, bicarbonate, phosphate, total bilirubin, BUN/urea, magnesium, total protein, creatine kinase, LDH, albumin, uric acid

5.3.2. Analysis of Laboratory Variables

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE criteria. Laboratory values with CTCAE Grade ≥ 3 will be presented in a data listing. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. Shift tables that present changes from baseline to worst on-study relative to CTCAE classification ranges will be presented. Shift tables will include results from unscheduled visits.

For several key laboratory parameters, box plots on measurements over time as well as by-patient plots for patient-level measurements over time may be presented.

A listing of possible Hy's law cases (ALT or AST > 3 x upper limit of normal [ULN] with simultaneous total bilirubin > 2 x ULN) will be presented. Plots examining possible cases of Hy's law may also be presented.

5.4. Vital Signs, ECOG, and Physical Examination Variables

Assessment of vital signs are performed during screening, day 1 of each cycle, and the end of treatment visit. The examinations include height (measured during screening visit only), weight, temperature, heart rate, and systolic and diastolic blood pressure.

An ECOG score assessment with grades 0-5 will be performed during screening and day 1 of each cycle.

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs including pulse, temperature, systolic blood pressure, diastolic blood pressure, BSA and weight. Shift tables that present changes from baseline to worst on-study and last on-study for systolic blood pressure, diastolic blood pressure, and ECOG performance status values will be produced.

Abnormal vital signs results will be summarized in the threshold/range analyses.

All vital signs, ECOG, and physical examination findings will be presented in data listings.

6. REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). *Eur J Cancer.* 2009:45:228-247
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3. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar 1;18(3):e143-52.
4. Karyopharm Biostatistics and Statistical Programming Rule Book, Karyopharm Therapeutics Inc., version 2.0

Document Approvals

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