STATISTICAL ANALYSIS PLAN

KCP-330-004 (KING)

A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF SELINEXOR (KPT-330) IN PATIENTS WITH RECURRENT GLIOMAS

Protocol Version:	**6.0 (13 November 2015)**
SAP Version:	**2.0**
Date:	**March 05, 2020**

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

The undersigned has developed this statistical analysis plan (SAP):

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DOCUMENT HISTORY

Version	Date	Author(s)	Brief Summary of Changes
2.0	March 05, 2020	PPD	SAP v2.0 differs from SAP v1.0 since SAP v1.0 was written based on Protocol v4.0. This version of SAP is based on Protocol v6.0
1.0	September 09, 2014	PPD	SAP v1.0 was written based on Protocol v4.0 of August 12, 2014

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	**Definition**
6mPFS	6-Month Progression-Free Survival
AE	Adverse Event
AG	Anaplastic Gliomas
ATC	Anatomical Therapeutic Class
BMI	Body Mass Index
BSA	Body Surface Area
C1D1	Cycle 1 Day 1
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoT	End-of-Treatment
GBM	Glioblastoma
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
CCI	[redacted]
PFS	Progression-Free Survival
CCI	[redacted]
PP	Per-Protocol
PR	Partial Response
PT	Preferred Term
RANO	Response Assessment in Neuro-Oncology Criteria
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Stable Disease
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TRAE	treatment-emergent treatment-related adverse event
WHO DDE	World Health Organization Drug Dictionary Enhanced

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN

KCP-330-004 (KING) is an open-label, multicenter, Phase 2 study to evaluate the efficacy and safety of oral selinexor in patients with recurrent gliomas. Patients were enrolled into either an CCI Medical Arm (Arm B, Arm C and Arm D) for patients who are not eligible for surgery.

Initially, the study included 2 arms: CCI medical arm (Arm B) for patients who are not eligible for surgery. The starting dose for Arms CCI B was 50 mg/m^2 twice weekly, with one cycle defined as 28 days or 8 doses.

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Enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0 to potentially improve tolerability. Two arms (Arms C and D) were added to the Medical Arm in Protocol Version 4.0. Patients in the primary population enrolled under Protocol Version 4.0 or above were randomized to Arm C and Arm D (approximately 30 patients per arm). CCI

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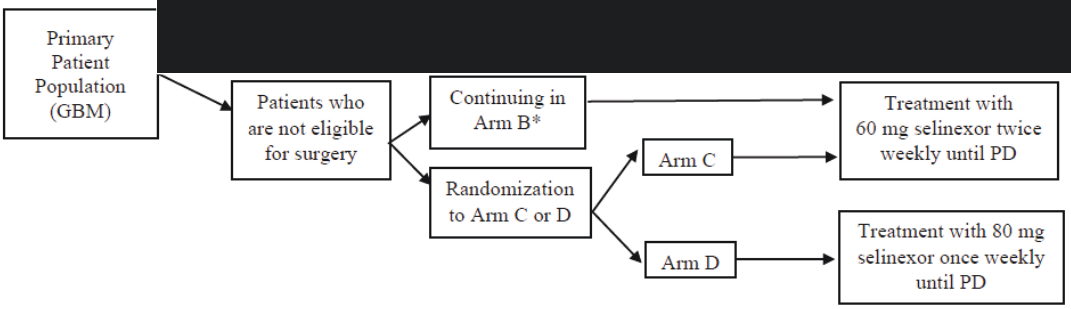

Abbreviations: AG: anaplastic glioma, GBM: glioblastoma; PD: progressive disease
* If the dose for a patient continuing in Arm CC B is < 35 mg/m^2, the Investigator should contact the medical monitor to determine the starting dose for flat dosing Refer to Table below for dose modifications:

Dose Level	Starting Dose of Selinexor	
	Arm CCI C	Arm D
Dose level 0	60 mg twice per week	80 mg once per week
Dose level -1	40 mg twice per week	60 mg once per week
Dose level -2	40 mg once per week	40 mg once per week
Dose level -3	20 mg once per week	20 mg once per week
Dose level -4	Discontinue dosing	Discontinue dosing

Patients received treatment until occurrence of PD, death, consent withdrawal, loss to follow-up, or toxicity that could not be managed by standard care, whichever occurred first. Patients were also followed for survival status. End of study is defined as when the last patient in the study died, completed 12 months of study follow-up, was lost to follow-up, or withdrew consent, whichever occurred first.

Enrollment in Arms C and D is based on Simon's two-stage design. Formal statistical analyses for efficacy will pertain only to the medical arms in the primary population (Arms B, C, and D).

1.2 OBJECTIVES

1.2.1 Primary Objective

- To determine the efficacy of selinexor in adults with recurrent GBM as determined by the 6-month progression-free survival (6mPFS) rate (Arms B, C and D).

1.2.2 Secondary Objectives

Secondary objectives of the study (Arms B, C and D) are:

- To determine the efficacy of selinexor in adults with recurrent GBM as determined by overall response rate (ORR) according to the Response Assessment in Neuro-Oncology (RANO) criteria.
- To determine the efficacy of selinexor in adults with recurrent GBM as determined by median overall survival (OS).
- To determine the efficacy of selinexor in adults with recurrent GBM as determined by median progression-free survival (PFS).
- To evaluate safety and tolerability of selinexor.

1.2.3 Exploratory Objectives

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1.3 DETERMINATION OF SAMPLE SIZE

- **Arm B (50 mg/m^2 twice weekly)**

- **Flat Dosing Arms (Arm C and Arm D)**

1.4 INTERIM ANALYSIS

For all medical arms (Arms B, C, D), interim analyses were planned to be performed at the end of Stage 1 according to the Simon's two-stage design specified in Section 8.5 in the protocol. Interim analysis of Arm B did not show sufficient efficacy, therefore enrollment in Arm B was stopped to explore alternative dosing in Arm C and Arm D. Arm C was also stopped due to safety and tolerability reasons before its planned interim analysis. Arm D's interim analysis showed sufficient efficacy evidence so that Arm D continued to enroll up to 30 patients.

1.5 CHANGES IN THE STATISTICAL ANALYSIS PLAN

There are substantial changes between protocol version 3.0 and current protocol version 6.0. Thus, this new version of SAP is rewritten based on version 6.0 of study protocol, which is the latest version of study protocol.

2 GENERAL STATISTICAL METHODS AND DATA HANDLING

This statistical analysis plan (SAP) outlines the methods to be used in the analysis of clinical data to answer the study objectives. Populations for analysis, data handling rules, and statistical methods are provided. This SAP does not include endpoints and methods to be used in the analysis of CCI [redacted], which will be included in a separate plan.

2.1 GENERAL ANALYSIS METHODS

All summary statistics will be computed and displayed among the corresponding analysis population, and by each assessment time point whenever applicable. Tabulations will be produced for appropriate demographic, baseline, efficacy and safety endpoints. Summary statistics for continuous variables will in general include the number of patients (n), median, mean, standard deviation, minimum, and maximum. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals (CI), unless otherwise stated. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations.

2.2 OBSERVATION PERIOD

The observation period will be divided by the following:

- The pre-treatment period is defined as the time from the signed informed consent date up to the time before the first dose of study treatment.
- The treatment period is defined as the time from the first dose of study treatment up to the date of last study treatment + 30 days, or the day before initiation of a new anti-neoplastic treatment, whichever comes first, inclusive.
- The post-treatment period is defined as the time beyond the treatment period.

2.3 MISSING DATA HANDLING IN DATA PRESENTATION

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

- Categorical data at baseline will be summarized using counts (n) and percentages (%). Denominator will be the total number of people in the corresponding treatment arm, based on the 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.

2.3.1 Handling of Computation of Treatment Duration if Study End of Treatment 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 study treatment dosing reported on the electronic case report form (eCRF) dosing page. If all the dosing dates are missing, then the duration is missing.

2.3.2 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. However, for categorization purpose, if the partial AE onset date information does not indicate whether the AE started prior to treatment or during the treatment period or after the treatment period, the AE will be classified as treatment-emergent.

The data imputations are only for categorization purpose or calculation of AE duration, and will not be used in listings.

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book v1.0 for details on imputation methods.

2.3.3 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 is considered as related.

2.4 STUDY DAY CALCULATION

Study Day 1 is the date of first study treatment. The day before Day 1 is considered Day -1. There is no Day 0. 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

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug for Medical Arms (Arms B, C and D), or CCI [redacted].

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 the table below. 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.

Visit Windows for Hematology (CBC), Limited Serum Chemistry and Vital Signs for Patients in Treatment

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline (C1)	Day 1	Prior to or on Day 1
Day 8	Day 8	Day 2 to 11
Day 15	Day 15	Day 12 to 18
Day 22	Day 22	Day 19 to 25
Day 29 (C2)	Day 29	Day 26 to 32
Day 36	Day 36	Day 33 to 39
Day 43	Day 43	Day 40 to 46
Day 50	Day 50	Day 47 to 53
Day 57 (C3)	Day 57	Day 54 to 64
Day 71	Day 71	Day 65 to 78
Day 85 (C4)	Day 85	Day 79 to 92
Day 99	Day 99	Day 93 to 106
Day 113 (C5)	Day 113	Day 107 to 120
Day 127	Day 127	Day 121 to 134
Day 141 (C6)	Day 141	Day 135 to 155
Day 169 (C7)	Day 169	Day 156 to 183
…		
(every 28 days)		
NOTE: Day 1 is the start date of treatment period. The visit window for each Target Visit Date is listed in the 3rd column "Study Day Range in Window". Analysis visit and visit window may change for certain parameters depending on the data availability.		

2.7 SUBGROUPS

Subgroup analyses on selected efficacy endpoints will be conducted by:

- Age groups
- Baseline Karnofsky performance status scores
- Number of lines of prior systematic therapy (1 vs. >1)

2.8 POOLING OF CENTERS FOR STATISTICAL ANALYSES

Patient data from all study centers will be combined for analysis.

2.9 COMPUTING AND CODING STANDARDS

Activities will be performed using the following tools:

Table, listing, and figure production	SAS Version 9.4 or higher
Coding	
AEs	MedDRA Version 22.0 or higher
Medical Histories	MedDRA Version 22.0 or higher
Concomitant Procedures	MedDRA Version 22.0 or higher
Prior and Concomitant Medications	WHO DDE B3 Version Sep2018
Prior and Post Treatment Antineoplastic Therapies	WHO DDE B3 Version Sep2018
Grading	
AEs	CTCAE Version 4.03
Labs	CTCAE Version 4.03

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 still on treatment
  - Patients who discontinued treatment and primary reason for treatment discontinuation
- Survival follow-up status
  - Patients in survival follow-up
  - Patients who are lost to survival follow-up
- End of study:
  - Patients who complete or withdrew from study and primary reason for study discontinuation

The number of patients in each analysis population will be presented.

3.1.1 Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population will consist of all enrolled patients in Arms B, C and D who have received at least one dose of study medication and have at least one post-baseline efficacy follow-up assessment, unless the patient discontinued treatment prior to the first post-baseline assessment due to death, toxicity, or disease progression. This population will be used for primary analyses of efficacy.

3.1.2 Per-protocol (PP) Population

The per-protocol population (PP) will consist of all Arms B, C and D patients who have been administered at least 2 months of study drug treatment, who are compliant with study assessments and have received at least 80% of their prescribed study medication, and who have no major protocol violations that would compromise the assessment of efficacy. Major violations will be determined independently of knowledge of response to therapy. This population will be used for supportive inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

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3.1.4 Safety Population

The safety population will consist of all patients from Arms C, B, C, and D who have received any amount of study medication. Patients in the safety population will be analyzed by each Arm.

3.2 DEMOGRAPHICS, MEDICAL HISTORY AND BASELINE CHARACTERISTICS

Demographics, medical history and baseline characteristics will generally be summarized among mITT and safety populations, unless otherwise specified.

3.2.1 Demographic Data

The demographic characteristics to be summarized will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

3.2.2 Prior Treatment

There are 3 types of prior treatments for GBM: radiation therapy, antineoplastic therapy and surgery. Number and percentage of prior radiation therapy, prior antineoplastic therapy, and prior surgery will be summarized.

3.2.3 Medical History - Conditions and Procedures

Medical history other than GBM will be summarized by 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.

A separate summary will be provided for ongoing medical history conditions.

3.2.4 Disease History

The following summary statistics will be summarized using descriptive statistics:

- Number and percentage of initial diagnosis
- Stage at initial diagnosis
- Time since initial diagnosis to first recurrence/relapse
- Time since initial diagnosis to most recent recurrence/relapse
- Stage at most recent recurrence/relapse
- Time since initial diagnosis to informed consent
- Stage at study entry

- Time since most recent recurrent/relapse to informed consent

3.2.5 Baseline Characteristics

Summary statistics will be presented separately in each treatment arm for the following variables:

- Baseline height (cm), weight (kg), body surface area (m^2), and BMI (kg/m^2)
- Baseline Karnofsky performance status
- Baseline creatinine clearance (mL/min) (summarized as a continuous variable and as a categorical variable, with cutoff of < 30, 30 to < 60 and ≥ 60)

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. Note that a medication can be classified as both a prior medication and a concomitant medication. All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE).

Concomitant medication will generally be summarized among mITT and safety populations, unless otherwise specified. Concomitant medications will be summarized according to the WHO DDE by the ATC level 2 (therapeutic level), level 4 (generic level) and preferred name. A patient taking the same drug multiple times will only be counted once.

Concomitant medications will be tabulated by arm and overall, where any medications that did not end prior to first dose will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The use of prior and concomitant medications and procedures may also be provided in a data listing.

Please refer to Section 2.3 for details on data handling rules related to computation, dates, imputation for missing dates.

3.4 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

Extent of exposure and compliance will be summarized among the safety population.

3.4.1 Extent of Study Treatment Exposure

The extent of exposure for the study treatment will be assessed using the following variables:

- Duration of study treatment exposure (summarized as a continuous variable and as a categorical variable)

- Total dose received (summarized as a continuous variable)
- Average dose received per week (summarized as a continuous variable)
- Occurrence of dose reduction
- Occurrence of dose interruption

Duration of study treatment exposure is defined as the date of last study treatment - date of first study treatment + 1.

Average dose received per week is defined as total dose received divided by duration of exposure, presented in mg/week.

Duration of study drug exposure for each patient will be provided in a data listing and dosing information for each patient may also be provided in a data listing.

3.4.2 Compliance

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

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

A study treatment dose is considered scheduled if selinexor is scheduled. The number and percentage of patients with study treatment compliance ≥ 80% will be provided. 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. Patients with study treatment compliance < 80% will be excluded from the PP population.

4 EFFICACY

The efficacy analyses will be conducted by arms using the mITT population, unless otherwise specified. Efficacy analyses using the PP population will be considered as supportive.

4.1 PRIMARY EFFICACY ENDPOINTS

4.1.1 Rate of 6-Month Progression-Free Survival (6mPFS)

The analysis of 6mPFS will be performed by calculating the estimated survival probability of having PFS ≥ 6 months based on Kaplan-Meier method, where PFS will be calculated from the date of start of study treatment to the date of progression based on RANO criteria, or date of death should progression not have occurred. To accommodate potential changes in individual patient's visit schedules, a window of ±14 days will be allowed around the 6-month visit for the primary analysis of rate of 6-month PFS. This window will be applied to the calculation of the estimate of 6mPFS; actual times of events (progression or death) will be used for the Kaplan-Meier statistical summary of PFS.

The primary analysis was planned to be performed when all patients have died, completed 6 months of study treatment, have withdrawn, or have been lost to follow-up. A preliminary efficacy analysis was performed; however, the primary analysis is now planned for after database lock. A nominal two-sided 95% CI will also be calculated. The 6mPFS results will be presented for Arm B, C and D separately.

A sensitivity analysis of the primary endpoint of 6mPFS will be performed to assess the potential influence of causality of deaths on study, where deaths due to causes that are clearly unrelated to the disease or study drug would not be considered as a PFS event and instead would be censored on the last response assessment before a censoring event.

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4.2 SECONDARY EFFICACY ENDPOINTS

4.2.1 Objective Response Rate (ORR)

ORR is defined as either complete response (CR) or partial response (PR) using the RANO criteria, calculated as a proportion and including a 95% exact CI. The ORR for each Arm will be presented separately.

4.2.2 Overall Survival (OS)

OS will be calculated from the date of start of study treatment to the date of death. Patients who are still alive prior to the data cutoff for final efficacy analysis, or who dropout prior to study end, will be censored on the day they were last known to be alive. The analysis of OS will be based on the Kaplan-Meier method for estimation of summary statistics including 50^{th} percentiles (median) and associated 95% CIs.

4.2.3 Progression-free Survival (PFS)

PFS will be calculated from the date of start of study treatment to the date of progression based on RANO criteria, or date of death should progression not have occurred. The analysis of

median PFS will be similar to that of OS, using the Kaplan-Meier method; as noted above, actual event time will be used in this analysis.

Duration is calculated as end date – treatment start date +1. For instance, if a PFS event occurs, then PFS time (in days) is defined as event date – date of treatment +1. If a censoring event occurs, then PFS time is defined as the censoring date – date of treatment +1.

Please refer to Table 4-1 for details on PFS outcome status (PFS event vs. censored) and censoring definitions.

Table. 4-1 PFS outcome and censoring definition

Situation	**Date of event or censoring**	**Outcome**
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment or withdrawal of informed consent	Start of Study Treatment	Censored
Death before PD without a gap of 2 or more consecutively missed scheduled disease status assessments before death	Date of Death	PFS event
PD without a gap of 2 or more consecutively missed scheduled disease status assessment before progression	Date of PD	PFS event
No PD or death on or before a. database cut, b. withdrawal of informed consent, c. lost to follow-up, d. one day before start of new GBM treatment, whichever occurs first	Date of last adequate disease assessment prior to the earliest occurrence of the events (a. – e.) listed in the left column	Censored
No PD or death before a gap of 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

4.3 EXPLORATORY ANALYSIS

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5 SAFETY

Safety analyses will be conducted using the Safety Population by arm.

5.1 ADVERSE EVENTS

An AE is defined as any untoward 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 related to the study treatment.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset beginning at the day of first administration of study drug, throughout the treatment period until 30 days after the last dose of study drug, or the day before the initiation of a new anti-neoplastic treatment, whichever occurs first, inclusive. Any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study will also be considered treatment-emergent.

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

The severity of all AEs will be graded according to the NCI CTCAE v4.03 Grading Scale. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE.

5.1.1 Definitions

- ***Treatment-emergent adverse event (TEAE)*** is 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, from the first dose of study treatment to 30 days after the last dose of study treatment or the day before initiation of a new anti-neoplastic treatment, whichever occurs first, inclusive. Additionally, any AEs that occur 30 days after the last dose of study treatment will also be considered as TEAE, if assessed by the Investigator as related to any study treatment.
- ***Serious adverse event (SAE)*** is any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect.
- ***Treatment-emergent treatment-related adverse event (TRAE)*** is any TEAE that is considered by the Investigator to be related to any study treatment.

5.1.2 Analysis Methods

Analyses of AEs will be performed only for 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 2.3.2.

AE summaries will include number and percentage of patients who have experienced an TEAE. The denominator for computation of percentages is the number of patients in the corresponding treatment arm. Multiple occurrences of the same event in the same patient will be counted only once in the tables. Common AEs occurring in > 10% of the safety population will be presented by arm and overall.

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.

5.1.3 Analysis of Treatment-Emergent Adverse Event (TEAE)

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

- 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
- All TEAEs, by maximum grade
- Grade 3 or higher TEAEs
- TEAEs leading to dose modifications of study treatment

- TEAEs leading to study treatment discontinuation

5.1.4 Analysis of Serious Adverse Event (SAE)

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

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

All AEs and SAEs will be provided in a data listing.

5.2 DEATH

The following summaries and listings on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (death as an outcome on the AE report page as reported by the Investigator), by primary SOC and PT
- TRAEs leading to death and are related to study treatment, by primary SOC and PT
- Listing of all TEAEs leading to death
- Listing of all death events

5.3 LABORATORY SAFETY VARIABLES

Lab values in conventional units will be converted using the international system of units.

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE v4.03 criteria. Laboratory values with CTCAE Grade ≥ 3 will be presented in a data listing and summary table. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. Shift tables that present changes from baseline to the worst value and baseline to last value on-study will be presented.

For key laboratory parameters, summary and box plots of actual value and change from baseline over time may be presented.

5.4 VITAL SIGNS AND PHYSICAL EXAMINATION VARIABLES

Vital signs include height, weight, systolic and diastolic blood pressure (SBP and DBP), pulse rate, and body temperature. Body surface area (BSA) will be calculated by the Dubois (Dubois and Dubois, 1916) Method.

Shift tables that present changes from baseline to worst on-study and last on-study for systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature. Abnormal vital signs results will be summarized in the threshold/range analyses.

Abnormal physical examination findings will be provided in a data listing. All examination findings will be presented in a data listing.

5.5 NEUROLOGICAL EXAMINATIONS

Neurological examination findings will be presented via shift tables, summarizing the changes from baseline to worst value for each parameter.

All neurological examination findings will be presented in a data listing.

5.6 ELECTROCARDIOGRAM (ECG)

Standard 12-lead ECG will be performed at screening (or predose on C1D1) and EoT visits.

Changes from baseline for PR interval, QRS interval, QT interval and QT corrected using Fridericia's formula will be summarized using shift tables. For heart rate, changes from baseline will be presented. Abnormal ECG results will be summarized in the threshold/range analyses.

ECG data for each patient will be provided in a data listing.

5.7 KARNOFSKY PERFORMANCE STATUS

Karnofsky performance status at each time point will be summarized to indicate change in status score from baseline to each post-baseline assessment.

Karnofsky performance status data for each patient will be provided in a data listing.

6 REFERENCES

Simon R. Optimal two-stage designs for phase II clinical trials[J]. Controlled clinical trials, 1989, 10(1): 1-10.