# STATISTICAL ANALYSIS PLAN

## Protocol KCP-330-020

## A PHASE 2-3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY OF SELINEXOR (KPT-330) VERSUS PLACEBO IN PATIENTS WITH ADVANCED UNRESECTABLE DEDIFFERENTIATED LIPOSARCOMA (DDLS)

**Protocol Version:** **9.0**

**Version:** **2.0**

**Date:** **20 September 2020**

# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

*See last page for signatures.*

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

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# DOCUMENT HISTORY

| Version | Date | Author(s) | Brief Summary of Changes |
|---|---|---|---|
| 1.0 | 15 Aug 2019 | PPD<br>PPD | Original |
| 2.0 | 20 Sep 2020 | PPD | Increase the number of enrolled patients in the Phase 3 portion of the study based on protocol version 8.0 dated 30 January 2020.<br>Time-to-progression (TTP) was changed from a key secondary endpoint to a secondary efficacy endpoint. In sensitivity analysis for OS, the two-stage estimation method will be implemented to assess the impact of cross-over on the effect of selinexor on OS based on protocol version 9.0 dated 21 May 2020. |

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ALT | alanine transaminase (SGPT) |
| AST | aspartate transaminase (SGOT) |
| ATC | Anatomic Therapeutic Class |
| BSA | body surface area |
| CHW | Cui, Hung, and Wang |
| CMH | Cochran-Mantel-Haenszel |
| CI | confidence interval |
| CR | complete response |
| C1D1 | Cycle 1 Day 1 |
| cm | centimeter |
| CP | conditional power |
| CSR | clinical study report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CCI | [redacted] |
| DDLS | dedifferentiated liposarcoma |
| DOR | duration of response |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EoBT | End of Blinded Treatment |
| EoS | End of Study |
| EoT | End of Treatment |
| EORTC | European Organization for Research and Treatment of Cancer |
| EQ-5D-5L | EuroQoL Group Health Questionnaire |
| FDG | $^{18}$F-fluorodeoxyglucose |
| HR | hazard ratio |
| ICR | Independent Centralized Review |
| ITT | intent-to-treat |
| kg | kilogram |
| KM | Kaplan-Meier |

| Abbreviation | Definition |
|---|---|
| LLN | lower limit of normal |
| $m^2$ | square meters |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |
| min | minute |
| mL | Milliliter |
| MLS | Myxoid/round cell liposarcoma |
| MRI | Magnetic resonance imaging |
| NCI | National Cancer Institute |
| ORR | overall response rate |
| OS | overall survival |
| OS12 | overall survival at least 12 months |
| PD | progression of disease |
| CCI [redacted] | |
| PET | positron emission tomography |
| PFS | progression-free survival |
| CCI [redacted] | |
| CCI [redacted] | |
| CCI [redacted] | |
| CCI [redacted] | |
| PP | per-protocol |
| PR | partial response |
| PT | preferred term |
| QLQ-C30 | quality of life questionnaire-C30 |
| QoL | quality of life |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SD12 | stable disease at 12 weeks |
| SINE | selective inhibitor of nuclear export |
| SOC | system organ class |
| Std Dev | standard deviation |
| SUV | standardized uptake value |

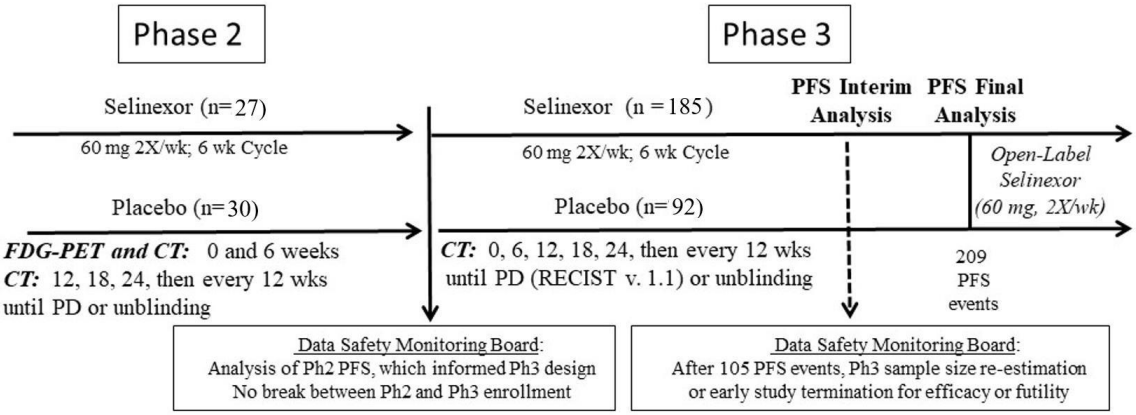
| Abbreviation | Definition |
|---|---|
| CCI | |
| TEAE | treatment-emergent adverse event |
| TRAE | treatment-related adverse event |
| TTP | time to progression |
| ULN | upper limit of normal |
| WBC | white blood cell |
| Wk | week |
| WHO | World Health Organization |
| XPO1 | exportin 1 |

# 1. OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1. STUDY DESIGN

This is a Phase 2-3, multicenter, randomized, double-blind, placebo-controlled study. Approximately 334 total patients were planned to be enrolled. At the conclusion of enrollment, three hundred and forty-two (342) patients have been randomized (57 patients in Phase 2 and 285 patients in Phase 3).

The study overview is presented in the figure below.




Patients in the placebo arm who have PD will have the option to cross over to open-label selinexor.

**Phase 2:**

Fifty-seven patients were randomized to selinexor or placebo in a 1:1 allocation. Randomization was stratified based on the following stratification factors for patients enrolled under protocol Versions ≤ 4: number of prior systemic therapies (1 versus ≥ 2) and prior eribulin use (prior eribulin versus no prior eribulin). The preplanned analysis of progression-free survival (PFS; (after 40 PFS events were observed) was performed and served as a guideline to inform the final design of the Phase 3 portion of the study.

**Phase 3:**

Two hundred and eighty-five (285) patients have been randomized to selinexor or placebo in a 2:1 allocation.

Randomization was based on

- Prior eribulin use (prior eribulin versus no prior eribulin)
- Prior trabectedin (Yondelis®) use (prior trabectedin versus no prior trabectedin)
- The number of prior systemic therapies excluding eribulin and trabectedin (≤2 versus ≥ 3).

All radiographic responses will be determined by the Independent Centralized Review (see the *Imaging Manual* for more details). Patients who have progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 (Eisenhauer 2009) per central review, will discontinue blinded study treatment and their treatment assignment will be unblinded.

- Patients in the placebo arm who have PD will have the option to cross over to open-label selinexor.
- Patients in the selinexor arm who have PD will only be allowed to continue on selinexor (as open-label treatment) if the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor.

Patients who discontinue blinded study treatment at the discretion of the Investigator for reasons other than centrally confirmed PD are not allowed to receive open-label selinexor.

An interim analysis was conducted after 108 PFS events were observed. The interim analysis was designed to allow early stopping for efficacy, futility (non-binding), or sample size re-estimation (up to a maximum of 50% increase in sample size). Based on interim analysis results, DSMB recommended the study to continue.

Approximately 34 months will be required to complete the primary Phase 3 PFS analysis. The primary endpoint analysis will be performed approximately 4 months after enrollment of the last patient, once 209 PFS events are observed. Treatment assignment for all patients will be unblinded at the time of the primary PFS analysis and all Phase 3 patients will be evaluable for assessment of the primary endpoint.

Patients who are on blinded study treatment at the time of the primary PFS analysis at the end of Phase 3 may proceed as follows:

- Patients in the placebo arm may cross over to open-label selinexor (60 mg twice weekly).
- Patients in the selinexor arm will continue selinexor but as open-label treatment.

All patients who have PD while receiving open-label selinexor will discontinue selinexor and be followed for survival, unless the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor.

## 1.2. OBJECTIVES

### 1.2.1. Phase 2 Objectives

#### 1.2.1.1. Phase 2 Primary Objective

- Assess and compare progression-free survival (PFS) of patients with advanced unresectable DDLS treated with selinexor (60 milligrams [mg]) or placebo twice weekly. PFS is defined as the time from date of randomization until the first date of PD, per RECIST v. 1.1 (Eisenhauer 2009), or death due to any cause.

#### 1.2.1.2. Phase 2 Secondary Objectives

- Compare time to progression (TTP) on study treatment, per RECIST v. 1.1, with TTP on the patient's last prior systemic therapy.
- Determine the overall response rate (ORR: Complete Response [CR] + Partial Response [PR]), supported by duration of response (DOR). Responses will be defined by RECIST v. 1.1.
- Assess changes at 6 weeks in tumor glucose metabolism, density, and size using $^{18}$F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) (diagnostic).
- Assess safety of each treatment arm.

#### 1.2.1.3. Phase 2 Exploratory Objectives

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### 1.2.2. Phase 3 Objectives

#### 1.2.2.1. Phase 3 Primary Objective

Assess and compare PFS of patients with advanced unresectable DDLS treated with selinexor (60 mg) or placebo twice weekly. PFS is defined as time from date of randomization until the first date of progression per RECIST v.1.1, or death due to any cause. Evaluation of the radiographic data for the PFS primary endpoint will be based on data from a scan review by Independent Centralized Review (ICR).

#### 1.2.2.2. Phase 3 Secondary Objectives

- Assess overall survival (OS), measured from date of randomization until death due to any cause.
- Compare TTP on study treatment, per RECIST v.1.1, with TTP on the patient's last prior systemic therapy.
- Assess Quality of Life (QoL) and patient-reported outcomes as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) and the EuroQoL Group Health Questionnaire (EQ-5D-5L).
- Determine the ORR, supported by DOR. Responses will be defined by RECIST v.1.1.
- Assess PFS according to the Investigator based on clinical and/or radiologic criteria.
- Assess safety of each treatment arm.

#### 1.2.2.3. Phase 3 Exploratory Objectives

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[redacted]

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[redacted]

## 1.3. DETERMINATION OF SAMPLE SIZE

### 1.3.1. Determination of Sample Size for Phase 2

Fifty-seven patients were randomized to selinexor or placebo in a 1:1 allocation. Randomization details are provided in Section 7.7 of the Protocol.

The preplanned analysis of PFS was performed and served as guideline to inform the final design of the Phase 3 portion of the study.

### 1.3.2. Determination of Sample Size for Phase 3

Per protocol, the Phase 3 sample size was re-evaluated based on the Phase 2 results. Sample size calculations were conducted under the following assumptions:

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Based on these assumptions, approximately 277 eligible patients will be randomized 2:1 to receive either selinexor (60 mg twice weekly) or placebo, respectively in a blinded manner to observe 209 PFS events. Sample size may be adjusted based based on the interim analysis results (see Section 14.1.1.2.1 of the Protocol).

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## 1.4. STUDY PLAN

For each patient that signs the informed consent, the study consists of:

- Screening/baseline visit: occurs within 21 days prior to receiving the 1st dose of study treatment
- Blinded treatment: expected to be up to 12 months, but there is no maximum treatment duration. Patients will be treated until disease progression, death, toxicity that cannot be managed by standard care, or withdrawal from study, whichever occurs first
- (Optional) Open-label selinexor treatment: patient in the placebo arm may cross over to open-label selinexor. Patients in the selinexor arm who have PD will discontinue blinded study treatment and be followed for survival, unless the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefits from continued treatment with selinexor (see Protocol Section 7.2.4)
- Follow-up period: after last dose of selinexor or placebo blinded treatment/open-label selinexor treatment, patients will be contacted approximately every 3 months for durability of response and survival follow-up

End of Study (EoS) will be upon completion of the follow-up period for the last patient treated in the study. Completion of follow-up for the last patient will occur when the last patient in the study has expired, has been followed for 24 months after enrollment, has been lost to follow-up, or has withdrawn consent, whichever occurs first.

Please refer to protocol schedule of assessment and study activities for patients NOT proceeding to open-label selinexor and patients proceeding to open-label selinexor respectively.

## 1.5. INTERIM ANALYSIS

An interim analysis is scheduled to be conducted after 105 PFS events (50% of the events) or 3 months before enrollment is expected to complete, whichever occurs first. DSMB will review interim analysis results and consider the following recommendations:

- Stop trial early for efficacy
- Continue trial as planned
- Adjust sample size
- Stop trial early for futility (non-binding)

The boundary p value for the stratified log-rank test used at the time of interim PFS analysis will depend on when the interim analysis actually takes place. The early-stopping boundary for efficacy is calculated using the Lan DeMets (Lan and DeMets, 1983) alpha spending function with the O'Brien-Fleming type of boundary. If the null hypothesis for the primary PFS endpoint is rejected at the interim analysis, it will remain being rejected and will not be re-tested at any subsequent point.

If efficacy stopping boundary is not reached at the interim analysis, the unblinded sample size re-estimation will be conducted. It is based on the method of conditional power (CP), defined as the probability to detect a statistically significant difference for the primary PFS endpoint at the end of study given the current data observed at this interim analysis, assuming this interim trend continues. The CP will be calculated for the primary PFS endpoint using East software with CHW method (Cui et al., 1999).

The hazard ratio (HR) and associated Z statistic will be obtained for PFS between selinexor vs. placebo arms based on the observed data at the interim analysis, then the CP will be calculated using East. The calculated CP will be assigned to one of the 3 zones:

1. favorable (CP ≥90%)
2. promising (30% ≤ CP <90%)
3. unfavorable (CP< 30%)

The original planned total sample size of 222 patients (209 PFS events) will be increased to achieve the targeted power of 90%, up to a maximum of 333 patients when the conditional power is in the promising zone. If the CP is <30%, the trial may be stopped for futility (non-binding). Otherwise, if the CP is ≥90% the trial continues as planned.

Overall type I error for the final PFS analysis is maintained using the CHW method (Cui et al, 1999) if the unblinded sample size re-estimation is conducted.

The interim analysis has occurred with a data cut date of July 31, 2019 and 108 PFS events. Based on interim analysis results, the DSMB recommended the study to continue without sample size adjustment.

## 1.6. DATABASE LOCK

Approximately 4 months after enrollment of the last patient, once the targeted 209 PFS events are observed, database interim lock will be conducted. The primary PFS analyses will be performed including analyses of efficacy and safety data. A clinical study report (CSR) will be prepared after the primary PFS analyses.

The final analysis will be performed at the end of the study after all patients have completed the follow-up period with database final lock.

## 1.7. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The current SAP is based on Protocol v9.0 dated 21 May 2020.

The following endpoints will not be analyzed as the corresponding data are not available. All endpoints correspond to Phase 2 and Phase 3 Exploratory Objectives except 1 endpoint from Phase 2 Secondary Objective as noted below.

- Assess changes at 6 weeks in tumor glucose metabolism, density, and size using $^{18}$F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) (diagnostic) (Phase 2 Secondary Objective).
- CCI
- [redacted]

The Phase 3 Per-Protocol Population (Ph3-PP) definition was modified. Please refer SAP section 3.1.1 for the definition.

## 1.8. STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

**Changes to Version 1.0**

Changes throughout the document include minor editorial changes.

- Increase the number of enrolled patients in the Phase 3 portion of the study based on protocol version 8.0 dated 30 January 2020.
- Time-to-progression (TTP) was changed from a key secondary endpoint to a secondary efficacy endpoint. In sensitivity analysis for OS, the two-stage estimation method will be implemented to assess the impact of cross-over on the effect of selinexor on OS based on protocol version 9.0 dated 21 May 2020.
- Add more details to the TEAE definition

# 2. GENERAL STATISTICAL METHODS AND DATA HANDLING

This statistical analysis plan (SAP) outlines the methods to be used in the analysis of clinical data in order 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]; these will be included in a separate plan.

## 2.1. GENERAL ANALYSIS METHODS

This is a multicenter randomized double-blind Phase 2-3 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, median, mean, standard deviation, minimum, 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.

Data from phase 2 and phase 3 will be presented separately.

## 2.2. 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 analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: summaries will be based on observed data only.

### 2.2.1. Handling of Computation of Treatment Duration if Study Treatment 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 study treatment dosing form. If all the dosing dates are missing, then the duration is missing.

The last dose intake should be clearly identified on the 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 information does not indicate whether the AE started prior to treatment or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent. Handling of missing or partial dates for AE or concomitant medications will consider the start date of selinexor for patients who cross over from placebo to open-label selinexor.

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 possibly related.

### 2.2.6. Handling of Missing Severity of AEs

If the severity is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

### 2.2.7. Handling of Missing Data in Patient-Reported QoL Measurements

For patient-reported QoL measurements, missing data will be handled as described in the EORTC-QLQ-C30 and EQ-5D-5L scoring manuals.

## 2.3. STUDY TREATMENT DOSING DATE

Study treatment dosing date is the date on which a patient actually received study treatment (selinexor or placebo, partial or complete).

For blinded treatment,

- Except for few patients who were randomized to selinexor in blinded treatment and entered open-label phase, the date of first study treatment is defined as the earliest date of non-zero dose of either selinexor or placebo. The date of last study treatment is defined as the latest date of non-zero dose of either selinexor or placebo before end of blinded treatment.
- For patients who were randomized to selinexor in blinded treatment and entered open-label phase, the date of first study treatment is defined as the earliest date of non-zero dose of selinexor, the date of last study treatment is defined as the latest date of non-zero dose of selinexor, regardless of blinded or open-label phase.

For open-label treatment, the date of first study treatment is defined as the earliest date of non-zero dose of open-label selinexor. The date of last study treatment is defined as the latest date of

non-zero dose of open-label selinexor. This definition only applies to patients who were randomized to placebo in blinded treatment and entered open-label phase.

## 2.4. OBSERVATION PERIOD

For the patients who do not enter open-label selinexor, the observation period will be divided by the following:

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

For the patients who were randomized to placebo in blinded phase and entered open-label selinexor, the observation period will be divided by the following:

- The pre-treatment period is defined as the time since the signed informed consent date up to the time before the date of first blinded study treatment.
- The blinded treatment period is defined as the time from the date of first blinded study treatment up to the date of last blinded study treatment + 30 days inclusive, or the date of first open-label study treatment exclusive, whichever occurs first.
- The open-label treatment period is defined as the time since the date of first open-label study treatment to the date of last open-label study treatment + 30 days inclusive, (or the day before initiation of a new anti-neoplastic treatment, whichever occurs first).
- The post-treatment period is defined as the time beyond the open-label treatment period.

For the few patients who were randomized to selinexor in blinded phase and entered open-label selinexor, the observation period will be divided by the following:

- The pre-treatment period is defined as the time since the signed informed consent date up to the time before the date of first study treatment.
- The blinded treatment period is defined as the time 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. Please note that open-label selinexor is not considered a new anti-neoplastic treatment here.
- The post-treatment period is defined as the time beyond the blinded treatment period.

Please refer to Section 2.3 for the definitions of dates of first and last study treatment.

## 2.5. STUDY DAY CALCULATION

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

The study day in open-label selinexor will also be calculated using the start date of open-label selinexor treatment as reference point. For example, the first dose date of open-label selinexor will be referred as open-label Day 1 or OL Day 1.

A patient is considered as treated in a cycle if the patient received any non-zero dose of either selinexor or placebo 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.

## 2.6. BASELINE MEASUREMENT

For blinded treatment period, the baseline value is defined as the latest value prior to the first dose of blinded study treatment. In the case an assessment performed on the same date as the first dosing date, 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.

For patients who proceed to open-label period, the baseline value for assessments in open-label treatment period will be the latest value prior to the date of first open-label study treatment.

## 2.7. 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 to 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 for Patients in Blinded Treatment**

| Analysis Visit Name | Target Visit Day | Study Day Range in Window |
|---|---|---|
| Baseline | Day 1 | Prior to or on Day 1 |
| Day 43 | Day 43 | Day 2 to 64 |
| Day 85 | Day 85 | Day 65 to 106 |
| Day 127 | Day 127 | Day 107 to 148 |
| Day 169 | Day 169 | Day 149 to 190 |
| … | | |
| (every 42 days) | | |
| NOTE: Day 1 is the start date of blinded treatment period. The visit window is Target Date – 20 days to Target Date + 21 days for post-baseline visits, except Day 43 analysis visit. | | |

| |
|---|
| Analysis visit and visit window may change for certain parameters depending on the data availability. |

**Table 2-2 Visit Windows for Clinical Laboratory Tests for Patients Who Enter Open-Label Treatment**

| Analysis Visit Name | Target Visit Day | Study Day Range in Window |
|---|---|---|
| OL Baseline | OL Day 1 | Prior to or on OL Day 1 |
| OL Day 43 | OL Day 43 | OL Day 2 to 64 |
| OL Day 85 | OL Day 85 | OL Day 65 to 106 |
| OL Day 127 | OL Day 127 | OL Day 107 to 148 |
| OL Day 169 | OL Day 169 | OL Day 149 to 190 |
| … | | |
| (every 42 days) | | |
| NOTE: Day 1 is the start date of open-label treatment period. The visit window is Target Date – 20 days to Target Date + 21 days for post-baseline visits, except OL Day 43 analysis visit. Analysis visit and visit window may change for certain parameters depending on the data availability. | | |

## 2.8. SUBGROUPS

The following subgroup analyses on selected efficacy endpoints will be conducted for Phase 3 part:

- Prior eribulin use (prior eribulin vs. no prior eribulin).
- Prior trabectedin use (prior trabectedin vs. no prior trabectedin).
- Number of prior systemic therapies excluding eribulin and trabectedin ($\leq 2$ vs. $\geq 3$).

## 2.9. POOLING OF CENTERS FOR STATISTICAL ANALYSES

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

## 2.10. 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 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 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 were randomized:
    - Patients who were randomized but did not receive any dose of study treatment (partial or complete)
    - Patients who were randomized and received at least one dose of study treatment (partial or complete)
- End of blinded treatment:
    - Patients who were still on blinded treatment
    - Patients who discontinued blinded treatment and primary reason for treatment discontinuation
- Patients who proceeded to open-label period (this applies to blinded placebo arm only)
- Survival follow-up status post end of blinded treatment for patients who did not proceed to open-label period:
    - Patients in survival follow-up
    - Patients who have completed survival follow-up
    - Patients who died during survival follow-up
    - Patients who discontinued from the study without starting or completing survival follow-up.
- End of study for patients who did not proceed to open-label period
    - Patients who withdrew from study and primary reason for study withdrawal

A separate disposition summary will be presented for patients who entered open-label period including end of open-label treatment status, survival follow-up status post end of open-label treatment, and end of study status. This applies only to patients randomized to the placebo arm in the blinded phase eho entered open-label.

For few patients who were randomized to selinexor in blinded phase and entered open-label selinexor, their end-of-treatment status, date, and reason will be used for end of blinded treatment summary.

### 3.1.1. Efficacy Populations

The following populations are defined:

- The ***Phase 3 Intent-to-Treat Population (Ph3-ITT)*** will consist of all patients randomized to study treatment in Phase 3, regardless of whether or not they received study treatment. This population will be used for primary analyses of efficacy. Patients

will be analyzed in the treatment arm to which they are randomized and strata assignment at the time of randomization.

- The ***Phase 3 Per-Protocol Population (Ph3-PP)*** will consist of all ITT patients who have received at least 1 dose of study treatment, have no major protocol violations expected to affect assessment of efficacy, and have ≥70% compliance to study treatment (see Section 3.4.2 for definition on study treatment compliance). Patients who progress or die are included regardless of duration of time on study treatment. This population will be used for supportive analyses of efficacy. Patients will be analyzed in the treatment arm to which they were randomized.

### 3.1.2. Safety Populations

For evaluation of safety, the following safety populations are defined:

- The ***Phase 3 Safety Population*** (***Ph3-SAF***) will consist of all patients in Phase 3 who have received at least one dose of blinded study treatment.
- The ***Phase 2 Safety Population*** (***Ph2-SAF***) will consist of all patients in Phase 2 who have received at least one dose of blinded study treatment.

Patients in safety populations will be analyzed according to the actual treatment received.

### 3.1.3. Additional Analysis Populations

- The ***Phase 3 Open-Label Population*** (***Ph3-OL***) will consist of all patients in Phase 3 who were randomized to placebo in blinded phase, entered open-label period and have received at least one dose of open-label selinexor.
- The ***Phase 2 Intent-to-Treat Population*** (***Ph2-ITT***) will consist of all patients randomized to study treatment in Phase 2, regardless of whether or not they received study treatment. Patients will be analyzed in the treatment arm to which they were randomized and strata assignment at the time of randomization.
- The ***Phase 2 Open-Label Population*** (***Ph2-OL***) will consist of all patients in Phase 2 who were randomized to placebo in blinded phase, entered open-label period and have received at least one dose of open-label selinexor.

## 3.2. DEMOGRAPHICS, MEDICAL HISTORY, AND BASELINE CHARACTERISTICS

Demographics, medical history and baseline characteristics will generally be summarized among the Ph3-ITT, Ph3-SAF, Ph3-OL, Ph2-ITT, Ph2-SAF, and Ph2-OL populations, unless otherwise specified. No formal hypothesis testing will be performed. P-values on demographic, medical history and baseline characteristic data will not be calculated.

In general, the baseline value is defined as latest value prior to the first dose of blinded study treatment.

### 3.2.1. Demographic Data

Demographic data will be summarized by treatment arm, as well as overall, and will include sex (female, male), race, ethnicity, country, and age at time of consent.

### 3.2.2. Prior Antineoplastic Therapy

#### 3.2.2.1. Prior Antineoplastic Therapy- Medication

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

- Number of prior antineoplastic regimen (summarized as a continuous variable and as a categorical variable)
- Number of unique prior antineoplastic medications
- Whether patient had prior exposure to eribulin
- Whether patient had prior exposure to trabectedin
- Best response to most recent antineoplastic regimen
- Duration of most recent antineoplastic regimen
- Days since discontinuation of most recent antineoplastic medication to randomization date, which will be calculated as randomization date – stop date of most recent antineoplastic medication + 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 radiation therapy
- Number of prior radiation therapies (summarized as a continuous variable and as a categorical variable, with cut-off of 1 and > 1 prior radiation therapy)
- Best response to most recent radiation therapy

#### 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 (summarized as a continuous variable and as a categorical variable, with cut-off of 1 and > 1 prior surgery therapy)

### 3.2.3. Medical History

Medical history 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. When more than one PT has the same frequency, the order of presentation will be alphabetical in PTs.

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

### 3.2.4. Disease History

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

- Time since first initial diagnosis to randomization date
- Time since most recent progression to randomization date
- Stage of current liposarcoma diagnosis

### 3.2.5. Baseline Characteristics

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

- Baseline height (cm)/ weight (kg)/ body surface area (m2)/ BMI (kg/m2)
- Baseline ECOG performance status
- Number of unique ongoing medical history (Preferred Terms) per patient
- Number of unique ongoing medications (Anatomical Therapeutic Class [ATC] Level 4 and preferred name) per patient

## 3.3. PRIOR AND CONCOMITANT MEDICATIONS AND PROCEDURES

Concomitant medications consist 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 any medications used to treat symptoms, concomitant diseases such as diabetes, hypertension, etc., AEs and intercurrent illnesses that are medically necessary as part of standard care. 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 generally be summarized among ITT and safety populations, unless otherwise specified.

All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE).

### 3.3.1. Prior and Concomitant Medications and Procedures

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

For Ph3-ITT, Ph3-SAF, Ph2-ITT, and Ph2-SAF populations, summaries will be presented among medications concomitant to blinded treatment period i.e., any treatments received by the patient concomitantly during the blinded treatment period from first dose of blinded study treatment to last dose of blinded study treatment + 30 days inclusive, or if applicable, the date of first open-label study treatment exclusive, whichever occurs first. Please refer to Section 2.4 for definitions of blinded treatment period for patients who did or did not proceed to open-label period respectively.

For Ph2-OL and Ph3-OL populations, summaries will be presented among medications concomitantly to open-label treatment period, i.e., any treatments received by the patient concomitantly during the open-label treatment period from first dose of open-label study treatment to last dose of open-label study treatment + 30 days.

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.

Note that a medication can be classified as both a prior medication and a concomitant medication.

## 3.4. EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

Extent of study treatment exposure and compliance will be summarized among the Ph3-ITT, Ph3-SAF, Ph3-OL, Ph2-ITT, Ph2-SAF, and Ph2-OL populations, unless otherwise specified.

### 3.4.1. Extent of Study Treatment Exposure

For Ph3-ITT, Ph3-SAF, Ph2-ITT, and Ph2-SAF populations, summary on exposure will be presented using the following variables:

- Duration of exposure during blinded treatment (summarized as a continuous variable and as a categorical variable), which is defined as the date of last blinded treatment – date of first blinded treatment + 1
- Total dose received during blinded treatment
- Average dose received per week during blinded treatment, which is defined as total dose received during blinded treatment divided by duration of exposure during blinded treatment, presented in mg/week.
- Number and percentage of patients with dose modification including dose reduction and interruption during blinded treatment
    - Number and percentage of patients with dose reduction
    - Number and percentage of patients with drug interruption
- Number and percentage of patients in which blinded treatment was discontinued

For Ph3-OL and Ph2-OL populations, summary on exposure will be presented using the following variables:

- Duration of exposure during open-label treatment (summarized as a continuous variable and as a categorical variable), which is defined as the date of last open-label treatment – date of first open-label treatment + 1
- Total dose received during open-label treatment
- Average dose received per week during open-label treatment, which is defined as total dose received during open-label treatment divided by duration of exposure during open-label treatment, presented in mg/week.
- Number and percentage of patients with dose modification including dose reduction and interruption during open-label treatment

- Number and percentage of patients with dose reduction during open-label treatment
- Number and percentage of patients with drug interruption during open-label treatment

- Number and percentage of patients with open-label treatment discontinued

### 3.4.2. Treatment Compliance

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

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

Note that the number of scheduled study treatment doses (selinexor or placebo) does not include doses missed due to treatment interruption or other reasons not related to patient choice. Patients with study treatment compliance < 70% will be excluded from the PP population.

Study treatment compliance will be calculated for blinded treatment period and if applicable, open-label treatment period separately. The number and percentage of patients with blinded study treatment compliance ≥70% will be provided among Ph3-ITT, Ph3-SAF, Ph2-ITT, and Ph2-SAF populations. The number and percentage of patients with open-label study treatment compliance ≥70% will be provided among Ph3-OL and Ph2-OL populations.

# 4. EFFICACY

Patient response will be assessed centrally by ICR, according to RECIST v.1.1 (Eisenhauer 2009). Unless otherwise specified, response assessment refers to assessment determined by ICR.

The primary efficacy analyses will be conducted using the ITT population, unless otherwise specified. Efficacy analyses using the PP population will be considered as supportive.

If the interim analysis of unblinded sample size re-estimation is conducted, CHW method will be applied to the primary analysis of the PFS endpoint, with details in Section 1.5.

## 4.1. PRIMARY EFFICACY ENDPOINTS

### 4.1.1. Progression-Free Survival (PFS)

Progression-free survival (PFS), defined as the time from date of randomization until ICR-determined PD per RECIST v.1.1, or death due to any cause, whichever occurs first.

The primary analysis of PFS will be performed by treatment arm (selinexor versus placebo) using the Ph3-ITT population. The analysis will be repeated for the Ph3-PP population as a supportive analysis.

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

| # | Situation | Date of event or censoring | Outcome |
|---|---|---|---|
| 1 | No baseline disease assessment | Randomization | Censored |
| 2 | No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment | Randomization | Censored |
| 3 | ICR-determined PD without a gap of 2 or more consecutively missed scheduled disease assessment before PD. | Date of PD | PFS Event |
| 4 | Death before ICR-determined PD and without a gap of 2 or more consecutively missed scheduled disease assessment before death. | Date of death | PFS Event |
| 5 | No ICR-determined PD or death on or before<br>• Database cut<br>• Withdrawal of informed consent<br>• Lost to follow-up<br>• Date of discontinuation from blinded treatment + 30 days<br>• A gap of 2 or more consecutively missed scheduled disease assessment<br>• Start of new antineoplastic therapy*, whichever occurs first | Date of last adequate disease assessment prior to the events listed in the left column | Censored |

*For the purpose of calculating PFS for blinded treatment, start of open-label selinexor will be considered as initiating a new antineoplastic therapy.

The number and percentage of patients who had a PFS event will be reported. Median PFS with 95% confidence interval (CI) will be summarized using the Kaplan-Meier (KM) method for each treatment arm. The KM curves for PFS will be provided by treatment arm.

A stratified log-rank test will be used to compare the PFS between treatment arms (selinexor versus placebo) for the primary efficacy assessment. The strata will be those used for stratified randomization (i.e., prior eribulin use, prior trabectedin use, number of prior systemic therapies excluding eribulin and trabectedin).

Hazard ratios and its 95% CI will be estimated by a stratified Cox proportional hazards model, with Efron's method of tie handling, with treatment as the factor. The strata will be those used for stratified randomization. A non-stratified log-rank test and a Cox proportional hazards model will be used as sensitivity analyses.

For exploratory purposes, PFS in Ph3-ITT population will also be analyzed:

- In subgroups based on the stratification factors as randomized
- In a sensitivity analysis similar to the primary PFS analysis but where initiation of new antineoplastic therapy is considered as a PFS event
- In a sensitivity analysis similar to the primary PFS analysis but where clinical progression is considered as a PFS event. Clinical progression is defined as the event where a patient discontinues blinded treatment with reason being either disease progression or clinical progression but is not classified as PD by ICR.
- Based on response assessment per investigator

## 4.2. SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints will be summarized by randomized treatment arm (selinexor vs. placebo), unless otherwise specified.

For time-to-event endpoints, a stratified log-rank test and stratified Cox proportional hazards model analysis will be conducted to assess the effect of selinexor. The strata will be those used for stratified randomization. Median event times with 95% CIs will be estimated based on the KM method for each treatment arm. The KM curves will be provided. The number and percentage of patients with the corresponding events (e.g., death) will be provided. If nominal p-values are computed for those secondary efficacy analyses, they should be interpreted with caution due to potential issues of multiplicity.

For dichotomous endpoints, treatment differences will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization stratification factors. The number and percentage of patients will also be summarized by treatment arm.

### 4.2.1. Key Secondary Efficacy Endpoints

The following 2 overall survival (OS) endpoints are defined as key secondary endpoints: OS defined as time since randomization until death due to any cause. Patients who are alive will have their OS follow-up time censored at the latest date for which the patient was known to be alive

- OS for non-inferiority in Ph3-ITT population with a non-inferiority margin of HR=1.15.
- OS for superiority in Ph3-ITT population.

Statistical significance of key secondary endpoints will not be claimed until the primary analysis of PFS has reached significance. The key secondary endpoints will be tested using the hierarchical testing procedure to maintain the overall type I error at a 1-sided 0.025 level of significance. More details on the strategy to address multiplicity issues are provided in Section 4.4.

The testing sequence will be:

- OS for non-inferiority in Ph3-ITT population with a non-inferiority margin of HR=1.15.
- OS for superiority in Ph3-ITT population.

#### 4.2.1.1. Overall Survival (OS)

OS is defined as time since randomization 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, or date of last participating visit (e.g., a telephone contact with patient status being alive) on or before database cut-off date, whichever occurs first.

The OS analyses will be conducted among the Ph3-ITT, Ph3-PP, and Ph2-ITT populations.

In sensitivity analysis for OS, the two-stage estimation method will be implemented to assess the impact of cross-over on the effect of selinexor on OS.

For exploratory purposes, OS will be analyzed among Ph3-ITT and Ph2-ITT populations respectively:

- Among the subset of Ph3-ITT population removing patients with the blinded phase treatment unblinded without ICR-confirmed PD
- In a sensitivity analysis in which patients will be censored at the start date of first new antineoplastic therapy including open-label selinexor.
- Among the subset of Ph3-ITT and Ph2-ITT populations, respectively, who did not enter open-label period.
- Assessing the proportion of patients whose OS ≥ 12 months (OS12). Patients who were censored before 12 months is considered not meeting the criteria of having OS ≥ 12 months. Treatment differences between the selinexor and placebo arms will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization stratification factors. The number and percentage of patients will also be summarized by treatment arm.

### 4.2.2. Other Secondary Efficacy Endpoints

#### 4.2.2.1. Time to Progression (TTP)

Time to progression (TTP) is defined as the time from date of randomization until ICR-determined PD per RECIST v.1.1, or death due to disease progression, whichever occurs first. TTP outcome and censoring definitions are similar to the outcome and censoring definitions for PFS in Table 4-1, with the only exception that only death due to disease progression will be considered a TTP event. Death due to reasons other than disease progression will be a new censoring event under situation #5.

TTP on patient's last prior systemic therapy is defined as time since start of last prior systemic therapy to date of disease progression. For patients without a disease progression date, their TTP will be censored on the discontinuation date of last prior systemic therapy.

The comparison of TTP on study treatment to TTP on last prior therapy will be performed using a stratified Cox proportional hazards regression model stratifying on patient IDs to account for correlation within patient. This analysis will be conducted respectively among Ph3-ITT and Ph2-ITT patients randomized to selinexor.

For exploratory purpose, TTP will be summarized among Ph3-ITT patients randomized to placebo arm, Ph3-OL population, Ph2-ITT patients randomized to placebo arm, and Ph2-OL population respectively. For open-label selinexor, TTP is measured as time since the start of open-label treatment until ICR-determined PD per RECIST v.1.1, or death due to disease progression, whichever occurs first. Median TTP time with 95% CIs will be presented using the KM method.

#### 4.2.2.2. QLQ-C30

QLQ-C30 contains 30 questions and includes five functional scales (Physical, Role, Emotional, Social, and Cognitive Functioning), three symptom scales (Fatigue, Nausea/Vomiting and Pain) and a Global Health Status/QoL scale, and six single-item symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The principle for scoring these scales is the same: 1. Calculate the mean of the items that contribute to the scale; this is the raw score. 2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100.

For functional scales and the global heath status/QoL, a higher score represents a better level of functioning (better health status); for symptom scales/items, a higher score represents a higher level of symptomatology/problems (worse health status).

The missing data will be handled based on EORTC QLQ-C30 scoring manual (Fayers et al., 2001). The raw score (mean of the items that contribute to the scale) will only be calculated if at least half of the items (i.e., 3 of 6 items, or 3 of 5 items) from the domain have been answered. As a result, none of the single-item measures will be imputed.

The actual value and change from baseline before initiating a new antineoplastic treatment will be summarized using descriptive statistics over time for each of the five functional scales, three symptom scales and six items, and the global health status/QoL scale.

QLQ-C30 analyses will be summarized by treatment arm among Ph3-ITT, Ph3-PP, and Ph2-ITT populations. For exploratory purpose, QLQ-C30 will also be summarized in Ph3-OL and Ph2-OL populations, in which changes from baseline will be calculated using baseline values for the open-label period, i.e., last assessment on or before the start of open-label treatment.

**Table 4-2 Scoring the QLQ-C30 version 3.0**

| | Scale | Number of items | Item range* | **Version 3.0** Item numbers | Function scales |
|---|---|---|---|---|---|
| **Global health status / QoL** | | | | | |
| Global health status/QoL (revised)† | QL2 | 2 | 6 | 29, 30 | |
| **Functional scales** | | | | | |
| Physical functioning (revised)† | PF2 | 5 | 3 | 1 to 5 | F |
| Role functioning (revised)† | RF2 | 2 | 3 | 6, 7 | F |
| Emotional functioning | EF | 4 | 3 | 21 to 24 | F |
| Cognitive functioning | CF | 2 | 3 | 20, 25 | F |
| Social functioning | SF | 2 | 3 | 26, 27 | F |
| **Symptom scales / items** | | | | | |
| Fatigue | FA | 3 | 3 | 10, 12, 18 | |
| Nausea and vomiting | NV | 2 | 3 | 14, 15 | |
| Pain | PA | 2 | 3 | 9, 19 | |
| Dyspnoea | DY | 1 | 3 | 8 | |
| Insomnia | SL | 1 | 3 | 11 | |
| Appetite loss | AP | 1 | 3 | 13 | |
| Constipation | CO | 1 | 3 | 16 | |
| Diarrhoea | DI | 1 | 3 | 17 | |
| Financial difficulties | FI | 1 | 3 | 28 | |

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

#### 4.2.2.3. EQ-5D-5L

The EQ-5D-5L is a validated quality of life questionnaire developed by the EuroQol group in order to provide a simple, generic utility measure for characterizing current health states of patients. It consists of 2 parts, the descriptive system and the visual analogue scale (VAS).

EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems and extreme problems). EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, will be converted into a single index value according to the U.S. population (van Hout et al, 2012). The VAS records the respondent's self-rated health status on a vertical visual analogue scale. The VAS 'thermometer' has 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

The actual value and change from baseline before initiating a new antineoplastic therapy will be summarized using descriptive statistics over time for EQ-5D-5L health states and VAS.

EQ-5D-5L analyses will be summarized by treatment arm among Ph3-ITT, Ph3-PP, and Ph2-ITT populations. For exploratory purpose, EQ-5D-5L will also be summarized in Ph3-OL and

Ph2-OL populations, in which changes from baseline will be calculated using baseline values for the open-label period, i.e., last assessment on or before the start of open-label treatment.

#### 4.2.2.4. ORR

ORR is defined as the proportion of patients who achieve an ICR-determined best overall response of PR or CR per RECIST v.1.1, before ICR-confirmed PD or initiating a new antineoplastic therapy. Open-label selinexor is considered a new antineoplastic therapy for the purpose of assessing ORR for blinded study treatment.

The number and percentage of patients achieving PR or CR will be summarized by treatment arm among Ph3-ITT and Ph2-ITT populations respectively.

#### 4.2.2.5. Time to Next Treatment (TTNT)

TTNT is defined as time since randomization until the first new antineoplastic therapy or death due to any cause, whichever occurs first. For patients without an event, their follow-up time will be censored at the date of discontinuation from the study, or date of last participating visit (e.g., a telephone contact with patient status being alive) on or before database cut-off date, whichever occurs first.

TTNT on patient's last prior systemic therapy is defined as time since start of last prior systemic therapy to start of blinded study treatment or death due to any cause, whichever occurs first. For patients who were randomized but never received study treatment, and did not die before discontinuation from study, their follow-up time will be censored at the date of discontinuation from the study, or date of last participating visit (e.g., a telephone contact with patient status being alive) on or before database cut-off date, whichever occurs first.

The analysis comparing TTNT on study treatment vs. on last prior systemic therapy will be conducted among patients in the Ph3-ITT population randomized to selinexor and placebo arms separately. To account for within-person correlation, a stratified Cox proportional hazards model analysis will be conducted stratifying on patient IDs. KM median TTNT times with 95% CIs, and KM curves will be provided.

## 4.3. EXPLORATORY ENDPOINTS

CCI

CCI

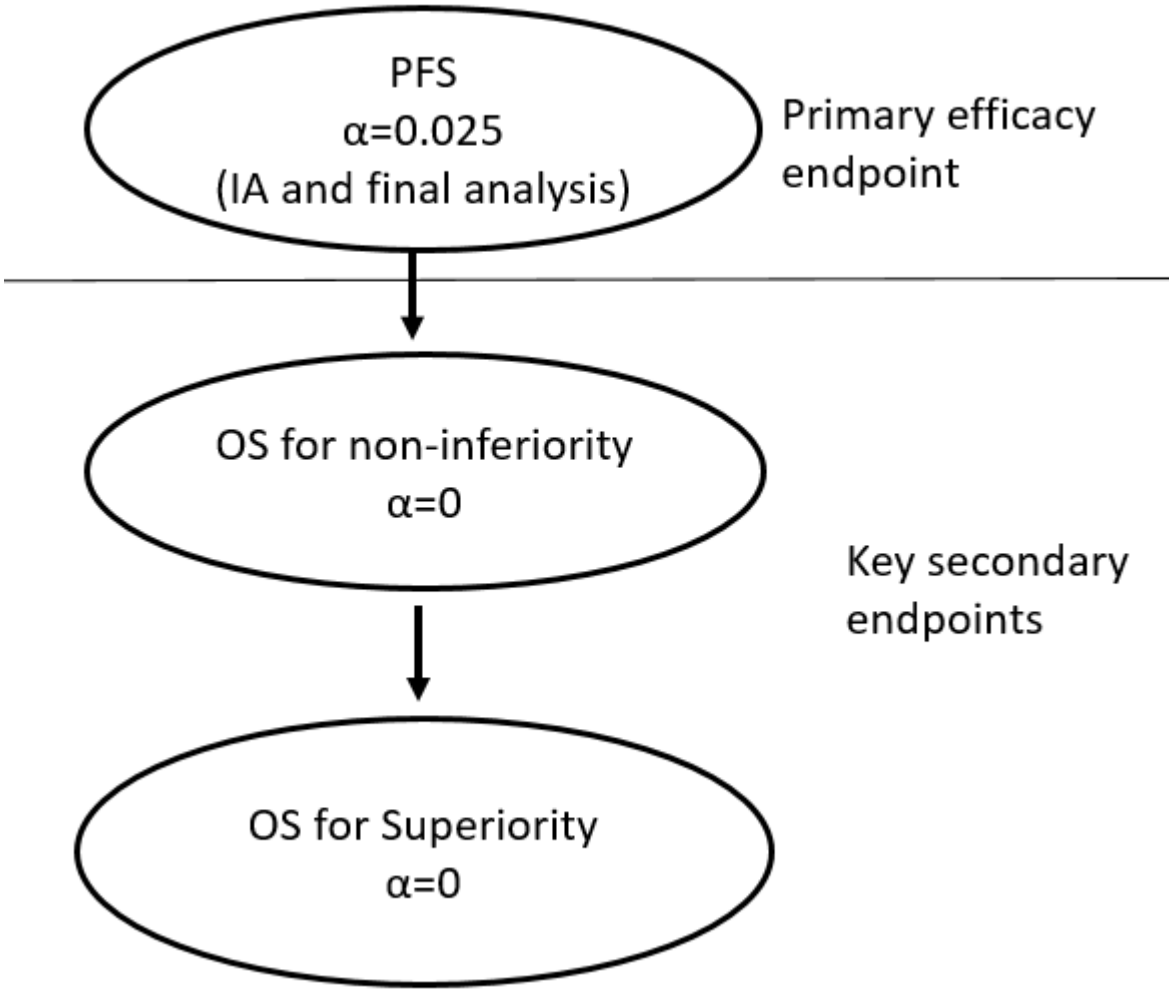
[redacted]

## 4.4. MULTIPLE COMPARISONS/MULTIPLICITY

The overall type I error for the primary endpoint and each key secondary endpoint is strictly controlled at 0.025 (one-sided).

The graphical multiple testing procedure in Bretz et al (2009) will be used to test the primary and key secondary endpoints. It is a Bonferroni-based closed test procedure, so it strongly controls the family-wise error rate across the endpoints. See the figure below for the alpha reallocation for the primary and key secondary endpoints.

**Figure 4-1: Graphical illustration of the propagation of endpoint-specific alpha**



To account for the interim analysis with options to stop for futility (non-binding) or efficacy, type I error is adjusted using the Lan DeMets (Lan and DeMets, 1983) alpha spending function with the O'Brien-Fleming type of boundary. If the interim analysis is conducted for the unblinded sample size re-estimation, the overall type I error for the final analysis of the primary efficacy PFS endpoint will be maintained using the CHW method (Cui et al, 1999) (see Section 1.5).

Statistical significance of key secondary endpoints will not be claimed until the primary endpoint of PFS have reached significance. The key secondary endpoints will be tested using the hierarchical testing procedure as shown in Figure 4-1 to maintain the overall type I error.

# 5. SAFETY

Safety analyses will be reported by the actual treatment arm patients received and overall, among the Ph3-SAF and Ph2-SAF populations respectively. Unless otherwise specified, only data from the blinded treatment period will be presented. Please refer to Section 2.4 on definitions of observation periods.

For patients in the Ph3-OL and Ph2-OL populations respectively, selected safety data from the open-label period will be presented in separate summaries.

Safety analyses will be based on the reported AEs and other safety information, such as 12-lead electrocardiogram (ECG), vital signs, physical examination, ECOG performance status, clinical laboratory assessments including hematology and serum chemistry.

***General rules***

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 first dose of study treatment. Please refer to Section 2.6 for details.
- The analyses of the safety variables will be essentially descriptive with no systematic testing planned.

## 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 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 MedDRA.

The severity of all AEs will be graded according to the NCI CTCAE Grading Scale, v. 4.03. 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. For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” “severe”, “life-threatening” (corresponding to Grades 1 to 4) 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)

For AE summaries for blinded treatment period, treatment-emergent adverse events (TEAEs) are defined as any event that developed or worsened or became serious during the blinded treatment period, i.e., from the date of first blinded study treatment up to the date of last blinded study treatment + 30 days inclusive (or the day before initiation of a new anti-neoplastic treatment, whichever occurs first), or if applicable, the date of first open-label study treatment exclusive, whichever occurs first. Please refer to Section 2.4 on definitions on observation periods. Additionally, TEAEs also include any event that developed post the blinded treatment period but was assessed by the Investigator as related to study treatment. Please note for few patients who were randomized to selinexor in blinded phase and entered open-label selinexor, their blinded study treatment period ends on the date of last non-zero dose of open-label selinexor + 30 days inclusive. To these patients, open-label selinexor is not considered a new anti-neoplastic therapy.

For AE summaries for the open-label period, TEAEs are defined as any event that developed or worsened or became serious during the open-label treatment period, i.e., from the date of first open-label study treatment up to the date of last open-label 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 open-label treatment period but was assessed by the Investigator as related to open-label selinexor. This definition applies to Ph3-OL and Ph2-OL populations only.

#### 5.1.1.2. Serious Adverse Event (SAE)

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

- 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
- Results in a congenital anomaly/birth defect

SAE needs to be clearly documented on the 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.

For summaries on TRAEs for the open-label period, a TRAE is any TEAE that is assessed by the Investigator as related to open-label selinexor.

#### 5.1.1.4. Adverse Event of Clinical Interest (AECI)

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

### 5.1.2. Analysis Methods

The primary focus of AE reporting will be on 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. Multiple occurrences of the same event in the same patient will be counted only once in the tables.

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.

Based on the entries on the eCRF AE page, an AE is considered related to study treatment if the entry for "Relationship to study treatment" is "Related" or "Possibly Related".

### 5.1.3. Analysis of TEAE

An TEAE overview summary table will be provided, which will include the number of patients with at least one of the 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
- All TEAEs, by maximum grade
- Grade 3 or higher TEAEs
- TEAEs leading to dose modifications 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 TRAEs, a lower cut-off (e.g., 5% or 2% depending on TRAE frequency) will be used.

### 5.1.4. Analysis of SAE

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.

### 5.1.5. Analysis of AECI

Standard MedDRA Query (SMQ), Customized MedDRA Query (CMQ), or specific Preferred Terms will be utilized for AECI analysis. Analyses of treatment-emergent AECI will be performed separately for each pre-specified AECI category. Overview summary of all AECI will be summarized similarly as in Section 5.1.3.

The following AECI will be summarized by PT:

- All TEAEs
- Serious TEAEs

The list of AECI categories are provided in Table 5-1. The search strategy of preferred terms for each category will be provided in a separate document.

**Table 5-1 AECI Categories**

| Group Category | AECI Category |
|---|---|
| Hematologic events | Neutropenia |
| | Thrombocytopenia |
| Eye disorders events | Blurred Vision |
| | Cataract |
| Gastrointestinal events | Nausea |
| | Vomiting |
| | Decreased Appetite |
| | Weight Decreased |
| Infection | Pneumonia |
| | Sepsis |
| Metabolism and nutrition disorders | Hyponatremia |
| Nervous system disorders | Neurological Toxicity |

## 5.2. DEATH

The following summaries on death events will be provided:

- An overview of all death events that occurred during the blinded/open-label treatment period, 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, by primary SOC and PT
- Listing of all TEAEs leading to death
- Listing of all death events

## 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** (blood sample: ethylenediaminetetraacetic acid) will include hemoglobin, , white blood cell (WBC) count, lymphocytes, neutrophils, platelets. WBC differential

may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.

- **Serum Chemistry** (blood sample: serum)
    - Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), total protein, albumin, creatinine kinase, uric acid.
    - Limited Serum Chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, and LDH.
    - If the total bilirubin concentration is increased above 1.5 times the upper normal limit, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

### 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. These shift tables will include results from unscheduled visits.

For selected 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 cases where ALT or AST > 3x upper limit of normal (ULN) with simultaneous total bilirubin > 2x ULN will be presented.

Thresholds/Range analyses for selected laboratory parameters will be conducted. The number and percentage of patients classified into each category based on worst values will be presented.

## 5.4. VITAL SIGNS, ECOG, AND PHYSICAL EXAMINATION VARIABLES

The physical examination (PE) will be performed according to the standards at each institution.

Physical examination, including vital signs, will be performed on the scheduled day, even if study treatment is being interrupted. Physical examinations should include general appearance, dermatological, head, eyes, ears, nose, throat, respiratory, cardiovascular, abdominal, lymph nodes, musculoskeletal, and neurological examinations.

Vital signs include height (without shoes) in centimeters (cm), weight (indoor clothing without shoes) in kilograms (kg), body surface area (BSA), systolic and diastolic blood pressure (SBP and DBP), pulse measurements, and body temperature (ºC). BSA will be calculated by the Dubois (Dubois 1916) method.

An ECOG score assessment with grades 0-5 will be performed during screening, day 1 of each cycle, and EoBT and/or EoT visits.

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 highest on-study and lowest on-study for systolic blood pressure and diastolic blood pressure will be presented. Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status values will also be produced.

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

Abnormal PE findings will be provided in a data listing.

## 5.5. ELECTROCARADIOGRAM (ECG)

Standard 12-lead ECGs will be performed. The ECGs performed on Day 1 of Cycles 1 and 2 during blinded study treatment are to be performed just prior to the blood sample taken 2 hours postdose (approximately at the expected $t_{max}$ of plasma selinexor). ECGs may also be performed as clinically indicated during the study.

Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The following will be assessed: heart rate, PR interval, QT interval, QRS interval, and QT corrected Bazett's or Fredericia's formula.

Changes from baseline to highest on-study post baseline measurement for PR interval, QRS interval, and QT corrected will be summarized using shift tables. For heart rate, changes from baseline to lowest and highest on-study post baseline measurement will be presented.

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

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# 7. APPENDICES

## 7.1. Appendix I: World Health Organization (WHO) Tumor Response Criteria

**Table 7-1 World Health Organization (WHO) Tumor Response Criteria**

(Adapted from Miller AB, et al., Reporting results of cancer treatment. Cancer. 1981;47:207-214.)

| Characteristic | Criteria |
|---|---|
| Tumor Burden | No maximal number of lesions specified.<br>No limitations specified per organ site |
| Measurability of lesions at baseline | 1. *Measurable, bidimensional* (product of LD and greatest perpendicular diameter)[a]<br>2. *Nonmeasurable/evaluable* (e.g., lymphangitic pulmonary metastases, abdominal masses) |
| Objective response | 1. *Measurable disease* (change in sum of products of LDs and greatest perpendicular diameters, no maximum number of lesions specified)<br>CR: disappearance of all known disease, confirmed at ≥ 4 wk<br>PR: ≥ 50% decrease from baseline, confirmed at ≥ 4 wk.<br>• Bidimensional: single lesion, greater than or equal to 50% decrease in tumor area (multiplication of longest diameter by the greatest perpendicular diameter); multiple lesions, a 50% decrease in the sum of the products of the perpendicular diameters of the multiple lesions.<br>• Unidimensional: greater than or equal to 50% decrease in linear tumor measurement.<br>• No new lesions or progression of any lesions.<br>PD: ≥ 25% increase of one or more lesions, or appearance new lesions<br>NC (SD): neither PR or PD criteria met<br>2. *Nonmeasurable disease*<br>CR: disappearance of all unknown disease, confirmed at ≥ 4 wk<br>PR: estimated decrease of 50%, confirmed at ≥ 4 wk<br>PD: ≥ 25% in existent lesions of appearance of new lesions<br>NC (SD): neither PR or PD criteria met<br>3. *Bone Metastases*<br>CR: Complete disappearance of all lesions on x-ray or scan for at least four weeks.<br>PR: Partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least four weeks.<br>PD: Increase in size of existent lesions or appearance of new lesions. |

| Characteristic | Criteria |
|---|---|
| | NC (SD): Because of the slow response of bone lesions, the designation of no change should not be applied until ≥ 8weeks have passed from start of therapy.<br>Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy. |
| Overall response | 1. Best response recorded in measurable disease<br>2. NC in nonmeasurable lesions will reduce a CR in measurable lesions to an overall PR<br>3. NC in nonmeasurable lesions will not reduce a PR in measurable lesions |
| Duration of response | 1. *CR*: From date CR criteria first met to date PD first noted.<br>2. *Overall Response*: From date of treatment start to date PD first noted.<br>3. In patients who only achieve a PR, only the period of overall response should be recorded |

LD = longest diameter; CR = complete response; PR = partial response; PD = progressive disease; NC = no change; SD = stable disease.

[a]Lesions that can be measured only unidimensionally are considered measurable (e.g., mediastinal adenopathy, malignant hepatomegaly).

## 7.2. Appendix II: RECIST Version 1.1

(Modified from Eisenhauer 2009)

All patients will have their BEST RESPONSE on study classified as outlined below:

**Complete Response (CR)**

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to < 10mm.

**Partial Response (PR)**

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Stable Disease (SD)**

Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

**Progressive Disease (PD)**

At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions will also constitute PD.

**Response Duration**

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded since the treatment started.

**Stable Disease Duration**

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

**Table 7-2-1 Evaluation of Best Overall Response – Patient with Target (+/- non-target) Disease**

| Target lesions | Non-Target lesions | New Lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR-Non-PD | No | PR |
| CR | NE | No | PR |

| Target lesions | Non-Target lesions | New Lesions | Overall response |
|---|---|---|---|
| PR | Non-PD/or not all evaluated | No | PR |
| SD | Non-PD/or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

**Table 7-2-2 Evaluation of Best Overall Response – Patient with Non-Target Disease Only**

| Non-Target lesions | New Lesions | Overall response |
|---|---|---|
| CR | No | CR |
| Non-CR-Non-PD | No | Non-CR/Non-PD[1] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

**Note:** Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

**Method of Measurement**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT (preferred) or MRI

CT (preferred) and MRI imaging might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be an adverse drug reaction of the treatment) and/or progressive disease.

Document Approvals

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