# STATISTICAL ANALYSIS PLAN

# PROTOCOL OPZ-003

Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Combination With Lenalidomide or Oral Cyclophosphamide in Patients with Newly Diagnosed Multiple Myeloma

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## LIST OF ABBREVIATIONS

| Abbreviation or Term | Definition |
|---|---|
| AE | adverse event |
| CRF | case report form |
| CBR | clinical benefit response |
| CR | complete response |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DOR | duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| MM | multiple myeloma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Mg | Milligram |
| MTD | maximum tolerated dose |
| N | number of subjects |
| ORR | overall response rate |
| PD | progressive disease |

| | |
|---|---|
| PDn | pharmacodynamic |
| PFS | progression-free survival |
| PK | Pharmacokinetic |
| PR | partial response |
| PT | MedDRA preferred term |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| sCR | stringent complete response |
| SD | stable disease |
| SOC | MedDRA system organ class |
| TEAEs | treatment emergent adverse events |
| TTP | time to progression |
| VGPR | very good partial response |

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# 1. INTRODUCTION

This statistical analysis plan (SAP) is prepared in accordance with OPZ-003 amendment 2, dated 15 October 2014. The dose expansion to the phase 2 of this study has been removed from the study design by internal decisions after the approval of 2nd amendment. Therefore the scope of this study and SAP is limited only to phase 1 data that was collected until the study closure. This document describes the analyses of data collected within the changed scope of the study. Any changes that are made to the planned analyses after the SAP is finalized, along with an explanation as to when and why they occurred, will be noted in the abbreviated clinical study report (aCSR) produced for the study. Any changes made to the planned analyses that are in the protocol will be identified and documented in this document.

# 2. STUDY OVERVIEW

## 2.1 Overall Study Design

This is an open-label, Phase 1b/2, two-combination regimen, non-randomized, multicenter study in which patients with newly diagnosed multiple myeloma (NDMM hereafter) will receive oprozomib tablets administered orally, in combination with lenalidomide and dexamethasone (ORd), or with cyclophosphamide and dexamethasone (OCyd). This trial will enroll patients with newly diagnosed, symptomatic multiple myeloma for whom a hematopoietic stem cell transplant is not planned or scheduled during the study, or are considered ineligible for hematopoietic stem cell transplant at the discretion of the investigator.

The ORd combination regimen treatment cycles are 28 days in duration. Subjects enrolled under the original protocol and Amendment 1 will receive oprozomib once daily on Days 1 through 5 and Days 15 through 19 (referred to as the 5/14 schedule). Subjects enrolled under Amendment 2 will receive oprozomib once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (referred to as the 2/7 schedule). All subjects on the ORd arm will receive lenalidomide at a dose of 25 mg will be given on Days 1 through 21 and dexamethasone at a dose of 20 mg will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle. The ORd combination will be administered until progression of disease, unacceptable toxicity, or for 24 cycles (approximately 24 months), whichever occurs first. Subjects who complete 24 cycles of treatment, and have stable disease or better, will continue on oprozomib, with or without dexamethasone premedication (4 mg/day) until progression of disease or unacceptable toxicity. Lenalidomide will be administered for a maximum of 24 cycles. Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.

The OCyd regimen treatment cycles are 28 days in duration. One (1) oprozomib dosing schedule (2/7) will be assessed during dose escalation. All study subjects will receive oprozomib administered orally, once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (referred to as the 2/7 schedule) in combination with oral cyclophosphamide at a dose of 300 mg/m$^2$ on Days 1, 8, and 15, and dexamethasone at a dose of 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles (see dose administration schema below). Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. The OCyd combination will be administered until progression of disease, unacceptable toxicity, or for 8 cycles (approximately 8 months), whichever occurs first. Subjects who complete 8 cycles of treatment and who have stable disease or better will continue on oprozomib, with dexamethasone premedication. Dexamethasone dosing, premedication and low-dose (e.g., 20 mg or 10 mg), should continue for a total of 24 cycles or until progression of disease or unacceptable toxicity. Subjects who complete 24 cycles of oprozomib therapy (total) without evidence of progression may continue therapy with or without dexamethasone, premedication or low-dose. A taper of dexamethasone after 24 cycles may be utilized per institutional guidelines. Cyclophosphamide will be administered for a maximum of 8 cycles.

During the Phase 1b portion of the study, a standard 3+3 dose-escalation scheme will be used. Assessment of dose-limiting toxicities (DLTs hereafter) will occur during the first 2 weeks of Cycle 1. Refer to the study protocol for the detail definition of DLT. Oprozomib doses will be escalated in sequential cohorts of 3 subjects with expansion to 6 subjects if a DLT is observed in one of the first 3 subjects. Dose escalation will proceed only after the safety and tolerability of the previous dose level has been assessed as acceptable by the Cohort Safety Review Committee (CSRC) comprised of Onyx's study medical monitor, Onyx's drug safety representative, and the investigators, or until a MTD has been determined.

Enrollment in the initial cohort for the ORd arm was entered at a daily dose level of 210 mg on the 5/14 schedule. Two DLTs (syncope) were observed in the first 3 subjects and the cohort dose was decreased by 1 dose level to 180 mg of oprozomib. The dosing cohort was de-escalated to 150 mg after 2 DLTs (abdominal pain and hypotension) in 6 DLT evaluable subjects were reported at the 180 mg dosing level. With the introduction of the ER Tablet with Amendment 2, there will be no further attempt at dose escalation in the 5/14 schedule with the tablet formulation.

The starting dose for subjects enrolled in the ORd and OCyd arms under Amendment 2 will be 210 mg on the 2/7 schedule. The dose of oprozomib for subsequent cohorts will be escalated or de-escalated by 30-mg increments until the MTD is established. The maximum dose to be tested has not been defined.

**Table 1. Dose-Escalation Scheme: Oprozomib Tablets in Combination with Lenalidomide and Dexamethasone (ORd) for 5/14 Dosing Schedule (Original Protocol and Amendment 1)**

| Cohorts | Oprozomib Daily Dose (mg)[a, b] | Lenalidomide Doses (mg) | Dexamethasone Doses (mg) |
|---|---|---|---|
| -102 | 150 | 25 | 20 |
| -101[c] | 180 | 25 | 20 |
| 101 | 210 | 25 | 20 |
| 102 | 240 | 25 | 20 |
| 103 | 270 | 25 | 20 |
| 104 | 300 | 25 | 20 |

[a] Subjects enrolled in the Phase 1b prior to the availability of Oprozomib ER Tablets, will initiate treatment with oprozomib tablets. These subjects may have their oprozomib tablets replaced with Oprozomib ER Tablets after they have completed the 1st cycle of ORd treatment and when the Oprozomib ER Tablets are available.

[b] Re-escalation of oprozomib dosing in the ORd arm may occur if significant differences in the pharmacokinetic profile of the extended and modified release formulations are observed. In this case, enrollment would start at 150 mg or the MTD established with the ER formulation and subsequent cohorts of 3-6 subjects enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) with the new formulation is defined.

[c] DLTs were observed in 2 subjects in the 101 cohort at a dose level of 210 mg, and in the -101 cohort at a dose level of 180 mg. Dosing will proceed at 150 mg as agreed with the Cohort Safety Review Committee (CSRC). The number of subjects may be expanded to include up to 6 evaluable subjects.

**Table 2. Dose-Escalation Scheme: Oprozomib Tablets in Combination with Lenalidomide and Dexamethasone (ORd) for 2/7 Dosing Schedule (Amendment 2)**

| Cohorts | Oprozomib Daily Dose (mg)[a,b] | Lenalidomide Doses (mg) | Dexamethasone Doses (mg) |
|---|---|---|---|
| -202 | 150 | 25 | 20 |
| -201[a] | 180 | 25 | 20 |
| 201[b] | 210 | 25 | 20 |
| 202 | 240 | 25 | 20 |
| 203 | 270 | 25 | 20 |
| 204 | 300 | 25 | 20 |
| 205 | 330 | 25 | 20 |
| 206 | 360 | 25 | 20 |

[a] If DLTs are observed in 2 or more subjects at the first dose level of 210 mg, dosing of Cohort -201 will proceed at 180 mg, or a lower dose as agreed with the Cohort Safety Review Committee (CSRC) and may be expanded to include up to 6 evaluable subjects.

[b] Cohorts of 3–6 subjects will continue to be enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) is defined.

**Table 3. Dose-Escalation Scheme: Oprozomib ER Tablets in Combination with Cyclophosphamide and Dexamethasone (OCyd) for the 2/7 Dosing Schedule (Amendment 2)**

| Cohorts | Oprozomib ER Tablets Daily Dose (mg) | Cyclophosphamide Doses (mg/m$^2$) | Dexamethasone Doses (mg) |
|---|---|---|---|
| -302 | 150 | 300 | 20 |
| -301[a] | 180 | 300 | 20 |
| 301[b] | 210 | 300 | 20 |
| 302 | 240 | 300 | 20 |
| 303 | 270 | 300 | 20 |
| 304 | 300 | 300 | 20 |
| 305 | 330 | 300 | 20 |

[a] If DLTs are observed in 2 or more subjects at the first dose level of 210 mg, dosing of Cohort -301 will proceed at 180 mg, or a lower dose as agreed with the Cohort Safety Review Committee (CSRC) and may be expanded to include up to 6 evaluable subjects.

[b] Cohorts of 3–6 subjects will continue to be enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) is defined.

## 2.2 Study Objectives

### 2.2.1 Primary Objective:

- To establish the MTD of oprozomib given in combination with lenalidomide and dexamethasone (ORd) or with cyclophosphamide and dexamethasone (OCyd).
- To evaluate the safety and tolerability of the ORd and OCyd combination regimens, as assessed by the type, incidence, severity and seriousness of AEs, and abnormalities in selected laboratory analytes.

### 2.2.2 Secondary Objectives:

- To evaluate population PK parameter estimates of oprozomib, and may include its metabolite(s), and the variability in these estimates
- To estimate the duration of response (DOR)
- To estimate progression-free survival (PFS)

## 2.3 Sample Size Justification

During the Phase 1b portion of the study, a standard 3+3 design will be used for dose escalation as described in Section 2.1. Up to 40 subjects will be enrolled for the ORd combination (16 subjects have been enrolled in 5/14 schedule by 2$^{nd}$ amendment, and up to 24 subjects expected in 2/7 schedule), and 24

subjects for the OCyd regimen. It is expected that 2-6 dosing cohorts of 3-6 subjects per cohort will be required to establish the MTD for each treatment regimen.

### 2.4 Changes to the current version of the Protocol (amendment 2)

The decision to remove the phase 2 portion of this study, which has not been implemented in an amendment to the current version of the protocol has impacted the data. The efficacy analysis planned for the Phase 2 will be performed on Phase1b subjects as exploratory analysis.

## 3. STUDY ENDPOINTS

### 3.1 Primary Endpoints

- Incidence, nature, and severity of AEs, SAEs, and DLTs (Phase 1b only) of oprozomib, given in combination with dexamethasone, and either lenalidomide or cyclophosphamide
- Changes from baseline in selected laboratory analytes, vital signs and ECG findings.

### 3.2 Secondary Endpoints

- Duration of response, defined as the time from the first evidence of PR or better to confirmed disease progression or death due to any cause
- PFS, defined as duration from the start of treatment to disease progression or death (due to any cause), whichever comes first
- Population-based PK parameters including, but not limited to clearance and volume of distribution

### 3.3 Exploratory Endpoints

- Overall Response Rate (ORR) defined as the rate of MM subjects who reached a BOR of sCR, CR, VGPR, or PR by schedule and cohort. Multiple myeloma response will be assessed according to International Myeloma Working Group (IMWG) Uniform Response criteria. (see appendix F of the protocol)

## 4. ANALYSIS POPULATIONS

### 4.1 Safety Population

The safety population, defined as all subjects who receive at least 1 dose of any study treatment, will be the primary population for all safety and efficacy analyses.

### 4.2 Dose Limiting Toxicities (DLT) Evaluable Population

The DLT evaluable population consists of the subjects who meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period:

- A minimum of 8 of 10 planned doses of oprozomib must be received for the 5/14 dosing schedule
- A minimum of 7 of 8 planned doses of oprozomib must be received for the 2/7 dosing schedule
- A minimum of 6 of 8 planned doses of dexamethasone must be received
- All 3 planned doses of cyclophosphamide must be received (OCyd regimen only)
- A minimum of 17 of 21 planned doses of lenalidomide must be received (ORd regimen only)

Subjects not meeting all of the above criteria, or who discontinue study treatment for any reason during Cycle 1 or assessed as DLT-unevaluable will be replaced. Subjects who do not meet the criteria above because of a DLT will be considered DLT-evaluable. The AEs flagged as DLTs will be listed for this population.

### 4.3 Efficacy- Evaluable Population

The efficacy-evaluable population is defined as all subjects in the safety population who have baseline response assessments and at least one post-baseline response assessment. Subjects who discontinued from the study treatments due to an AE before the first post-baseline response assessment are included in the efficacy-evaluable population if and only if the AEs are related to the study treatments as assessed by the investigator. This population will be considered for selected efficacy analyses.

All summaries will be presented by the assigned schedule and dose levels for all subjects.

## 5. ANALYTIC DEFINITIONS

Definitions of terms used to identify study day and baseline are provided in this section. Definitions of the efficacy variables are provided in Section 7.5.

### 5.1 Study Day 1

Study day 1 corresponds to the date of the first dose of any study drug.

### 5.2 Study Day

For events, assessments, and interventions after study day 1, study day represents the elapsed number of days from study day 1, inclusive:

Study Day n = (Date of assessment – Date of Study Day 1) + 1 day

Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to study day 1. Study day −1 will be the day before study day 1, and in general for assessments prior to study day 1, study day is defined as:

Study Day n = (Date of assessment – Date of Study Day 1)

For listings (such as for adverse events) that include the derivation of "days since last dose," this is defined as event date – date of last dose. Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

### 5.3 Baseline

The baseline value is defined as the last assessment prior to the first dose of study drug.

## 6. INTERIM ANALYSES AND EARLY STOPPING GUIDELINES

There are no formal interim analyses planned for this study. A Cohort Safety Review Committee (CSRC) will review the clinical and laboratory data of each dose cohort before escalating the oprozomib dose for the next dose cohort.

## 7. STATISTICAL METHODS

### 7.1 General Considerations

All statistical summaries and analyses will be performed in SAS® version 9.3or higher (SAS Institute Inc., Cary, NC, USA).

In general, summaries of all data will be presented by dose levels, defined as initial dose level cohort. Summary statistics will be provided for selected endpoints. For continuous variables, the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum will be presented. For discrete data, the frequency and percent distribution will be presented. Unless otherwise indicated, percentages will be calculated based upon the number of subjects in the Safety population in each dose group as the denominator. Graphical methods will be used, as appropriate, to illustrate study endpoints.

### 7.2 Disposition of Subjects

The following subject disposition information will be summarized for all subjects by each dose group defined in Section 7.1 and for the combined dose groups (labeled as total group).

- number of screened subjects
- number of subjects screened but not treated (screen failures)
- reason for screen failure

- number of treated subjects (Safety population)
- number (%) of subjects who discontinue from the study drug
- primary reason for study drug discontinuation

Violations of the inclusion and exclusion criteria in the protocol will be summarized by criterion for the safety population.

## 7.3 Demographic and Baseline Characteristics

### 7.3.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for the safety population.

- Sex
- Ethnicity
- Race
- Age (years) and age categorized (years) as <65, > =65, >=75
- Baseline ECOG performance status
- Baseline fertility status/ pregnancy test result
- Baseline weight (kg)
- Baseline height (cm)

### 7.3.2 Medical History

Subjects who experienced a prior disease or disorder will be provided in data listings.

### 7.3.3 Disease Characteristics

The following disease characteristics will be provided in data listings:

- Time (months) since initial diagnosis, defined as date of informed consent signed minus date of diagnosis
- Marker used to follow multiple myeloma
- Heavy chain and light chain status
- Plasma cell involvement (%) as assessed with bone marrow assessment (< 50%, ≥ 50%, unknown or missing)
- FISH (standard risk, high risk, unknown or not done)
    - High Risk: abnormal t(4:14), t(14:16), del(17p;13)
    - Standard Risk: None of the high risk finding.
- Baseline Beta-2 microglobulin mg/L (< 5.5 versus ≥ 5.5)
- ISS Stage at Initial Diagnosis

## 7.4 Treatments

### 7.4.1 Study Drug Administration

The overall extent of study treatment exposure and dose information will be summarized for the Safety population:

- Duration of treatment (weeks) for oprozomib, lenalidomide, cyclophosphamide, and dexamethasone defined as: (date of last dose – date of first dose + 1) / 7
- Number of treatment cycles started (at least one full daily dose ORd/ OCyd was administered)
- Number (%) of subjects dosed by cycle, where a subject will be considered to have been dosed in a cycle if at least one full daily dose of ORd or OCyd was administered
- Total doses received across all cycles of ORd/ OCyd
- Dose modifications of study drug based on AE action taken data

## 7.5 Efficacy Analyses

Disease and best overall response assessment collected at the end of treatment (end of study visit) as determined by the investigator will be used for these analyses.

### 7.5.1 Overall Response Rate (ORR)

The overall response rate (ORR) is defined as proportion of subjects for whom the best overall confirmed response is stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR), as defined by International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Appendix F). The frequency distribution will be provided for the best overall response. 95% Exact binomial confidence intervals will be presented for the estimated ORR for each cohort.

### 7.5.2 Progression Free Survival (PFS)

Progression free survival (PFS) is defined as number of months (one month = 30.4 days) between start of treatment and first evidence of documented disease progression or death (due to any cause), whichever occurs first. Disease progression will be determined using IMWG-URC and will be determined by the investigator: PFS = (Earliest date of disease progression, death, or censoring – Date of first dose + 1)/ 30.4

The duration of PFS will be right–censored for subjects who meet 1 of the following conditions: 1) starting a new anticancer therapy before documentation of disease progression or death; 2) death or disease progression immediately after more than 1 consecutively missed disease assessment visit or; 3)

alive without documentation of disease progression before the data cutoff date. For such subjects, the analysis of PFS will be right–censored according to the conventions described in Table 4.

**Table 4: Date of Progression or Censoring for Progression-Free Survival**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline disease assessments | Date of first study drug | Censored |
| New anticancer treatment started before documentation of PD or death | Date of last disease assessment prior to start of a new anticancer treatment | Censored |
| Death or PD immediately after more than 1 consecutively missed disease assessment visits | Date of last disease assessment visit without documentation of PD that is before the first missed visit | Censored |
| Alive and without PD documentation | Date of last disease assessment | Censored |
| Death or PD between planned disease assessments | Date of death or first disease assessment showing PD, whichever occurs first | Progressed |
| Death before first disease assessment | Date of death | Progressed |

PD = progressive disease.

The data listings will include the status of the PFS event (censored or not), the type of PFS event (progression, death), and the PFS duration. Due to small sample size, no summary statistics will be generated for PFS.

### 7.5.3 Duration of Response (DOR)

Duration of response (DOR) will be calculated for responders who are the subjects who achieve a best overall response of sCR, CR, nCR, VGPR, or PR. For such subjects, the duration of overall response is defined as the time from first evidence of PR or better to disease progression, death due to any cause, or censoring date: DOR = (Earliest date of disease progression, death, or censoring - Date of confirmed PR or better + 1) /30.4.

Duration of response will be right–censored according to the censoring conventions defined previously for PFS in Table 4.

The data listings will include the Best overall response (PR or better), the type of PFS event (progression, death), the Duration of response. Due to small sample size, no summary statistics will be generated for DOR.

## 7.6 Safety Analysis

The analysis of all safety endpoints will be based on the Safety Population.

### 7.6.1 Adverse Events

Each reported AE term will be mapped to a preferred term (PT) and a system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA version 19.0).

Treatment emergent adverse events (TEAEs) are defined as AEs that start on or after the first day of any study treatment and within 30 days of the last day of any study treatment. An AE that is present before the first administration of study treatment and subsequently worsens in severity during treatment is also considered to be treatment emergent.

Adverse events will be summarized based on the number (%) of subjects experiencing events by MedDRA system organ class and preferred term. The denominator for the percentage will be based on the number of subjects at in the Safety population.

A subject reporting the same AE more than once will be counted only once when calculating 1) within a given system organ class, and 2) within a given system organ class and preferred term combination. For such cases, the maximum National Cancer Institute (NCI; US) - Common Terminology Criteria for Adverse Events toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. AEs will also be summarized by severity and by relationship to study drug.

An overall summary of treatment emergent adverse events will summarize the number (%) of subjects with

- with at least one TEAE
- with at least one treatment-related TEAE
- with at least one grade 3 or higher TEAE
- with at least one treatment-related grade 3 or higher TEAE
- with at least one serious AE
- with TEAE leading to discontinuation of study drug
- with treatment related TEAE leading to discontinuation of study drug
- death within 30 days of last dose of study drug

Summaries of TEAEs will also be provided by

- SOC and PT

DLTs will be summarized by each dose group and for the combined dose groups.

All AEs, including treatment emergent events, will be included in listings by patient.

Listings of AEs determined to be DLTs during the first cycle of Phase 1, serious AEs, and AEs leading to discontinuation of study drug will be provided.

### 7.6.2 Laboratory Data

All available laboratory results will be included in the patient listings. Selected laboratory test results will be assigned toxicity grades using CTCAE 4.03 and their change from baseline will be presented. The analytes of interest are:

- Hematology: Hemoglobin, Plateles, WBC, Neutrophils (absolute), Lymphocytes (absolute);
- Serum Chemistry: ALT, AST, Total Bilirubin, BUN, Calcium, Albumin, Creatinine, Sodium, Potassium

### 7.6.3 Vital Signs

Vital sign results including blood pressure, pulse, and temperature will be listed without summary.

### 7.6.4 Additional Evaluations

ECOG performance status at the end of treatment will be listed without summary. Pregnancy results at Day 1 of each cycle and the end of treatment will be listed without summary.

An Analysis Dataset for Pharmacokinetic (PK) Concentrations (ADPC) will be provided to Clinical Pharmacology Modeling and Simulation (CPMS) from Biostatistics. Plasma concentrations for pharmacokinetics will be summarized in tabular/graphical format by time point and treatment group in a separate report by CPMS. Pharmacokinetic data from this study may be pooled with data from other oprozomib studies for PK analyses, for which results would be reported separately and provided by the CPMS group.

### 7.6.5 Prior and Concomitant Medications

All prior and concomitant medications will be coded using WHO Drug Dictionary. Concomitant medications are defined as medications with start date or end date on or after the date of first dose of any study treatment and before the date of the last dose + 30 days of any study treatment, or are ongoing at the time of first dose. Prior medications are defined as medications with a stop date before the date of first dose of any study treatment.

Concomitant medications and prior medications will be listed without summary.

## 7.7 Protocol Deviations

Protocol deviations will be included in the subject data listings. Major protocol deviations will be either captured on the designated eCRF (e.g., eligibility violations) or identified through data review and surveillance.

# 8. STATISTICAL / ANALYTICAL ISSUES

## 8.1 Handling of Dropouts or Missing Data

The algorithm for imputation of partial dates for concomitant and prior medications is described in Section 7.6.5. Missing data will not be estimated or carried forward for any of the other summaries.

## 8.2 Interim Analysis and Data Monitoring

During the Phase 1b portion of the study, the CSRC will review the clinical data of each dose cohort after three subjects have been treated for at least one cycle during phase 1 of the study. Based on the number of subjects with dose-limiting toxicity, escalation to the next higher oprozomib dose may occur, the cohort may be expanded to six subjects, or dosing at that dose level may stop and the next-lower dose cohort may be expanded. The committee must agree that dose escalation to the next cohort is appropriate before it proceeds. The CSRC will be comprised of Onyx's medical monitor, Onyx's drug safety representative, and the principal investigators.

## 8.3 Multiple Comparison/Multiplicity

No inferential analyses will be performed to compare dose cohorts. Adjustment for multiplicity is not a relevant issue for this study.

## 8.4 Imputation of Dates

For the calculation of years since diagnosis, if only the month and year of diagnosis are provided, then the day will be imputed as the 15$^{th}$ of the month. If only the year of diagnosis is provided, then the day and month of diagnosis will be imputed as January 1.

For the purpose of determining if a medication should be noted as a concomitant medication, start dates with missing day of the month will be completed by imputing the missing day of the month as the 1$^{st}$ day of that month and start dates with missing month will be completed by imputing the missing month as January. End dates with missing day of the month will be completed by imputing the missing day of the month as the 30$^{th}$ day of that month (28$^{th}$ for February) and end dates with missing month will be completed by imputing the missing month as December. Imputed dates for prior and concomitant medications will not be presented in the listings.

If the partial AE onset date information does not indicate whether the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent.

If the start day of subsequent anti-cancer therapy is missing, it will be assumed to be the first day of the month.