

Clinical Development

LBH589 / Panobinostat / Farydak®

CLBH589DUS106 / NCT02720510

A Randomized, Phase II trial evaluating the efficacy and safety of lenalidomide, bortezomib and dexamethasone (RVD) with or without panobinostat in transplant eligible, newly diagnosed Multiple Myeloma

Statistical Analysis Plan (SAP) – Short Closeout CSR deliverables

Author:



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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ASCT	Autologous Stem Cell Transplant
ATC	Anatomical Therapeutic Classification
Bid	bis in diem/twice a day
BSA	Body Surface Area
BTZ	Bortezomib
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
DAR	Dose Administration Record
Dex	Dexamethasone
DI	Dose Intensity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DRP	Data Review Plan
EBMT	European Group for Blood and Bone Marrow Transplant
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
iCR	Immunophenotypic Complete Response
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IVR	Interactive Voice Response
IWR	Interactive Web Response
mCR	Molecular Complete Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MM	Multiple Myeloma
MR	Minimal Response
MRD	Minimal Residual Disease
No Change	No Change
NCI	National Cancer Institute
nCR	Near Complete Response
o.d.	Once Daily
ORR	Overall Response Rate

OS	Overall Survival
PAN	Panobinostat
p.o.	per os/by mouth/orally
PD	Progressive Disease
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-reported Outcomes
PS	Performance Status
PT	Preferred Term
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDI	Relative Dose Intensity
REV	Revlimid
RVD	Revlimid, Velcade, Dexamethasone
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SD	Stable Disease
SEC	Special Event Category
SOC	System Organ Class
SS	Safety Set
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
VAP	Validation and Analysis Plan
VGPR	Very Good Partial Response
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods which will be used in the phase II clinical trial of the clinical study protocol (CSP) CLBH589DUS106. This statistical analysis plan (SAP) module is prepared based on Original CSP, Case Report Form (CRF) version 324. Mock tables and listing mocks are included in TLF shells. This SAP aims to provide information and details around the analysis to be performed for the short closeout CSR for the study.

In data presented at ASH 2015, the combination of RVD and panobinostat in newly diagnosed Multiple Myeloma (MM) patients showed an Objective response rate (ORR) of 94%, with a 46% CR/nCR rate after 4 cycles. This marked improvement from historical data reporting CR/nCR rates of approximately 7% warrants further investigation of this combination in this population.

Data will be analyzed by statistical software SAS® version 9.4 according to the data analysis section 10 of the CSP which is available in Appendix 16.1.1 of the Clinical Study Report (CSR). Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

The study has been terminated for further enrollment. The decision to terminate the study is not related to study efficacy or safety. However, it is because of availability of multiple drugs and their valuable treatment options in the market, for the treatment of multiple myeloma. Hence only a short closeout CSR will be published for currently enrolled patients. The SAP will cover the details only around the analysis to be performed for the short closeout CSR. All analyses as per the protocol will not be within the scope of this short closeout CSR. The modules to be included in this short closeout CSR will be demographic characteristics, disposition, exposure and key safety data for AEs.

1.1 Study design

This is a multicenter, open-label, randomized phase II study which will enroll 112 newly diagnosed symptomatic multiple myeloma patients in a 1:1 fashion. There will be no stratification done while randomization. Patients will be enrolled at approximately 20 centers in the United States. The dosing information is as follows:

After completing 4 cycles of induction, all patients will undergo stem cell mobilization with G-CSF and plerixafor as per institutional protocol for this mobilization regimen. Study treatment interruption for stem cell collection may not exceed 30 days. All patients will receive one additional cycle of study treatment after stem cell collection and then proceed to autologous transplant using melphalan 200mg/m² (140mg/m² for patients > 70), as conditioning. All patients must initiate transplant within 28 days of the completion of cycle 5.

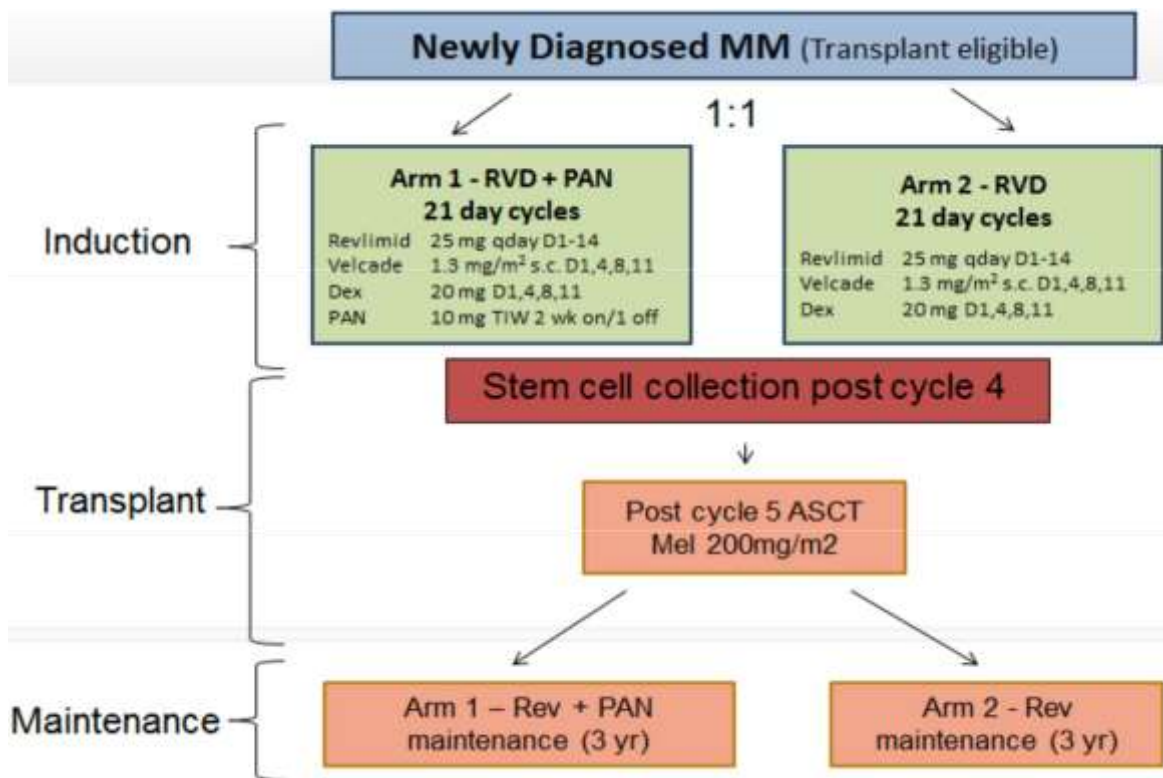
After Autologous Stem Cell Transplant (ASCT), patients still on study will initiate maintenance therapy within the 60-120 day period following ASCT, provided they have adequate blood count and clinical recovery. Criteria for starting a patient on maintenance therapy are as follows:

- The ANC is $\geq 1,000/\mu\text{L}$;
- The platelet count is $\geq 75,000/\mu\text{L}$
- Adequate organ function as detailed in inclusion criteria (Section 5.2 of the CSP)

Patients in the RVD arm will initiate maintenance therapy with lenalidomide alone, and patients in RVD-panobinostat arm will receive lenalidomide + panobinostat maintenance. Lenalidomide will be dosed orally at 10mg/day continuously in both arms. After the first 84 day cycle, the dose of lenalidomide should increase to 15mg/day. Panobinostat will be dosed at 10mg three times a week, every other week. Total planned duration of maintenance therapy will be 3 years.

Patients will remain on study treatment until they complete the maintenance phase, or until they experience disease progression, unacceptable toxicity, or at the discretion of the Investigator.

Figure 1-1 Study Design



1.1.1 Timing of interim analyses and design adaptations

Not Applicable

1.1.2 Definition of end of the study

Not Applicable

1.1.3 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible to perform an end of treatment visit. Patients in survival follow-up should be contacted for a final survival visit for Study Evaluation Completion assessments. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Board (IRB) and/or Ethics Committee (EC) of the early termination of the trial.

The study design and other plans were for the initially planned study. However since the trial is terminated, patients have been switched to follow up phase directly after induction phase.

1.2 Study objectives and endpoints

Table 1-1 Table for study objectives and related endpoints

Objectives	Endpoints
<u>Primary:</u> To evaluate the efficacy of the combination of RVD + panobinostat compared to RVD alone	<u>Primary:</u> nCR/CR rate of the combination of panobinostat with bortezomib, lenalidomide and dexamethasone (P-RVD) vs RVD in newly diagnosed multiple myeloma patients after 4 cycles of therapy
<u>Key Secondary:</u> To assess MRD negativity (mCR) after 4 cycles of induction by Next Gen Sequencing	<u>Key Secondary:</u> MRD negativity by ClonoSEQ™ assay (Adaptive Biotechnologies)
<u>Other Secondary:</u> <ul style="list-style-type: none">• To assess best overall response rate (ORR) and MRD negativity after ASCT and maintenance• To assess depth of response by IMWG criteria• To assess the duration of response• To assess overall survival and progression free survival at three years• To assess the toxicity and tolerability	<u>Other Secondary:</u> <ul style="list-style-type: none">• ORR (CR + PR) and MRD negativity after ASCT and maintenance• Rate of VGPR, CR and sCR• Duration of response• Overall survival and progression free survival at three years• Rates of AEs and SAEs

These were the objectives and related endpoints for the initially planned study. However, since the trial is terminated and only a short closeout CSR is to be published, these objectives and endpoints will not be assessed any more. Only key safety endpoints will be assessed and reported as stated in below sections.

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis and/or the designated Contract Research Organization (CRO), according to the data analysis section of the CSP. All statistical analyses will be performed using SAS® Version 9.4.

The planned statistical analysis is described in Section 10 of the protocol (Appendix 16.1.9 of the CSR). Data from all participating centers will be combined so that an adequate number of patients are available for analysis.

The CSR will be updated with key safety data from patients in the study.

Analysis visit windows will not be applied to the data analysis to handle unscheduled measurements unless otherwise specified.

For descriptive summaries, categorical data will be presented as frequencies and percentages, and continuous data as mean, standard deviation, median, 25th and 75th percentile, minimum, and maximum.

Unless otherwise specified, all statistical tests will be performed at a two-sided significance level of 0.05 and confidence intervals will be calculated with 95% confidence.

2.1.1 General definitions

2.1.1.1 Study drug and study treatment

The terms “investigational study drug(s)” or “study drug(s)” or “study treatment component(s)” will refer to:

- Oral panobinostat (also known as LBH589 or Farydak® or PAN) Capsules
- Sub-cutaneous bortezomib (also known as BTZ or Velcade®) Injection
- Oral revlimid (also known as REV or Revlimid®) Capsules
- Oral dexamethasone (also known as Dex) Tablets

“Study treatment” refers to the combination of PAN, BTZ, REV and Dex or BTZ, REV and Dex, depending on treatment assignment.

2.1.1.2 Date of first administration of study drug/study treatment component

The date of first administration of study drug/study treatment component is derived as the first date when a non-zero dose of study drug was administered and recorded on the dose administration record (DAR) CRF. For the sake of simplicity, the date of first administration of study drug will also be referred as start of study drug.

2.1.1.3 Date of last administration of study drug/study treatment component

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug/study treatment component was administered and recorded on the DAR CRF.

2.1.1.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered and recorded on the DAR CRF. For example, if the 1st dose of study drug A is administered on 04JAN2010, and the 1st dose of its combination partner, drug B, is administered on 03JAN2010, the date of the first administration of study treatment is on 03JAN2010. For the sake of simplicity, the date of the first administration of study treatment will also be referred as the start of study treatment.

2.1.1.5 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered and recorded on the DAR CRF. For example, if the last dose of study drug A is administered on 15APR2010, and the last dose of a combination partner, drug B, is administered on 17MAY2010, the date of last administration of study treatment is then on 17MAY2010.

2.1.1.6 Baseline

Baseline is the result of an investigation describing the “true” uninfluenced state of the subject. The last available assessment before the day of study treatment administration, or any measurement at the day of study treatment administration, definitely taken before study treatment administration, should be taken as the “baseline” assessment.

General guidance for baseline definition:

Dependent on the variable, the baseline assessment will be done at screening (Day -21 to 1) or baseline (Cycle 1 Day 1 [C1D1]). Some assessments might be performed on both screening and C1D1. For such instances, C1D1 will be considered as baseline, provided the assessment has happened before the study drug administration.

Baseline assessments should be obtained before the first study treatment intake based on the variables. Any assessment which is obtained outside of the protocol-defined screening period will not be considered for baseline unless otherwise specified.

2.2 Analysis sets

The following analysis sets will be used in the analyses:

Full Analysis Set: The Full Analysis Set (FAS) comprises of all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment (and strata, if applicable) they have been assigned to during the randomization procedure.

Safety Set: The Safety Set (SS) includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment (regimen) they actually received, i.e. if a patient was randomized to RVD+PAN treatment arm but mistakenly received RVD arm only, then the patient will be counted in the RVD arm for all analysis pertaining to safety set.

Per-Protocol Set: The Per-Protocol Set (PPS) consists of all patients from the FAS population who received at least one dose of the study drug and had no major protocol deviation. Protocol deviations leading to exclusion from the PPS will be justified and specified in the study Appendix 1 of Data Review Plan (DRP) and documents prior to the data base lock.

2.2.1 Subgroup of interest

Not Applicable.

3 General Strategies for Data Presentation

All categorical data will be summarized by frequencies and percentages. Wherever categorical data is missing, a 'Missing' row will be included at the bottom with frequencies and percentages presented for it.

Continuous data will be summarized with either standard descriptive statistics (i.e. the number of non-missing data points, arithmetic mean, standard deviation, minimum, median, 25th and 75th percentile and maximum), or will be collapsed into categorical data and summarized as categorical data.

3.1 Patient disposition, demographics and other baseline characteristics

3.1.1 Patient disposition

3.1.1.1 Study discontinuation

A complete account of patients randomized, treated and not treated will be provided, by number and % of patients for the FAS. The number and percentage of patients who complete study, and those who prematurely discontinue from the study will be summarized together with reasons for premature study discontinuation.

The possible reasons for discontinuation of study are as follows:

- Death

- Lost to follow up
- Study terminated by the sponsor
- Subject/Guardian withdrew consent
- Physician decision

A listing for data on final status of the patient in the study will be provided. A data listing of screened patients who did not take study drug will be also provided with reasons for screening failure.

3.1.2 Demographic and baseline characteristics variables

Demographic and baseline characteristics data will be summarized using the FAS. All demographic and background data will also be listed.

The following variables will be summarized by treatment group:

- Age (years)
- Age category
 - <65 years
 - ≥65 years
 - missing
- Sex
 - Male
 - Female
 - missing
- Race
 - Caucasian
 - Black
 - Asian
 - Native American
 - Pacific Islander
 - Other
 - missing
- Ethnicity
 - Hispanic/latino
 - Chinese
 - Indian (Indian subcontinent)
 - Japanese
 - Mixed ethnicity
 - Other
 - missing
- Child bearing potential for female patients
 - Able to bear children
 - Premenarche

- Post menopausal
- Sterile-of child bearing age
- Eastern Cooperative Oncology Group - Performance Status (ECOG PS)
 - 0 - Fully active, able to carry on all pre-disease performance without restriction
 - 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
 - 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
 - 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
 - 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
 - Missing
- Body weight (kg)
- Body height (cm)
- Respiratory rate (per min)
- Body surface area (BSA) (m²)
- Body mass index (BMI) (kg/m²)

3.2 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

3.2.1 Study treatment / compliance

The duration of exposure (in weeks) of each of the overall study treatment will be summarized using the SS.

Listings of all doses of the study treatment along with dose change reasons will be produced.

3.2.1.1 Duration of exposure to study treatment/study treatment component

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the RVD and Panobinostat:

$$\text{Duration of exposure to study treatment (days)} = (\text{latest of last dates of exposure to study treatment}) - (\text{date of first administration of study treatment}) + 1.$$

Duration of exposure will be divided into following categories:

- <3 weeks
- ≥3 - <6 weeks
- ≥6 - <12 weeks
- ≥12 - <24 weeks

- ≥ 24 - < 48 weeks
- ≥ 48 weeks

The date of last administration of study treatment (treatment component) is taken from CRF treatment completion page 'last dose date'.

Thus, duration of exposure will be calculated for study treatment as a whole. Summary of duration of exposure of study treatment will include continuous summaries using appropriate units of time.

The duration includes the periods of temporary interruption (of any component of the study treatment for any reason). 'Date of last administration of study treatment/ study treatment component' and 'date of first administration of study treatment/ study treatment component' is defined in Section 2.1.1.

For patients who did not take any study treatment the duration of exposure is defined as zero. If duration is calculated in months, the duration in days will be divided by 30.4375.

3.2.1.2 Study day

For the study day calculation, if the event or assessment date is after the treatment start date, the study day will be calculated as:

The date of the assessment / event - start date of study treatment + 1 day.

For any assessment or events that happened prior to the treatment start date, e.g., time since diagnosis of disease, the study days (in negative) will be calculated as:

The date of the assessment / event - start date of study treatment.

Note that the day of first dose of study treatment is Day 1 and the day before the date of first study treatment is Day - 1, not Day 0.

3.3 Efficacy Evaluations

3.3.1 Disease assessment

Not Applicable

3.4 Analysis of the primary objective

The primary objective for this trial is to evaluate the efficacy of the combination of RVD + panobinostat compared to RVD alone.

As stated earlier, the primary objectives and related endpoints for the initially planned study are no longer being assessed. Since the trial is terminated, only a short closeout CSR is to be published. Hence, all the analysis, as mentioned in protocol, will not be performed. Only key safety endpoints will be assessed and reported, and data listings will be provided as appropriate.

3.4.1 Primary endpoint

The primary endpoint is based on nCR/CR rate of the combination of panobinostat with bortezomib, lenalidomide and dexamethasone (P-RVD) vs RVD in newly diagnosed multiple myeloma patients after 4 cycles of therapy.

For purpose of short closeout CSR, data for the responses of patients based on Investigator provided responses, will be listed. The primary endpoint will not be analyzed/summarized.

3.4.2 Statistical hypothesis, model, and method of analysis

The response data will not be analyzed.

3.4.3 Handling of missing values/censoring/discontinuations

Not Applicable

3.4.4 Supportive analyses

Not Applicable

3.5 Analysis of the key secondary objective

The key secondary objective for the study is to assess the MRD negativity (mCR) after 4 cycles of induction by Next Gen Sequencing.

As stated earlier, the secondary objectives and related endpoints for the initially planned study are no longer being assessed.

3.5.1 Key secondary endpoint

The key secondary endpoint was to assess MRD negativity after 4 cycles of induction by Next Gen Sequencing.

3.5.2 Statistical hypothesis, model, and method of analysis

The MRD data will not be analyzed.

3.5.3 Handling of missing values/censoring/discontinuations

Not Applicable

3.6 Analysis of secondary efficacy objective(s)

The secondary objectives for the study are:

- To assess overall response rate (ORR) and MRD negativity after ASCT and maintenance. ORR will be assessed based on Investigator's assessed responses for both IMWG and EBMT criteria.
- To assess depth of response by IMWG and EBMT criteria based on Investigator's assessed responses
- To assess the duration of response by IMWG and EBMT criteria based on Investigator's assessed responses

- To assess overall survival and progression free survival three years after the study by IMWG and EBMT criteria based on Investigator's assessed responses
- To assess the toxicity and tolerability

Out of the above stated secondary endpoints, only toxicity and tolerability will be assessed based on the AE and SAE assessments.

3.6.1 Secondary endpoints

The secondary end points for the study is to assess AEs and SAEs to check the toxicity and tolerability of the study treatment. Please refer to the Section 3.7 for Safety analysis details.

3.6.2 Handling of missing values/censoring/discontinuations

Not Applicable

3.7 Safety analyses

For all safety analyses, the SS will be used. All listings and tables will be presented by study treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 30+1 after last dose of study medication.

3.7.1 Adverse events (AEs)

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the Study Evaluation Completion page. Adverse events will be coded using the most recent version of the medical dictionary for regulatory activities (MedDRA) available at the time of each analysis.

The AEs experienced by the patients in all the observation periods will be listed. The AEs reported in pre-treatment and post-treatment period will be flagged in the listing. In an AE listing, details will be provided for severity grade of AE, seriousness of AE, its relationship to study treatment, its duration, action taken, outcome, and whether medication or therapy was given to patient.

Treatment Emergent Adverse Events (TEAEs) are defined as events, which start in on-treatment period, or which start in pre-treatment period but worsen in on-treatment period. Summary tables for all TEAEs will be provided by study treatment group.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. The tables will be summarized alphabetically by SOC and in decreasing frequency of PTs. The decreasing order of PTs will be based on the total count.

AE overview table will be provided with information on number and percentage of patients having any AE, any SAE, any Severe AE, any AE leading to discontinuation of study drug, any fatal AE and deaths due to any cause.

AEs will be presented by SOC-PTs-Severity, regardless of its relationship to study drug. AEs having relationship to study drug will be presented by SOC-PTs-Severity. SAEs will be presented by SOC-PTs-Severity, regardless of its relationship to study drug. AEs leading to discontinuation will be presented by SOC-PTs-Severity, regardless of its relationship to study drug. Non Serious AEs will be presented by SOC-PTs, regardless of its relationship to study drug.

3.7.1.1 Adverse events of special interest / grouping of AEs

Specific safety event categories (SEC) may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, AEs will be listed as per SEC and number and percentage of patients with at least one event part of the SEC will be provided.

The following is the list of SECs, also referred to as AEs of special interest.

- Diarrhea
- Fatigue
- Cardiac events
 - Ischemic event
 - Severe arrhythmia [QT prolongation, T-wave changes, ST-T segment changes, ventricular tachycardia, torsade des pointes, severe bradycardia]

3.7.2 Deaths

Separate summaries for on-treatment and all deaths (on-treatment and post-treatment) will be produced by study treatment group, SOC and PT. All deaths will be listed and post treatment deaths will be flagged.

3.7.3 Laboratory data

Not Applicable

3.7.4 Other safety data

3.7.4.1 ECG and cardiac imaging data

3.7.4.1.1 ECG data

Not Applicable

3.7.4.1.2 Cardiac Imaging Data

Not Applicable

3.7.4.2 Vital signs

Not Applicable

3.7.4.3 Pregnancy Test

Not Applicable

3.8 Pharmacokinetic endpoints

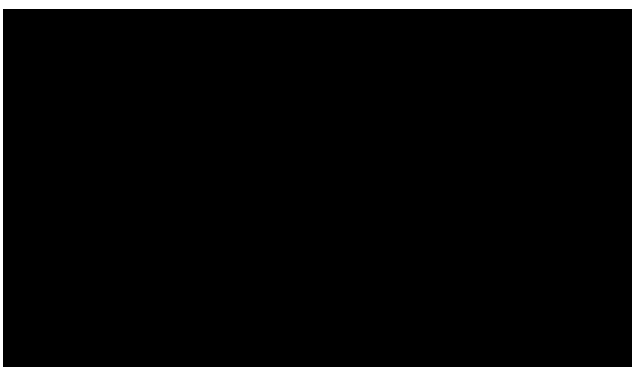
Not Applicable

3.9 PD and PK/PD analyses

Not Applicable

3.10 Patient-reported outcomes

Not Applicable



3.13 Interim analysis

Not Applicable

4 Sample size calculation

The sample size of the study is based on the assumption that in the RVD alone arm the nCR/CR rate will be 7% and adding Pano to RVD will improve the nCR/CR rate to 25%. For one sided $\alpha=0.05$, fifty patients in each arm will have 81% power to detect this

improvement. To get 50 evaluable patients in each arm an additional 6 patients will be randomized in each arm for a total of 112 patients.

PASS 2008 was used to calculate the sample sizes.

As mentioned earlier, the trial is terminated for further enrollment. There is only 7 patients' data available, before the closeout of the study.

5 Change to protocol specified analyses

Not applicable.

6 Appendix

6.1 Imputation rules

Where a date is recorded as a partial date, the missing day will be imputed as follows:

Start date: The day will be imputed by the 15th of the month. If day and month are missing day and month will be imputed by July 1st of the year. If there is a record indicating that the dose record started earlier, the start date will be imputed by the end date of the previous record + 1 day. In case the imputed start date is later than the complete end date, the record will not be considered for analysis.

End date: The day will be imputed by the 15th of the month, and if day and month are missing then by July 1st of the year. If there is a record indicating that this started later, the end date will be imputed by the start date of the next record - 1 day. In case the imputed end date is earlier than the complete start date, the record will not be considered for analysis.

For dates known to be within the trial period, the last known contact date will be used if this imputation makes the date later than the last known contact date but within the trial completion date. If the imputed date is earlier than the first medication date, the first medication date will be used.

6.1.1 Study drug

In the calculation of treatment exposure duration, if a dosing record has either a missing end date (for the last record for that treatment component) or an end date after the cut-off date, the cut-off date will be used as the end date. Such imputed data will be flagged in the listings.

The protocol allows for continuous dosing record entry with start dates and end dates for all compounds of study treatment. A separate dosing record should be entered whenever there is a change in the dosing which can be due to dose change, delay or missed doses. If the start date and end date is on the same date then that DAR record will be called single dose DAR record.

6.1.2 AE date imputation

For incomplete AE start dates, the date of treatment start will be used in case the imputation reveals in a date before the start of treatment. For the calculation of duration, the formula (end date – start date + 1 day) is used. If, as it might occur in AE pages, the end date is complete

and the start date is partial, the above rule is applied as long as the start date is not later than the end date; otherwise the start and end date are the same.

6.2 AEs coding/grading

Adverse events will be coded using the MedDRA version 18.1 or higher.

AEs will be assessed according to the CTCAE version 4.03.

6.3 Laboratory parameters derivations

Not Applicable

6.4 Statistical models

Not Applicable

6.5 Rule of exclusion criteria of analysis sets

Not Applicable

7 Reference

Paul G. Richardson,corresponding author1 Wanling Xie et al. (2014) A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma