NOVARTIS

Clinical Development

Panobinostat (LBH589)

Clinical Trial Protocol CLBH589D1201 / NCT02290431

A phase II, multi-center, single arm, open label study to evaluate the efficacy and safety of panobinostat in combination with bortezomib and dexamethasone in Japanese patients with relapsed/refractory multiple myeloma

RAP Module 3 – Detailed Statistical Methodology

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Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
Final 1.0	3-Apr-2015	
Amendment 1	17-Jul-2015	-Reflected protocol amendment 1 (Section 1.1) Added information regarding interim analysis. In the review process of panobinostat submission for indication of relapsed or refractory MM in Japan, [redacted] requested sponsor to conduct additional interim report to present the key efficacy and safety information in public per approximately 6 months basis. (Section 1.5.2, 1.11, 2.14.4, 3.1, 4.7.1) Deleted a sentence regarding 90% confidence interval. -Added clarifications (Section 4.1.3, Section 4.7.5.3) Clarified analysis plan for light chain Myeloma. (Section 4.8.7) Deleted qualitative ECG abnormalities analyses since these data are found as not collected. (Section 4.10) AUCinf, CL/F and Vz/F were added as PK parameters for BTZ.
Amendment 2	24-Feb-2016	- Changed Trial statistician's name. - Deleted the description of derivation of MM characteristics since the data is taken from CRF directly: added field to CRF.
Amendment 3	27-Jul-2016	- Added the category of number of patients who entered the survival follow-up phase into Section 4.4 Patient disposition. - Corrected eCRF page name. (Section 4.4, Section 4.8.1) - Corrected the description of last administration date.
Amendment 4	24-Jul-2017	- Definition of per protocol set (PP set) was added in section 1.2: Subjects and treatments to align with section 2.12: Definitions of analysis sets. - Primary analysis by the PP set was added into sensitivity analysis. (Section 1.5.4) - The instruction on eCRF page was deleted. (Section 2.15.2) - Safety follow-up period was corrected to 30 days. (Section 4.6) - Causality definitions for study drug and study treatment were clarified. Some summary tables for AE, SAE and CNAE were added and updated. (Section 4.8.1, 4.8.2 and 4.8.3) - AE analysis for clinical trial safety disclosure was added. (Section 4.8.4) - Heart rate was corrected to Pulse rate according to eCRF. (Section 4.8.6) - Drug-induced liver injury was added as part of safety assessments. (Section 4.8.9) - The description was corrected according to the study design. (Section 4.10)
Amendment 5	19-Nov-2018	- Statistical and analytical plan was updated. (Section 1.1)

Version	Date	Changes
		- Definition for pharmacokinetic analysis set was described in detail. (Section 1.2.4 and 2.12.4) and updated correctly (Section 1.10) - Primary endpoint was clarified and corrected. 95% exact C.I. was added as exploratory analysis. (Section 1.5.1) - Sensitivity analyses based on planned patients was added (Section 1.5.3) - Detailed description was added to original plan. (Section 1.6.1, 1.6.2, 4.7.2 and 4.7.3) - Unnecessary analysis plan for D1201 study was deleted and inappropriate plan was updated appropriately. (Section 1.3,1.6.2, 1.7, 1.8, 1.9, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7.4, 4.7.5, 4.8.2, 4.8.3, 4.8.5, 4.9 and appendix 3) - Name (CNAE and M8) was updated as per latest name. (Section 1.8, 4.5.5 and 4.8.3) - AESI list was updated based on latest eCRS. (Section 4.8.3)

Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Novartis according to the data analysis section 10 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

1 Draft of Section 9.7 of CSR on Statistical methods

1.1 Statistical and analytical plans

The final analysis of study data will be performed when all patients have been treated for 8 cycles (24 weeks) or discontinued prior to treatment for 8 cycles.

In the review process of panobinostat submission for indication of relapsed or refractory MM in Japan, [redacted] requested sponsor to conduct additional interim report to present the key efficacy and safety information in public per approximately 6 months basis. At the prior to the final analysis time point, no statistical testing will be conducted as key efficacy in the interim report.

1.2 Subjects and treatments

1.2.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who took at least one dose of any study treatment component.

1.2.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication.

1.2.3 Per-protocol (PP) set

The PP set consists of all patients from the FAS without any major protocol deviation.

1.2.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set for PAN (PAS-PAN) consists of all patients with at least one evaluable PK concentration of PAN.

A PK concentration is considered evaluable if:

- The patient took the full scheduled dose in a respective cycle day (C1D1, D3, D5 and D8)
- The patient did not vomit within 4 hours after dosing in a respective cycle day (C1D1 and D8)

The pharmacokinetic analysis set for BTZ (PAS-BTZ) consists of all patients with at least one evaluable PK concentration of BTZ.

A PK concentration is considered evaluable if:

- The patient took the full scheduled dose in a respective cycle day (C1D1, D4 and D8)

Additionally, a PK concentration can be considered to be not evaluable as per scientific judgement of PK scientist. When a PK concentration is considered not evaluable by PK scientist, the reason will be documented. Any PK samples with missing blood collection date or time, or missing associated study drug dosing date or time will be excluded from PK analysis.

1.3 Patient demographics and other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively for FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

1.4 Treatments (study drug, other concomitant therapies, compliance)

Data on the study treatment administration will be summarized. The duration of treatment and relative dose intensity of each of the components of study treatment will be summarized using descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized.

1.5 Analysis of the primary efficacy endpoint

1.5.1 Primary endpoint

The primary objective of the study is to assess efficacy of panobinostat (PAN) by nCR+CR rate after all patients have been treated for 8 cycles or discontinued from treatment which is based on modified EBMT criteria per investigator assessment in patients with relapsed or relapsed and refractory multiple myeloma.

The proportion of patients with a near Complete Response (nCR) or complete response (CR) as their best overall response is defined as nCR+CR rate. For all patients, the nCR+CR rate and its 2-sided 90% normally approximated confidence interval will be provided.

In addition, The nCR+CR rate and 2-sided 95% Clopper-Pearson exact confidence interval will be explored. Statistical hypothesis, model, and method of analysis

The primary analysis will be based on a single-sample binomial test (normal approximation) at the one-sided 5% significance level, analyzed in the FAS.

The study targets a nCR+CR rate of 25%. A nCR+CR rate of 10% or less is considered as an insufficient level of activity for the proposed patient population. Therefore the null and the alternative hypothesis are defined as follows: H_0: nCR+CR rate $\leq$ 10%, Ha: nCR+CR rate > 10%.

1.5.2 Handling of missing values/censoring/discontinuations

For the purposes of the primary analysis, patients with a best overall response of ‘Unknown’ (UNK) will be treated as non-responders in estimating the nCR+CR rate in the FAS.

1.5.3 Sensitivity analyses

For the primary endpoint, following sensitivity analyses will be performed.

- Primary analysis will be repeated using the PP set.
- Primary analysis will be repeated based on planned number of patients.

  If less than planned number of patients are available for the final analysis, then this analysis will be based on the planned number of patients and patients who have not be enrolled are considered non-responders.

1.5.4 Supportive analyses

Not applicable.

1.6 Analysis of secondary efficacy variables

The secondary efficacy variables will be analyzed using the FAS.

1.6.1 Key secondary endpoint

The key secondary objective is to evaluate progression free survival (PFS), defined as time from first dose of study treatment to the first documented PD (progressive disease) , relapse or death due to any cause per investigator based on modified EBMT criteria in patients with relapsed multiple myeloma or relapsed and refractory multiple myeloma.

Survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. Median PFS time and its two-sided 95% confidence intervals will be reported.

A patient who has not progressed/ relapsed, or died at the date of the last adequate response assessment or when he/she receives any further anti-cancer therapy would have his/her PFS censored at the time of the last adequate response assessment before/ at the date of the last adequate response assessment or before start of further anti-cancer therapy. An adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”.

1.6.2 Additional secondary efficacy endpoints

Other secondary efficacy objectives are to evaluate overall response rate (ORR), overall survival (OS), minimal response rate (MRR), time to response (TTR), time to progression/relapse (TTP) and duration of response (DOR).

The assessment of these endpoints will be based on modified EBMT criteria per investigator assessment.

Overall response rate (ORR) is defined as the proportion of patients with CR or nCR or PR.

Overall survival (OS) is defined as time from first dose of study treatment to death.

Time to response (TTR) is the time between date of first dose of study treatment until first documented response (CR or nCR or PR).

Duration of response (DOR) is defined as the time from the first documented occurrence of response (PR or nCR or CR) until the date of the first documented disease progression or relapse or death due to multiple myeloma.

Time to progression/relapse (TTP) is defined as the time from the date of first dose of study treatment to the date of the first documented disease progression, relapse or death due to multiple myeloma.

Estimated ORR along with corresponding 95% Clopper-Pearson exact confidence intervals will be presented.

Median TTR, DOR and TTP along with corresponding 95% confidence intervals will be presented.

ORR, MRR, TTR and TTP will be analyzed based on the FAS. However, DOR will be analyzed based on data from responders only (CR or nCR or PR) in the FAS.

[redacted]

1.8 Safety analyses

For all safety analyses, the safety set will be used.

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.

Adverse events

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Specific groupings of adverse events of special interest will be considered and summaries of these adverse events of special interest will be provided.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology version 21.0 or later.

Laboratory data

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry, urinary laboratory tests and thyroid function test:

- Frequency table for newly occurring on-treatment grades 1 - 4, any grade and grade 3/4 values
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

ECGs

Summary of worst change from baseline for QTcF will be generated.

Vital signs

Summary of worst change from baseline for vital signs (See Section 4.8.6) will be generated.

1.9 Patient-reported outcomes

The FACT GOG/Ntx will be scored in accordance with their specific scoring guidelines (Cella et al 1997). For these scores, lower values denote higher fatigue and neurotoxicity. FACT/GOG-NTX scores range from 0 - 44. Calculated scores will be summarized by visit.

1.10 Pharmacokinetics

For all PK analyses, PAS-PAN or PAS-BTZ will be used.

Plasma concentration of PAN and BTZ

Summary statistics (n, arithmetic mean, median, SD, geometric mean, coefficient of variation CV (%) and geometric CV (%), minimum and maximum) will be presented for plasma concentrations of PAN (and its metabolite BJB432, if available) and BTZ at each scheduled time point for each analyte. Graphical presentation will also be provided on geometric mean and arithmetic mean concentration time profile at each scheduled time point for each analyte.

PK parameters of PAN and BTZ

PK parameters will be calculated from individual concentration-time data for each analyte. Summary statistics included geometric and arithmetic means, n, SD, coefficient of variation (CV)% and CV% geometric mean, median, minimum and maximum will be presented for all

PK parameters except Tmax. For Tmax, only median, minimum, and maximum values will be presented.

1.11 Sample size calculation

Sample size assumptions in this trial are based on the data from the PANORAMA-1 study, which enrolled a similar patient population; i.e. patients with relapsed multiple myeloma or relapsed-and-refractory myeloma. Considering BTZ was currently widely used in newly diagnosed MM and relapsed/refractory MM in Japan, it is expected that most patients in this study have BTZ containing regimen as a prior line of therapy. Based on the data from the PANORAMA-1 study, for patients previously treated with BTZ, the nCR+CR rate for PAN is expected to be around 25 %. nCR+CR rate of 10 % or less is considered as an insufficient level of activity for the proposed patient population. Based on the normal distribution, approximately 33 patients are required to reject a null hypothesis of nCR+CR $\leq$ 10% vs. a target nCR+CR of 25% or more, with a one-sided alpha of 0.05 and at least 80% power.

1.12 Power for analysis of key secondary variables

Not applicable.

1.13 Interim analyses

Not applicable.

Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

2 Statistical methods

2.1 Study drug and study treatment

Study drug refers to PAN.

Study treatment refers to

- PAN + BTZ + Dex (investigational arm)

Study treatment components refer to

- PAN
- BTZ
- Dex

Study combination partner refers to BTZ and Dex.

2.2 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero dose of study drug was administered and recorded on the dose administration record (DAR) electronic case report form (eCRF). For the sake of simplicity, the date of first administration of study drug is also referred as ***start of study drug***.

2.3 Date of last administration of study drug

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

2.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered and recorded on the DAR eCRF. For example, if the 1st dose of study drug A is administered on 04JAN2015, and the 1st dose of its combination partner, drug B, is administered on 03JAN2015, the date of the first administration of study treatment is on 03JAN2015). For the sake of simplicity, the date of the first administration of study treatment also referred as the ***start of study treatment***.

2.5 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered and recorded on the end-of-treatment eCRF (PAN) or DAR eCRF (BTZ, Dex). For example, if the last dose of PAN is administered on 15APR2015, and the last dose of a combination partner, e.g., Dex, is administered on 17MAY2015, the date of last administration of study treatment is then on 17MAY2010.

2.6 Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the subject.

If more than one measurement (including additional and unscheduled visits) is obtained before first administration of study treatment, the last measurement sorted by date/time of assessment and/or number of repeat measurements, as applicable, that is prior to the first study treatment administration will be used as the baseline value.

For ECG, patients have more than 1 measurement at an assessment date, baseline is defined as average of the ECG measurements taken at pre-dose on C1D1 or if not available as average of the last available ECG assessment date within a 21 days window prior to C1D1.

If patients have no value as defined above, the baseline result was considered to be missing.

2.7 On-treatment assessment/event

All on-treatment assessments/events are any assessments/events obtained in the time interval:

> [date of first administration of study treatment; date of last administration of study treatment +30 days], i.e., inclusive lower and upper limit.

The calculation of study treatment duration may use different rules as specified in Section 4.5. of RAP Module 3.

2.8 Screening failure

Screening failures are patients who have been screened and have failed the inclusion and exclusion criteria; these patients are never study treatment administered.

2.9 Time windows

For calculation of the investigator's response assessment, the time window for (1) individual assessments and (2) confirmation of response are to be considered as defined in Appendix 4: Post-text supplement to the Study Protocol.

For analyses of the FACT/GOG-Ntx, the following time windows were used for the analyses by time point according to the planned assessment schedule:

Table 2-1 Time window for FACT/GOG-Ntx

Time window	Definition	Planned assessment day
Baseline		
Week 3	Baseline + 1 day to Day 32	22
Week 6	Day 33 to Day 53	43
Week 9	Day 54 to Day 74	64
Week 12	Day 75 to Day 95	85
Week 15	Day 96 to Day 116	106
Week 18	Day 117 to Day 137	127
Cont'd	. . .	. .

Time windows are defined based on the day of first administration of study treatment (Day 1). In case there is more than 1 assessment within a time window, the closest to the planned assessment is used for analysis. In case there are assessments being equidistant to the planned assessment date, the first assessment is used for analysis.

2.10 Last contact date

The last contact date was derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All assessment dates (e.g. vital signs assessment, performance status/QoL assessment, and also assessment date in third-party data)
- Medication dates including study medications, concomitant medications, and antineoplastic therapies administered after study treatment discontinuation
- Adverse events dates
- Last contact date collected on the 'Survival information' eCRF.

The last contact date was used for censoring of patients in the analysis of overall survival.

2.11 Data set

A unique ***cut-off date*** will be determined for 24-week analysis. Only data with an assessment or event start date (e.g., vital sign assessment date or start date of an AE) prior to or on the cut-off date will be included in the analysis. For example, if the cut-off date is 15JUN2015, an AE starting on 13JUN2015 is reported, whereas an AE with a start date of 17JUN2015 is not reported.

All events with a start date before or on the cut-off date and an end date after the cut-off date are reported as 'continuing at the cut-off date'. The same rule was applied to events starting before or on the cut-off date and not having a documented end date. This approach applies in particular to AE and concomitant medication reports. For these events, the end date is not imputed and therefore did not appear in the listings.

If it is required to impute an end date for performing a specific analysis (e.g., for a dose administration record with a missing end date or an end date after the cut-off date, the latter is imputed as end date to allow the calculation of treatment exposure duration and dose intensity), the imputed date is displayed and flagged in the listings.

2.12 Definitions of analysis sets

2.12.1 Full analysis set (FAS)

The Full Analysis Set (FAS) comprises all patients who took at least one dose of any study treatment component.

2.12.2 Safety set

The Safety Set includes all patients who received at least one dose of study medication.

2.12.3 Per-protocol (PP) set

The PP set consists of all patients from the FAS without any major protocol deviation.

2.12.4 Pharmacokinetic (PK) set

The pharmacokinetic analysis set for PAN (PAS-PAN) consists of all patients with at least one evaluable PK concentration available of PAN.

A PK concentration is considered evaluable if:

- The patient took the full scheduled dose in a respective cycle day (C1D1, D3, D5 and D8)
- The patient did not vomit within 4 hours after dosing in a respective cycle day (C1D1 and D8)

The pharmacokinetic analysis set for BTZ (PAS-BTZ) consists of all patients with at least one evaluable PK concentration available of BTZ.

A PK concentration is considered evaluable if:

- The patient took the full scheduled dose in a respective cycle day (C1D1, D4 and D8)

Additionally, a PK concentration can be considered to be not evaluable as per scientific judgement of PK scientist. When a PK concentration is considered not evaluable by PK scientist, the reason will be documented. Any PK samples with missing blood collection date or time, or missing associated study drug dosing date or time will be excluded from PK analysis.

2.13 Concomitant medications with specific impact on the analysis

2.13.1 Further anti-neoplastic therapy

Patients who take additional anti-neoplastic therapy before discontinuing study treatment (i.e., anti-neoplastic therapy other than study treatment) were identified as protocol deviations. Their efficacy data were censored so that response assessments made after the first intake of an anti-neoplastic drug were not included in analyses. Clinical review of individual study data is required in order to identify those anti-neoplastic medications which are considered disallowed.

2.14 General statistical methodology

2.14.1 Baseline comparability

Not applicable.

2.14.2 Multiple assessments within post-baseline visits

If there are multiple measurements within the same post-baseline visit, the last measurement within the visit (sorted by date and as available by time) will be used in the analysis by visit. For any analyses regarding outliers, abnormal assessments or changes from baseline, all post-baseline values will be included (i.e., scheduled, unscheduled, repeat). This applies to quantitative and qualitative variables.

2.14.2.1 12-lead ECG assessments

The visit date recorded in the database will be used as the date of ECG. For all patients, a minimum of 3 ECGs are usually measured at screening, and single ECG is measured at other time points. If any patient has more than 1 measurement at a specific timepoint, the average of all available measurements will be used for the analysis of change from baseline as well as for the identification of notable values. If there are unscheduled measurements, they were included for analyses of notable values and listing. For the unscheduled measurements, the individual records will be used for analyses.

2.14.3 Center pooling

All study centers will be combined for the analysis. Due to expected small size of centers, no center effect will be assessed. However, protocol deviations, the number of patients will be summarized by center.

2.14.4 Sample size calculation

Sample size assumptions in this trial are based on the data from the PANORAMA-1 study, which enrolled a similar patient population; i.e. patients with relapsed multiple myeloma or relapsed-and-refractory myeloma. Considering BTZ was currently widely used in newly diagnosed MM and relapsed/refractory MM in Japan, it is expected that most patients in this study have BTZ containing regimen as a prior line of therapy. Based on the data from the PANORAMA-1 study, for patients previously treated with BTZ, the nCR+CR rate for PAN is expected to be around 25 %. nCR+CR rate of 10 % or less is considered as an insufficient level

of activity for the proposed patient population. Based on the normal distribution, approximately 33 patients are required to reject a null hypothesis of nCR+CR ≤ 10% vs. a target nCR+CR of 25% or more, with a one-sided alpha of 0.05 and at least 80% power.

2.14.5 Power for analysis of critical secondary variables

Not applicable.

2.14.6 Conversion factors

A month will be calculated as (365.25 / 12) = 30.4375 days.

For the conversion of laboratory values measured in units as used by local laboratories to SI units, standard Novartis conversion factors will be used.

2.15 Implementation of response guidelines

Response and progression evaluation will be performed according to the modified European Group for Blood and Marrow Transplantation (EBMT) criteria as defined in Appendix 4: Post-text supplement to the Study Protocol. The text below gives more detailed instructions and rules to provide further details needed for programming.

2.15.1 Progressive disease/relapse

Progressive disease (PD)/relapse should only be assigned if it is documented by the investigator as per modified EBMT criteria per investigator's response assessment page. Thus, for analyses of PFS and variables of efficacy based on modified EBMT response assessment, only the investigator's response assessment eCRF page will be considered as data source.

2.15.2 Best overall response

The best overall response will be assessed by modified EBMT criteria as per investigator assessment. The definitions and the details on the derivation are given in Appendix 4: Post-text supplement to the Study Protocol.

Only response assessments performed before the start of any additional anti-neoplastic therapies were considered in the assessment of best overall response.

2.15.3 Determination of missing adequate response assessments and censoring reason

In this section, the 'missing adequate response assessment' is defined as an assessment not done or classified as 'unknown'. For simplicity, the 'missing adequate response assessment' was referred as 'missing assessment'.

As detailed in Table 2-2, the PFS censoring and event date options depend on the presence and the number of missing assessments. For example:

- In the analysis of PFS, an event occurring after 2 or more missing assessments is censored at the last adequate response assessment (i.e. at the last adequate response assessment before the 2 or more missing assessments)

An exact rule to determine whether there are any missing assessments is therefore needed. This rule was based on the distance between the last adequate response assessment date and the event date.

The threshold D1 is defined as the interval between the response assessments plus the protocol-allowed window around the assessments. Similarly, the threshold D2 is defined as 2 times the protocol-specified interval between the response assessments plus the protocol allowed window around the assessments. For these derivations, the end of treatment visit was considered as scheduled visit.

During treatment phase: The threshold D1 is defined as 21 + 6 = 27 days and the threshold D2 as (2 * 21) + 6 = 48 days.

During follow-up phase: The threshold D1 is defined as 42 + 6 = 48 days and the threshold D2 as (2 * 42) + 6 = 90 days.

Similarly, a threshold D3 is defined as (3 * 21) + 6 = 69 days in treatment phase and (3 * 42) + 6 days = 132 days during follow-up phase.

The analysis assumed 1 missing assessments if the distance between the last adequate response assessment and the event date is within (D1, D2] and 2 or more missing assessment if the distance is larger than D2. More than 2 missing assessments are assumed if the distance is larger than D3.

The same definition of D2 was used to determine the PFS-censoring reason. If the distance between the last adequate response assessment date and the earliest one of the following dates:

- Analysis cut-off date
- Start date of additional anti-neoplastic therapy
- Date of study discontinuation due to consent withdrawal to disease follow-up
- Date of study discontinuation due to loss to follow-up

is smaller or equal to D2, the censoring reason was then either 1.”*Ongoing without PFS event*”, 2. “*Adequate assessment not available*” including lost to follow-up, withdrawal of consent to disease follow-up and other, 3. “*New cancer therapy added*”. However, if this distance is larger than D2, the censoring reason was then designated as 4. “*Events documented after ≥2 missing adequate response assessments*”. Table 1-5 is summarizing the criteria to derive the PFS censoring reason.

Table 2-2 Derivation of PFS censoring reason

	PFS censoring reason	Definition
1	Ongoing without PFS event	Patient is still eligible for further disease follow-up at the analysis cut-off date
2	Adequate response assessment not available	Patient is not available for further disease follow-up at the analysis cut-off date. The patient stopped disease follow-up for any of the subordinated reasons
2.1	- Lost to follow-up	Patient is lost to follow-up as documented at end of treatment or study evaluation completion

	PFS censoring reason	Definition
2.2	- Withdrawal of consent to disease follow-up	Patient withdrew consent to disease follow-up as documented after end of treatment or study evaluation completion
2.3	- Other	Patient stopped disease follow-up due to the following reasons as documented at study evaluation completion: *Protocol deviation, technical problems*
3	New cancer therapy added	Start of new anti-cancer therapy as documented in the *"Antineoplastic therapies since discontinuation of study drug" eCRF.*
4	Events documented after ≥2 missing adequate response assessments	Patient experienced PFS event with 2 or more missing adequate response assessment preceding the PFS event.

3 Statistical analysis outputs

3.1 Hypothesis and test statistic

The null hypothesis and alternative hypothesis are stated in the Study Protocol (Section 10.4.2) for nCR+CR.

The primary analysis will be based on a single-sample binomial test (normal approximation) at the one-sided 5% significance level, analyzed in the FAS.

The study targets an nCR+CR of 25%. A response rate of 10% or less is considered as an insufficient level of activity for the proposed patient population. Therefore the null and the alternative hypothesis are defined as follows: Ho: nCR+CR ≤ 10%, Ha: nCR+CR > 10%.

3.2 Kaplan-Meier (KM) estimates

An estimate of the survival function will be constructed using the KM (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option (see example below).

```
PROC LIFETEST data=dataset METHOD=KM CONFTYPE=LOGLOG ;
      TIME survtime*censor(1) ;
RUN ;
```

- survtime represents variable containing event/censor times
- censor represents censoring variable (1=censored, 0=event)

The median survival was obtained along with 95% CIs calculated from PROC LIFETEST output using the method of Brookmeyer & Crowley (1982).

KM estimates of the survival function with 95% CIs were summarized for the median, the 25th and 75th percentile, if appropriate. The standard error of the KM estimate was calculated using Greenwood's formula (Collett 1994).

The PROC LIFETEST statement used the option CONFTYPE=LOGLOG. The CONFTYPE option specifies the transformation applied to the survival function to obtain the pointwise CIs and the CIs for the quartiles of the survival times. The LOGLOG keyword specifies the

complementary log-log transformation g(x)=log(-log(x)) which ensures that the pointwise CIs are always within interval [0,1] (Collett 1994; Lachin 2000).

4 Statistical methods used in reporting

4.1 Background and demographic characteristics

The FAS will be used for all baseline and demographic summaries and listings.

4.1.1 Basic demographic and background data

All demographic and background data will be listed in detail. Qualitative data will be summarized by means of contingency tables and quantitative data will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation, median, minimum, and maximum). The following variables will be summarized:

- Age [years]
- Age category (<65 years/ ≥65 years/ missing)
- Sex (male/ female/ missing)
- Race (Asian/ missing)
- Ethnicity (Japanese/ missing)
- ECOG PS (0/ 1/ 2/ Missing)
- Body weight [kg]
- Body height [cm]
- Body surface area (BSA) [m^2]

4.1.2 Protocol eligibility criteria

Protocol eligibility criteria deviation on eCRFs will be listed.

4.1.3 Diagnosis and characteristics of multiple myeloma

Summary statistics will be tabulated for diagnosis and characteristics of MM and depending on the data collected on the eCRF include the following:

- Time since diagnosis [months], (< 6 months/ ≥6 months and <1 year/ ≥1 year and <2 years/ ≥2 years and < 5 years/ ≥5 years/ missing)
- Involved light chains (kappa/ lambda/ indeterminate/ missing)
- Immunoglobulin (Ig) class (IgG/ IgA/ IgM/ IgD/ IgE/ indeterminate/ missing)
- Light chain Multiple Myeloma (yes/ no/ missing)
- Renal function (renal impairment/ no renal impairment/ missing)

  "No renal impairment" is defined as a baseline $C_{CR} \geq 90$ mL/min and "renal impairment" as a baseline $C_{CR} < 90$ mL/min (for calculation of C_{CR} see Appendix 1)
- Cytogenetic risk group (normal risk/ poor risk/ unknown/ missing)

Cytogenetic poor risk group includes all patients with any of the following cytogenetic abnormalities at baseline: t(4, 14), t(14, 16), 17p deletion. The cytogenetic normal risk group includes all patients with none of these abnormalities at baseline

- Clinical staging of MM according to the International Staging System (ISS, Appendix 2): (Stage I/ Stage II/ Stage III/ not assessed/ missing)
- Serum PEP assessment [g/dL]
- Serum M-protein by immunofixation (present/ absent/ not assessable/ missing)
- Urine PEP assessment [mg/24h]
- Urine M-protein by immunofixation (present/ absent/ not assessable/ missing)
- Plasma cells in bone marrow as assessed by aspirate or biopsy [%]
- Soft tissue plasmacytoma (present/ absent/ missing)
- Lytic bone lesions (present/ absent/ missing)

4.1.4 Medical history

Medical history and ongoing conditions, including MM-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term. Medical history/current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

4.1.5 Prior anti-neoplastic therapy

The number and percentage of patients receiving any prior anti-neoplastic therapy and prior anti-neoplastic radiotherapy will be summarized for the full analysis set:

For Prior antineoplastic therapy,

- Prior antineoplastic regimens (yes/ no/ missing)
- Number of prior line of therapy
- Prior lines of MM therapy (1/ 2 and 3/ >3/ missing)
- Prior use of medications:
  - Bortezomib
  - Lenalidomide
  - Thalidomide
  - Pomalidomide
  - Oral Melphalan (defined as setting is **not** CONDITIONING FOR SCT)
  - Combined bortezomib and lenalidomide
  - Combined bortezomib+IMiDs (defined as prior use of thalidomide and/or lenalidomide and/or pomalidomide)
  - Combined bortezomib+dexamethasone
  - IMiDs
  - Other
- Prior last line

- Bortezomib
- Lenalidomide
- Thalidomide
- Pomalidomide
- Oral Melphalan
- Combined bortezomib and lenalidomide
- Combined bortezomib+IMiDs
- Combined bortezomib+dexamethasone
- Other

For prior use of medications and last line, frequencies will be presented separately for additional drug(s) in case the frequency is ≥10%.

- Prior stem cell transplantation (yes/ no/ autologous/ allogenic)
- Number of prior stem cell transplantations
- MM characteristics (relapsed and refractory/ relapsed/ other)
- Best response to last line of anti-MM therapy (CR/ nCR/ PR etc.)
- Time from last therapy to progression [months]
- Reason for discontinuation of therapy (toxicity/ disease progression/ completed prescribed regimen/ adverse event (s)/ unknown/ other/ missing)

For Prior antineoplastic radiotherapy,

- Prior radiotherapy (yes/ no/ missing)
- Locations of prior radiotherapy

Prior anti-neoplastic therapy will be listed for medications and radiotherapy.

Prior anti-neoplastic medications will be summarized by ATC class, preferred term. Significant prior anti-neoplastic medications will be identified from the summaries mentioned above unless specified otherwise. Prior radio-, photo or light therapies will be summarized as prior radiotherapy.

4.1.6 Other

All data collected at baseline, including childbearing potential and pregnancy test results will be listed.

4.2 Protocol deviation summaries

The number and percentage of patients in the FAS with any protocol deviation will be tabulated by the deviation category (as specified in the SSD documents). All protocol deviations will be listed.

4.3 Groupings for analysis

The number and percentage of patients in each analysis set (definitions are provided in Section 2.12) will be summarized.

4.4 Patient disposition

The FAS will be used for the patient disposition summaries. The following frequencies will be provided:

- Number (%) of patients who are still on-treatment (based on the absence of the 'End of Treatment Phase Disposition' page)
- Number (%) of patients who entered study treatment phase 2 (See protocol Section 4.1)
- Number (%) of patients who discontinued prematurely the study treatment (based on 'End of Treatment' page)
- Number (%) of patients who completed the study per protocol (based on 'End of Post Treatment Phase Disposition' page)
- Number (%) of patients by reason for end of study treatment (based on 'End of Treatment Phase Disposition' page)
- Number (%) of patients who entered the post-treatment evaluation phase (based on 'End of Treatment Phase Disposition' page)
- Number (%) of patients who entered the post-treatment evaluation and who discontinued the study (based on 'End of Post Treatment Phase Disposition' page)
- Number (%) of patients who entered the post-treatment evaluation and who continues to be followed (based on the absence of the 'End of Post Treatment Phase Disposition' page)
- Reasons for discontinuation from the post-treatment evaluation phase (based on 'End of Post Treatment' page)
- Number (%) of patients who entered the survival follow-up phase (based on 'End of Treatment' or 'End of Post Treatment' page).

4.5 Study treatment

Duration of study treatment exposure [days], cumulative dose [PAN and Dex: mg, BTZ: mg/m^2], dose intensity (DI) [PAN and Dex: mg/day, BTZ: mg/(m^2 x day)] and relative dose intensity (RDI) [%] will be summarized. In addition, the duration of exposure to study treatment will be categorized into time intervals (Section 4.5.1); frequency counts and percentages will be presented for the number of patients in each interval. The number of patients who have dose changes or interruptions, as well as their reasons, will be summarized.

Cumulative dose, DI and RDI will be summarized by overall, by treatment phase and by cycle. Similarly, the number of patients who have dose changes or interruptions will also be summarized by treatment phase.

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

The safety set will be used for all summaries and listings of study treatment.

4.5.1 DAR date imputation

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 in case the cut-off date is earlier than the derived end date as per imputation rules. Such imputed data will be flagged in the listings.

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.

Imputed DAR start and end dates will be flagged in the listings.

4.5.2 Duration of study treatment exposure

Duration of study treatment exposure and study treatment component exposure will be summarized.

Duration of study treatment exposure

The following algorithm will be used to calculate the duration of study treatment exposure for patients who took at least one dose of any of the components of the study treatment:

> Duration of exposure (days) = [(date of last administration of study treatment) – (date of first administration of study treatment) + 1 day]

Duration of study treatment component exposure

Duration of exposure to any single component of study treatment will be calculated as

> Duration of exposure (days) = [(date of last administration of study treatment component) – (date of first administration of study treatment component) + 1 day]

For the date of last administration of study drug (PAN), BTZ and Dex, the DAR page will be used. The calculation of 'duration of exposure' does not consider the potential 'lagging effect' from the last dose.

The duration of exposure includes the periods of temporary interruption (of any component of the study treatment for any reason). 'Date of last administration of study drug /component' and 'date of first administration of study drug /component' is defined in Section 2. For patients who did not take any study treatment, the duration of exposure is defined as 0 days.

The following categories for exposure to study treatment will be analyzed:

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

- ≥ 24 weeks and ≤ 48 weeks
- > 48 weeks

4.5.3 Cycle definition

Cycle length will be calculated based on visit date. The beginning of a cycle will be calculated from the first visit with non-zero dose of any component of study treatment of that cycle. Each cycle ends the day before the next cycle starts. Cycle length will be calculated for all cycles (except the last cycle) as follows:

Cycle length= (date of Day 1 of the next cycle – date of Day 1 of the current cycle).

A patient can discontinue the study early. As a consequence, the **last cycle** may not be a complete treatment cycle. Therefore, the last cycle length will be calculated as follows:

Last cycle length= [(date of last administration of study treatment + X) – (day 1 of the last cycle date) + 1].

where X is the number of days remaining to complete the exposure time of the last dose of the study treatment component or the number of days from last administered dose to the next planned dose taking into account the minimal allowed dosing interval. In case the last dose of a cycle was taken later than the scheduled cycle length, X will be set to 0 days.

For example, for BTZ on a 21-day cycle with a Day 1 to 8 regimen, X=0 if the last BTZ dose is given on Day 1; X=13 if last dose is given on day 8.

The special handling of the last cycle length is to carefully calculate DI. This is different from the purpose of calculating 'duration of exposure', where the 'last dose lagging effect' is not included.

In case the length of the last cycle is more than scheduled, the actual length will be taken (date of end of treatment visit).

4.5.4 Study day

For the study day calculation, if the event or assessment date is after the treatment start date, the following calculations listed below apply:

The study day ***for all assessments*** 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 start of the study drug**, e.g., time since diagnosis of disease, the study days (in negative) will be calculated for safety assessments as:

Study Day = Event date - Date of first 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.

The study day will be displayed in the data listings.

4.5.5 Partial dates

As a common rule, whenever an imputation is implemented, the imputed date needs to be in the reasonable range of the event. For example, if a date is known to be within the trial period and imputation makes it after the last known contact date, the last known contact date would be used.

Partial dates will be listed as such. The general approach is to impute partial dates when further analysis is required. This includes in particular incomplete dates for AE start and end date, concomitant/prior medication start and end date, date of diagnosis of MM.

In general, no imputation will be made when the year is missing (exceptions are described in Programming Datasets Specifications: PDS). In case the imputed date reveals in date that is not plausible with study key dates, the imputed date is to be replaced with those (e.g. when an AE start date results in a date prior to start of study treatment then the AE start date will be set to the start of study treatment date). These rules do not apply when determining the censoring date for time-to-event variables (see Appendix 4: Post-text supplement to the Study Protocol for details).

4.5.6 Cumulative dose

The cumulative dose is defined as the total dose given during the study treatment exposure and will be summarized by study treatment component. For patients who did not take any drug the cumulative dose is by definition equal to 0.

4.5.7 DI and RDI

The following DI or planned DI (PDI) calculations apply for both Sc and oral dosing. In the case of s.c. dosing, the dose was given based on BSA; calculation of DI or PDI involves BSA in the division. If the dose is given regardless of BSA, the same formula can be used by replacing BSA by 1 m^2 in the formula. Both DI and RDI for the study period will be summarized separately for each of the study treatment components, in which the denominator of DI or PDI calculation uses “the sum of all cycle length”.

While the ‘sum of all cycle lengths’ is not the same as ‘duration of study treatment exposure’, they are identical in the continuous dosing regimen. DI, PDI, or RDI will be calculated for each study treatment component or study drug only. No calculation for study treatment combination will be done.

DI by cycle analysis

PAN and Dex

1. For cycles except last cycle or last cycle with length as scheduled or longer

- PDI_c [mg/day] = (Total planned dose per cycle [mg]) / planned cycle length [days]
- DI _c [mg/day] = (Total actual dose in an actual cycle [mg]) / actual cycle length [days]

2. For last cycle that is shorter than scheduled

- PDI_c [mg/day] = (Total planned dose for actual duration [mg]) / actual duration [days] of study treatment in last cycle (Section 4.5.3)
- DI_c [mg/day] = (Total actual dose for actual cycle [mg]) / actual duration [days] of study treatment in last cycle

3. For all cycles

- RDI_c [%] = DI_c [mg/day] / PDI_c [mg/day] * 100

BTZ

In this trial, BTZ is intravenously administered which requires an adjustment of dose intensity calculation by BSA. Since the body weight is provided at day 1 of each cycle the BSA needs to be derived for each cycle as:

BSA [m^2] = 234.94 * (height [cm]**0.422) * (weight [kg]**0.515) / 10000
(Gehan and George formula)

1. For cycles except last cycle or last cycle with length as scheduled or longer

- PDI_c [mg/m^2/day] = (Total planned dose [mg] / BSA [m^2]) / planned cycle length [days]
- DI _c [mg/m^2/day] = (Total actual dose in actual cycle [mg] / BSA [m^2]) / actual cycle length [days]

2. For last cycle that is shorter than scheduled

- PDI_c [mg/m^2/day] = (Total planned dose for actual duration [mg]/ BSA [m^2] in last cycle) / actual duration [days] of study treatment in last cycle (Section 4.5.3)
- DI_c [mg/m^2/day] = (Total actual dose for actual cycle (mg) / BSA (m^2)] / actual duration [days] of study treatment in last cycle

3. For all cycles

- RDI_c [%] = DI_c [mg/m^2/day] / PDI_c [mg/m^2/day] * 100

DI over study period

PAN and Dex

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

$$\mathrm{DI}\left[\mathrm{mg/day}\right] = \frac{\text{Cumulative dose } \left[\mathrm{mg}\right]}{\sum_{i=1}^{k} (\text{actual cycle lengths})_i \left[\mathrm{day}\right]}$$

and $i = 1,2,3,\ldots,k$ are the indices for the cycle.

For patients who did not take any drug the DI is by definition equal to zero.

Note: $\sum_i (\text{actual cycle length})_i$ may not be equal to the duration of the study treatment exposure.

Planned dose intensity (PDI) for patients with non-zero duration of exposure is defined as follows:

1. Last cycle length is shorter as or equal to the planned length

$$\mathrm{PDI}[\mathrm{mg/day}] = \frac{\mathrm{Total planned dose}\ [\mathrm{mg}]}{\sum_{i=1}^{k-1}(\mathrm{Planned cycle lengths})_i + \mathrm{actual\ last\ cycle\ lentgh}[day]}$$

i =1,2,3,…,*k* are the indices for the cycle. k is the actual total number of cycles

2. Last cycle length is longer than planned

$$\mathrm{PDI}[\mathrm{mg/day}] = \frac{\mathrm{Total\,planned\,dose}\ [\mathrm{mg}]}{\sum_{i=1}^{k}(\mathrm{Planned\,cycle\,lengths})_i\ [\mathrm{day}]}$$

i =1,2,3,…,*k* are the indices for the cycle. k is the actual total number of cycles

For patients who did not take any drug the PDI is by definition equal to zero.

Relative dose intensity (RDI) is defined as follows:

RDI [%] = DI [mg/day] / PDI [mg/day] * 100

BTZ

Dose intensity (DI) for patients with non-zero duration of exposure is defined as:

$$\mathrm{DI\,(mg/\,m^2/day)} = \frac{\sum_{i=1}^{k}\frac{(\mathrm{Cumulative\,dose})_i\,[\mathrm{mg}]}{\mathrm{BSA}_i\,[\mathrm{m}^2]}}{\sum_{i=1}^{k}(\mathrm{actual\ cycle\ lengths})_i\,[\mathrm{day}]}$$

i =1,2,3,…,*k* are the indices for the cycle.

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) for patients with non-zero duration of exposure is defined as:

1. Last cycle length is shorter as or equal to the planned length

$$\mathrm{PDI}\ [\mathrm{mg/m^2/day}] = \frac{\sum_{i=1}^{k}\mathrm{Total\ planned\,dose}\ [\mathrm{mg/m^2}]}{\sum_{i=1}^{k-1}(\mathrm{planned\,cycle lengths})_i + \mathrm{actual last\,cycle length}[\mathrm{day}]}$$

i =1,2,3,…,*k* are the indices for the cycle. k is the actual total number of cycles

2. Last cycle length is longer than planned

$$\mathrm{PDI}\ [\mathrm{mg/\,m^2/day}] = \frac{\sum_{i=1}^{k}\mathrm{Total\,planned\ dose}\ [\mathrm{mg/m^2}]}{\sum_{i=1}^{k}(\mathrm{planned\,cycle\,lengths})[\mathrm{day}]}$$

i =1,2,3,…,*k* are the indices for the cycle. k is the actual total number of cycles

For patients who did not take any drug the PDI is by definition equal to zero.

Relative dose intensity (RDI) is defined as:

$$RDI\ (\%) = 100 \times DI\ [mg/m^2/day] / PDI\ [mg/m^2/day]$$

Frequencies for RDI will be produced by study treatment component and treatment phase for the following categories:

- 0 to < 50%
- 50 to < 70%
- 70 to < 90%
- 90 to < 110%
- ≥ 110%

4.5.8 Dose changes or interruptions

The number of patients who have dose changes or interruptions and the reasons for such changes /interruptions will be summarized by study treatment component.

If one drug is permanently discontinued (before a protocol planned discontinuation date) while the other is ongoing, such discontinuations will be classified as a change.

Dose changes and interruptions will be tabulated separately.

4.6 Concomitant therapy and anti-neoplastic therapies since discontinuation of study drug

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that were intentionally administered to a subject preceding or coincident with the study assessment period.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List to allow for categorization by preferred term. In addition to categorizing medication data by preferred term, drugs are classified according to their ATC classification in order to present and compare how they are being utilized. The ATC classification allows to summarize medications by a high-level common drug class.

Concomitant medications and significant non-drug therapies taken concurrently with the study drug will be listed and summarized by ATC class and preferred term by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

The safety set will be used for all concomitant medication summaries and listings. Listings and summaries of prior medications and anti-neoplastic therapies since discontinuation of study drug will be based on the FAS.

Anti-neoplastic therapies since discontinuation of study drug will be summarized by ATC class and preferred term by means of frequency counts and percentages in separate summaries.

Bisphosphonates and anti-RANKL antibodies are not considered as anti-neoplastic therapy.

Number of patients with at least 1 transfusion of blood products by transfusion type will be summarized. For this analysis of transfusions, only transfusions received after start of study treatment and up to 30 days after last dose will be considered.

4.7 Efficacy evaluations

4.7.1 Primary efficacy

The primary endpoint of the study is nCR+CR rate based on modified EBMT criteria as defined in Appendix 4 to the Study Protocol and as assessed by the investigator. The nCR+CR rate is defined as the proportion of patients with a near Complete Response (nCR) or complete response (CR) as their best overall response. The nCR+CR rate and 2-sided 90% normally approximated confidence interval will be assessed.

The primary analysis will be based on a single-sample binomial test (normal approximation) at the one-sided 5% significance level, analyzed in the FAS.

The study targets an nCR+CR of 25%. A response rate of 10% or less is considered as an insufficient level of activity for the proposed patient population. Therefore the null and the alternative hypothesis are defined as follows: H_0: nCR+CR $\leq$ 10%, Ha: nCR+CR > 10%.

For the purposes of the primary analysis, patients with a best overall response of 'Unknown' (UNK) will be treated as non-responders in estimating the nCR+CR rate in the FAS.

4.7.2 Key secondary efficacy

The progression free survival (PFS) based on modified EBMT criteria, defined as time from first dose of study treatment to progression, relapse or death due to any cause per investigator. For PFS, survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. The 25th, 50th (median), and 75th percentile of the PFS and its two-sided 95% confidence intervals will be calculated in the FAS.

A patient who has not progressed/ relapsed, or died at the date of the last adequate response assessment or when he/she receives any further anti-cancer therapy would have his/her PFS censored at the time of the last adequate response assessment before/ at the date of the last adequate response assessment or before start of further anti-cancer therapy. An adequate response assessment is considered any disease assessment indicating response status apart from "unknown" or "not done".

The event and censoring times for PFS are depicted in Table 4-1.

Table 4-1 Event and censoring dates used in PFS

	Situation	Options for end-date[1]	Outcome
A	No baseline assessment	Start date of treatment	Censor

	Situation	Options for end-date[1]	Outcome
B	PD/relapse at scheduled assessment date or before next scheduled assessment	Date of PD/relapse	Event
C1	PD/relapse or death after **exactly one** missing assessment	Date of PD/relapse/death	Event
C2	PD/relapse or death after **two or more** missing assessments	Date of last adequate assessment before PD/relapse or death (i.e. before the 2 or more missing assessments)	Censor
D	No PD/relapse/death	Date of last adequate assessment[2]	Censor
E	Treatment discontinuation due to 'Disease PD/relapse' without documented PD/relapse, i.e. clinical PD/relapse based on investigator claim	N/A	Ignored
F	New anticancer therapy given[3]	Date of last adequate assessment before start of new anticancer therapy	Censor

[1] PD/relapse

[2] In case there is no adequate assessment, the end date is the date of first administration of study treatment

[3] New anticancer therapy given without documented evidence of PD/relapse

4.7.3 Secondary efficacy

Overall response rate (ORR) is defined as the proportion of patients with CR or nCR or PR per investigator's assessment based on modified EBMT criteria. The estimated ORR along with corresponding 2-sided 95% exact CIs as derived by the Clopper-Pearson method will be presented. The reasons for best overall response resulting in "unknown" will be summarized in the FAS.

Overall survival (OS) is defined as time from first dose of study treatment to death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact. Survival status, reason for censoring and death cause will be listed. Patients not known to have died will be censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date is longer than 3 months and 2 weeks (104 days). For OS, survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. The 25th, 50th (median), and 75th percentile of the OS and its two-sided 95% confidence intervals will be calculated in the FAS.

Time to response (TTR) is the time between date of first dose of study treatment until first documented response (CR or nCR or PR) by the investigator based on modified EBMT criteria. Patients who do not experience CR, nCR or PR will be censored at maximum follow-up (i.e. first patient-first visit (FPFV) to the date of the last adequate response assessment used for the analysis) for patients who had a PFS event (i.e., either progressed, relapsed or died due to any cause) or at the last adequate response assessment date otherwise. For TTR, survivorship

functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. The 25th, 50th (median), and 75th percentile of the TTR and its two-sided 95% confidence intervals will be calculated in the FAS.

Time to progression/relapse (TTP) is defined as the time from the date of first dose of study treatment to the date of the first documented disease progression, relapse or death due to multiple myeloma. For TTP, survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. The 25th, 50th (median), and 75th percentile of the TTP and its two-sided 95% confidence intervals will be calculated in the FAS.

Duration of response (DOR) is defined as the time from the first documented occurrence of response (PR or nCR or CR) until the date of the first documented disease progression or relapse or death due to multiple myeloma. For DOR, survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. The 25th, 50th (median), and 75th percentile of the DOR and its two-sided 95% confidence intervals will be calculated in the FAS. DOR will be analyzed based on data from responders (CR or nCR or PR) in the FAS.

[redacted]

4.7.5 Other variables

4.7.5.1 Bone marrow assessment

Bone marrow variables as assessed by aspirate and biopsy will be listed.

Bone marrow aspirate

- Plasma cells [%]
- Was the specimen adequate for assessment (Yes/ No)
  - If no:
    - Dry tap/ hemodiluted/ other
    - Repeated bone marrow aspirate/ bone marrow biopsy collected
- Was specimen adequate for cellularity (Yes/ No)

Bone marrow biopsy

- Plasma cells [%]
- Was biopsy specimen adequate for cellularity (Yes/ No)
- Cellularity (Hypocellular/ Normocellular/ Hypercellular/ Not assessable/ Aplastic)
- Percentage of cellularity [%]

4.7.5.2 Serum/ urine assessment by PEP

The following variables will be listed:

Serum

- Serum albmin
- Total serum protein
- Serum M-protein
- Globulin data (Alpha1, Alpha 2 …)

Urine

- Urine albmin
- Total utine protein
- Urine M-protein
- Globulin data (Alpha1, Alpha 2 …)

Serum and urine M-protein by PEP will be summarized individually.

4.7.5.3 Involved light chain and light chain MM

Serum and urine result will be listed.

4.7.5.4 Immunofixation

Serum and urine monoclonal band will be listed.

4.7.5.6 Soft Tissue Plasmacytoma (STP) assessment

The STP assessment variables by CT/MRI and clinical assessment will be listed individually.

4.7.5.7 Skeletal survey

The following skeletal survey variables will be listed:

- Method (XRAY/ CT SCAN (WITH CONTRAST) …)
- Number of lytic bone lesions
- Lesion location and number of lesion

4.7.5.8 ECOG Performance Status (PS)

Shift tables comparing the baseline PS with the worst result during post-baseline will be summarized.

4.8 Safety evaluation

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., ECG, vital signs and special tests) will be considered as appropriate.

All safety outputs will use the safety set. The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation. All safety assessments will be listed and those collected later than 30 days after study treatment discontinuation will be flagged.

4.8.1 AEs

Coding and grading of AEs

AEs will be assessed according to the Common Terminology Criteria for AEs (CTCAE version 4.03.

If CTCAE grading does not exist for an AE, grades 1 to 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) will not be used in studies; rather, this information will be collected in the “Death” eCRF pages.

Reporting of AEs

All AEs recorded during the study will be listed and summarized. AEs will be summarized by presenting the number and percentage of patients having at least one AE (regardless of study drug treatment in each primary system organ class) and for each preferred term using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category.

AE summaries will be presented by primary system organ class, preferred term, and maximum CTC grade. A patient with multiple CTC grades for an AE category will be summarized under the maximum CTC grade recorded for the event. In the summaries presented by grade, all AEs will be pooled regardless of whether they are CTC-gradable or not, i.e., regardless of whether the question “CTCAE” on the AE CRF is answered ‘Yes’ or ‘No’.

AE summaries will include all treatment-emergent AEs starting on or after Study Day 1 (i.e. on or after the day of the first intake of study treatment) and starting no later than 30 days after study treatment discontinuation. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class, severity (based on CTC grades), AE type, relation to the study drug. AEs starting prior to Study Day 1 and AEs starting later than 30 days after study treatment discontinuation will be flagged in the listings.

Regarding the relationship to the study drug, if the AE was considered as reasonable possibility that AE is related is 'Yes, investigational treatment' or 'Yes, other study treatment (non-investigational)' or 'Yes, both and/or indistinguishable', the AE is considered as with suspected relationship to study treatment. If causality is 'Yes, investigational treatment' or 'Yes, both and/or indistinguishable', the AE is considered as with suspected relationship to study drug.

The frequency of all CTC grades and grade 3 and 4 AEs will be summarized separately. Any information collected (e.g., CTC grades, relatedness to study drug, action taken etc.) will be listed as appropriate.

Summaries of AEs with suspected relationship to study treatment will be provided.

Deaths reportable as serious AEs (SAEs) and non-fatal SAEs will be listed by patient.

4.8.2 AE summaries

The following incidences of AE summaries will be produced:

- AEs regardless of study treatment relationship by primary system organ class and preferred term and maximum severity
- AEs with suspected relationship to study treatment by primary system organ class, preferred term and maximum severity
- AEs with an overall incidence rate of 10% or more, regardless of study treatment relationship by primary system organ class and preferred term
- On-treatment deaths by primary system organ class and preferred term
- SAEs regardless of study treatment relationship by primary system organ class and preferred term
- SAEs with suspected relationship to study treatment by primary system organ class and preferred term
- AEs leading to study drug discontinuation, regardless of study treatment relationship by primary system organ class and preferred term
- AEs requiring dose adjustment or temporarily study-drug interruption regardless of study treatment relationship by primary system organ class and preferred term
- AEs requiring additional therapy regardless of study treatment relationship by primary system organ class and preferred term.

4.8.3 Advers events of special interest (AESI)

Specific groupings of AESIs will be considered and the number of patients with at least 1 AE within each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with PAN (i.e. where PAN may influence a common mechanism of action responsible for triggering them) or which are similar in nature (although not identical). The groups are defined as per Table 4-3 and in PDS. These groupings are based on standardized MedDRA queries and Novartis MedDRA queries. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit to the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

In case that eCRS (electronic Case Retrieval Strategy) for LBH589 is updated at analysis timing, safety topic of interests should be align with latest eCRS with the condition of SP flag.

Table 4-2 Advers events of special interest

Safety topic of interest	MedDRA Term	MedDRA Qualifier
Carcinogenicity/Second primary malignancy	Carcinogenicity/Second primary malignancy [LBH589] (CMQ)	
Hepatic Dysfunction	Hepatic Dysfunction [LBH589] (CMQ)	Narrow
Hypothyroidism	Hypothyroidism [LBH589] (CMQ)	Narrow
Ischaemic colitis	Ischaemic colitis [LBH589] (CMQ)	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Narrow
Medication errors	Medication errors (SMQ)	Broad
QTc prolongation	Torsade de pointes/QT prolongation (SMQ)	Broad
Renal Dysfunction	Acute renal failure (SMQ)	Broad
Severe Diarrhea	Diarrhoea (excl infective) [DOVITINIB] (CMQ)	Broad
Severe haemorrhage and thrombocytopenia - for thrombocytopenia	Haematopoietic thrombocytopenia (SMQ)	Narrow
Severe Hemorrhage and thrombocytopenia - for hemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ)	
Severe infections (including reactivation of hepatitis B infection)	Hepatitis B Infection [STANDARD] (NMQ)	Broad
Severe infections (including leukopenia)	Haematopoietic leukopenia (SMQ)	Narrow
Severe infections (including pneumonia)	Infectious pneumonia [STANDARD] (NMQ)	Broad
Severe infections (including sepsis)	Sepsis [STANDARD] (NMQ)	Narrow
Tachyarrhythmias	Tachyarrhythmias [LBH589] (CMQ)	
Venous Thromboembolism	Embolic and thrombotic events, venous (SMQ)	

Overall summary of AESIswill be provided:

- All AEs
- CTC grade 3 or 4 AEs regardless of study treatment relationship
- CTC grade 3 or 4 AESIs with suspected study treatment relationship
- SAEs
- AEs leading to study drug discontinuation
- AEs requiring dose adjustment or temporarily study-drug interruption

4.8.4 Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment AEs (i.e., treatment-emergent AEs) which are not serious AEs with an incidence greater than 5% and on on-treatment serious AEs and serious AEs suspected to be related to study treatment will be provided by primary system organ class and preferred term.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same system organ class and preferred term:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one serious AE / serious AE suspected to be related to study treatment / non-serious AE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one serious AE is occurring, then one occurrence is calculated for that serious AE.

The number of deaths resulting from serious AEs suspected to be related to study treatment and serious AEs irrespective of study treatment relationship will be provided by primary system organ class and preferred term.

4.8.5 Laboratory data

On analyzing laboratory assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected no later than 30 days after study treatment discontinuation. All laboratory assessments will be listed and those collected later than 30 days after study treatment discontinuation will be flagged in the listings. The values will be listed by laboratory parameter and patient.

Laboratory data will be converted into SI units and classified into CTC grades according to the National Cancer Institute CTCAE (NCI-CTCAE). A severity grade of 0 will be assigned when the value is within normal limits. In the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of 0.

For analyses, values as reported from the laboratory and converted to SI units will be used. In addition, the following derivations will be done:

- Corrected calcium (mg/dL) = total serum calcium (mg/dL) + 0.8 * (3.5 - serum albumin [g/dL]). Both values (total serum calcium and serum albumin) have to be taken from the same sample (i.e. identical sample date)Absolute blood counts: In case the lab presented blood counts as percentage of the total white blood cell count, the absolute blood counts will be derived. Both the percent blood count and the total white blood cell count have to be taken from the same blood sample (i.e. identical sample date).

The following summaries will be produced for the laboratory data (by laboratory parameter):

- Number and percentage of patients with worst post-baseline CTC grade for hematology and biochemistry laboratory parameters. Each patient will be counted only for the worst grade observed post-baseline.

  Patients will be considered evaluable (included in “Total” column) for this analysis if they are at risk at baseline and have at least one post baseline value for the laboratory parameter. A patient is considered at risk at baseline, if the baseline of this patient is:

  - Missing or grade 0 for new or worsening from baseline to grade 1 category

  - Missing or less than grade 2 for new or worsening from baseline to grade 2 category
  - Missing or less than grade 3 for new or worsening from baseline to grade 3 category
  - Missing or less than grade 4 for new or worsening from baseline to grade 4 category
- Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.
- For laboratory parameters where CTC grades are not defined (eg., thyroid hormones), shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

The following listing will be produced for the laboratory data:

- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference.

Imputation rule for laboratory values

All safety laboratory values which are reported as '<x' or '>x' will be imputed as follows:

- Lab values '<x' will be imputed to 0
- Lab values '>x' will be imputed to x

Efficacy laboratory values (i.e. total serum protein, serum M protein, total urine protein and urine M band protein), '<x' and '>x' data entries will be imputed as follows:

- Lab values '<x' will be imputed to 0.99*x
- Lab values '>x' will be imputed to 1.01*x

These imputed values will be flagged in the listings.

For all the differential counts, values in % will be converted to absolute values, as
*Absolute Value = (value (%)*WBC) / 100*
In order to derive the corresponding **absolute normal range,** the following scenarios (depending on the availability of the % range and the absolute range for the differential) will be considered:

- 1st scenario: % range missing and absolute range missing

Use pre-defined normal range reported in the Merck manual

- 2nd scenario: % range missing and absolute range NOT missing

Use the absolute range provided by the site

- 3rd scenario: % range NOT missing and absolute range NOT missing

Use the absolute range provided by the site

- 4th scenario: % range NOT missing and absolute range missing

The % normal limits (i.e. LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for neutrophils (NEU):

  - LLN for NEU count = (LLN for WBC count) * (LLN for NEU % / 100)

- ULN for NEU count = (ULN for WBC count) * (ULN for NEU % / 100)

4.8.6 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The variables collected in studies: height [cm], body temperature [°C], pulse rate [beats per minute (bpm)], systolic and diastolic blood pressure [mmHg], and respiratory rate [breaths per minute].

Patients with clinically notable vital sign abnormalities will be listed and assessments collected later than 30 days after study treatment discontinuation will be flagged in the listings. The criteria for clinically notable abnormalities are depicted in Table 4-4 and Table 4-5.

Table 4-3 Clinically notable elevated vital sign values

Variable	Criteria
Systolic BP	≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
Diastolic BP	≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
Body temperature	≥ 39.1°C (102.3°F)
Pulse rate	≥ 120 bpm with increase from baseline of ≥ 15 bpm
Respiratory rate	≥ 30 bpm

Table 4-4 Clinically notable vital sign below normal values

Variable	Criteria
Systolic BP	≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
Diastolic BP	≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
Body temperature	≤ 35°C (95°F)
Pulse rate	≤ 50 bpm with decrease from baseline of ≥15 bpm
Respiratory rate	≤ 10 breaths per minute

The number of patients with notably abnormal vital signs will be provided.

Population for analysis

Systolic blood pressure, diastolic blood pressure and Pulse rate:

- Patients are considered at risk if they have a baseline and at least one post-baseline assessment.

Body temperature:

Patients are considered at risk if:

- Baseline is missing or < 39.1°C for abnormality "≥ 39.1°C".
- Baseline is missing or > 35°C for abnormality "≤ 35°C".

Respiratory rate:

Patients are considered at risk if:

- Baseline is missing or < 30 bpm for abnormality "≥ 30 bpm".
- Baseline is missing or > 10 bpm for abnormality "≤ 10 bpm".

All vital sign assessments will be listed by variable.

4.8.7 Handling of missing values

Any baseline AE or any post-baseline AE with a missing grade will be reported as missing.

4.8.8 ECG

Analyses of QT prolongation will be based on QTcF measurement. In general, QTcF would be referred to as QTc throughout the document.

Baseline definition

Quantitative ECG assessments:

Baseline is defined as an average of all pre-dose ECGs performed on Cycle 1 Day 1 if available. Otherwise, the average of all pre-dose ECG measurements taken on most recent day prior to the start of any study treatment within 21 days is considered as baseline. Unscheduled visits are included.

Qualitative ECG assessments:

Baseline is defined as the last assessment (or set of assessments) at prior to the first dose of study treatment within 21 days. Unscheduled visits are included.

Population for analysis

Quantitative ECG assessments:

Patients will be considered evaluable (included in "Total") for outlier analysis if they are at risk at baseline and have at least one post-treatment ECG measurement. For change from baseline analyses they have to have at least one baseline ECG measurement and one post-baseline measurement.

A patient is considered at risk at baseline, if the baseline of this patient is missing or:

- ≤ 450 ms for abnormality "value of > 450 ms and ≤ 480 ms"
- ≤ 480 ms for abnormality "value of > 480 ms and ≤ 500 ms"
- ≤ 500 ms for abnormality "value of > 500 ms"

Qualitative ECG assessments

A patient is considered at risk for each individual finding if the baseline of the patient is: missing or with baseline being normal for that particular finding.

QTc analysis

Notable abnormalities will be summarized for the following:

- An increase of 30 to 60 ms in QTc
- An increase of > 60 ms in QTc
- Patients with any QTc value of > 450 and ≤ 480 ms
- Patients with any QTc value of > 480 and ≤ 500 ms
- Patients with any QTc value of > 500 ms

Cardiac imaging

All cardiac imaging variables will be listed.

4.8.9 Drug-induced liver injury

All data recorded at the "Liver Events" eCRF pages for patients meeting the potential drug-induced liver injury (DILI) criteria will be listed if available.

4.9 Patient-reported outcomes

In this study, the Functional Assessment of Cancer Therapy Gynecology Oncology Group Neurotoxicity Scale (FACT/GOG-NTX, version 4.0) will be collected and assessed.

In order to summarize patient-reported outcome (PRO) variables, assessments will be time slotted using time-windows (Table 2-1). The baseline assessment is defined according to the rule for efficacy variables (Section 2.6).

The FAS will be used for all PRO summaries and listings.

4.9.1 FACT/GOG-NTX questionnaire

Assessment schedule

The questionnaire was to be completed at screening and at Cycle 1 Day 1 (C1D1) immediately prior to starting study drug, Day 1 of each cycle and again at the study completion visit.

Data derivation

For the FACT/GOG-NTX subscales (Table 4-6), lower values denote higher neurotoxicity ranging from 0 to 44. Scoring will be done according to the instructions of the authors (Cella 1997) as detailed in Appendix 3.

Table 4-5 FACT/GOG-NTX scales

(Sub)Scale	Item numbers	Score range
Physical well-being (PWB)	GP1 to GP7	0 – 28
Social/family well-being (SWB)	GS1 to GS7	0 – 28
Emotional well-being (EWB)	GE1 to GE6	0 – 24
Functional well-being (FWB)	GF1 to GF7	0 – 28
Neurotoxicity subscale (NtxS)	Ntx1 to Ntx9, HI12, An6	0 – 44
FACT/GOG-Ntx Total Score	PWB+SWB+EWB+FWB+NtxS	0 – 152

Analyses

- Calculated scores will be summarized by time window.

4.10 Pharmacokinetic analyses

Pharmacokinetics

The PK set-PAN and PK set-BTZ will be used for the following analyses for PAN and BTZ, respectively.

Plasma concentration data of PAN and BTZ:

Summary statistics will be presented for plasma PAN (and its metabolite BJB432, if feasible) and BTZ concentrations at each scheduled time point for PAN on C1D1 and C1D8, respectively, and for BTZ on C1D8. Graphical presentation will also be provided on mean concentration at each scheduled time point for PAN on C1D1 and C1D8, respectively, and for BTZ on C1D8. Summary statistics will include n, arithmetic mean, median, SD, geometric mean, coefficient of variation CV (%) and geometric CV (%), minimum and maximum.

PK parameters of PAN and BTZ:

The aforementioned summary statistics will be presented for all PK parameters except Tmax (specifically, if feasible, AUClast, AUC0-48h, AUC0-24h, AUCinf, Cmax, Lambda_z, T1/2, CL/F, Vz/F for PAN and BJB432 on C1D1 and C1D8, and AUClast, AUC0-48h, AUC0-24h, AUCinf, Cmax, Lambda_z, T1/2, CL/F, Vz/F for BTZ on C1D8). For Tmax, only median, minimum, and maximum will be presented.

Analytical method

The plasma samples from all patients will be assayed for PAN, BTZ, and its metabolite BJB432 (if feasible) concentrations by Novartis using a validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS). Values below the lower limit of quantification (LLOQ) will be reported as 0 ng/mL. Missing values will be labeled accordingly.

5 References

[Brookmeyer R. and Crowley J. (1982)] A Confidence Interval for the Median Survival Time, *Biometrics* 38, 29-41

[Collet D (1994)] Modelling survival data in medical research. London, Chapman & Hall

[Lachin J (2000)] Biostatistical methods: The assessment of relative risk. New York; John Wiley & Sons, Inc.

Appendix 1 – Calculation of glomerular filtration rate (GFR)

The baseline GFR will be calculated for each patient according to the following Cockcroft-Gault equitation (Cockcroft & Gault 1976).

$$C_{CR}\ [\mathrm{mL/min}] = \frac{(140 - \text{age [years]}) \times \text{body weight [kg]}}{72 \times S_{CR}\ [\mathrm{mg/dL}]} \times \text{const}$$

,

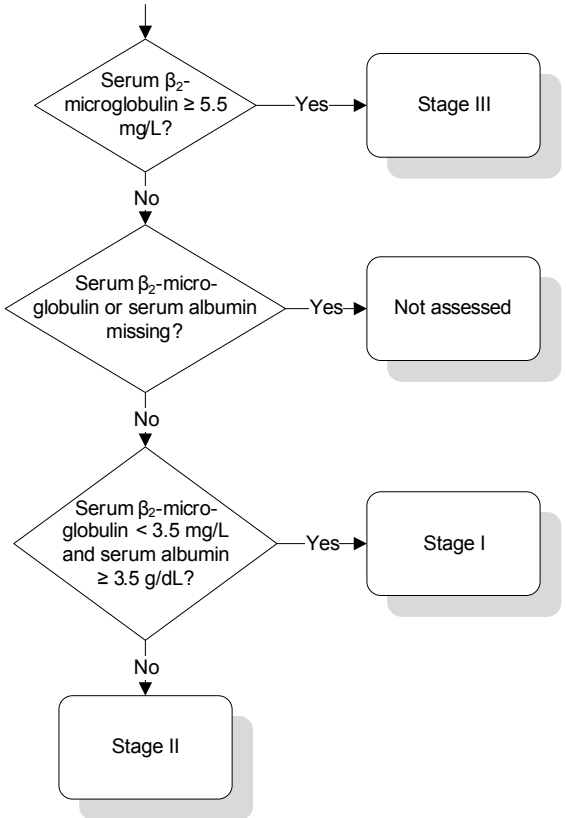
where

C_{CR} Creatinine clearance (used to estimate GFR)
S_{CR} Serum creatinine
const factor = 1.0 for males
0.85 for females

Appendix 2 – Calculation: clinical staging of MM

Patient's clinical stage of multiple myeloma will calculated according to the International Staging System (ISS, Greipp et al 2005) as depicted in Figure 5-1.

Figure 5-1 ISS classification



Appendix 3 - Scoring guides

FACT/GOG-NTX

FACT/GOG-Ntx Scoring Guidelines (Version 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.

4. Add subscale scores to derive total scores (TOI, FACT-G & FACT/GOG-Ntx).

5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**PWB subscale core**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 6: _____

Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
NEUROTOXICITY SUBSCALE (NtxS)	Ntx1	4	-	_____	=_____
	Ntx2	4	-	_____	=_____
	Ntx3	4	-	_____	=_____
	Ntx4	4	-	_____	=_____
Score range: 0-44	Ntx5	4	-	_____	=_____
	HI 12	4	-	_____	=_____
	Ntx6	4	-	_____	=_____
	Ntx7	4	-	_____	=_____
	Ntx8	4	-	_____	=_____
	Ntx9	4	-	_____	=_____
	An6	4	-	_____	=_____

Sum individual item scores:_____
Multiply by 11 : _____
Divide by number of items answered: _____=**Ntx Subscale score**

To Derive a FACT/GOG-Ntx total score:
Score range: 0-152

_____ + _____ + _____ + _____ + _____ =_____=**FACT/GOG-Ntx Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**NtxS** score)

When there are missing data, prorating subscale scores is acceptable as long as more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The FACT/GOG Ntx total score is considered appropriate to score as long as overall item response rate is greater than 80% (e.g., at least 31 of 38 items completed)

In detail:

1. PWB, SWB, EWB, FBW and NtxS scores will only be derived in case > 50% of the corresponding items have been answered.

2. The FACT/GOG Ntx total score will be derived when >80% of the underlying items have been answered (>= 31 out of 38 items). If this is the case, it is derived out of the prorated subscores as described above (see 1). In addition, the total score will only be calculated if each of the component subscales scores is valid.