Statistical Analysis Plan for

Official Title of Study

MULTIPLE PHASE 1/2 SAFETY COHORTS OF NIVOLUMAB MONOTHERAPY OR NIVOLUMAB COMBINATION REGIMENS ACROSS RELAPSED/REFRACTORY HEMATOLOGIC MALIGNANCIES

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STATISTICAL ANALYSIS PLAN
FOR HEMATOLOGIC MALIGNANCY

MULTIPLE PHASE 1/2 SAFETY COHORTS OF NIVOLUMAB MONOTHERAPY OR NIVOLUMAB COMBINATION REGIMENS ACROSS RELAPSED/REFRACTORY HEMATOLOGIC MALIGNANCIES

PROTOCOL CA209039

VERSION # 3.2

REVISION HISTORY

Revision	Date	Revised By	Changes Made – Reasons for the Change
1.0		[redacted]	Original issue
2.0	April 19, 2017	[redacted]	1. Include protocol amendments 04-12 2. Include nivolumab + ipilimumab cohorts, nivolumab + lirilumab, and 2 daratumumab + pomalidomide cohorts and update corresponding sections. 3. Limit biomarker analyses to PD-L1 related analyses 4. Add section 7.3.3 Prior Anti-Cancer Therapy 5. Align safety and immunogenicity sections with nivolumab core safety SAP. 6. Add IRRC efficacy for cHL subjects receiving nivolumab monotherapy. 7. Change the primary definition of PFS and DOR and use the last efficacy assessment date prior to subsequent therapy for censoring. Change initial primary definition of PFS and DOR (use the last visit date prior to subsequent therapy for censoring) to sensitivity definition. 8. Add in section 1"In addition to the administrative interim analyses over the course of the study, an interim analysis is scheduled for the multiple myeloma (MM) cohorts when 30 treated patients in total from the nivolumab/daratumumab cohorts have 3 months of minimum follow-up".
3.0	Feb 26, 2018	[redacted]	1. Include protocol amendments 14 dated 15-Feb-2018 2. Add Cohort B (nivolumab+daratumumab) vs daratumumab monotherapy [ND, D])
3.1	Sep 24 2019	[redacted]	Changed analyses population for the randomized nivolumab/daratumumab cohorts from "all treated subjects" to "all randomized subjects".(disposition, demographics, baseline characteristics, efficacy and biomarker analyses). Updated PFS, OS definitions for nivolumab/daratumumab cohorts from "time from the first dose" to "time from randomization." Subject will be censored on randomization date for PFS when no post-baseline efficacy assessment. Added protocol amendment 15 dated 23-Apr-2019
3.2	Jan 27 2019	[redacted]	Added primary objective for nivolumab/daratumumab cohorts. Added refractory status definition prior anti-cancer therapy section. Added definition of time to best response. Added secondary PFS definition (ITT definition). Added definition of adequate tumor assessment for MM subjects. Added conventions for handling partial and missing dates for death/progression dates. Updated baseline disease characteristics for MM subjects.

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[redacted]

2 STUDY DESCRIPTION

2.1 Study Design

A Phase 1/2 Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity and Preliminary Antitumor Activity of Nivolumab Monotherapy or Nivolumab Combination Regimens in Subjects with Relapsed or Refractory Hematologic Malignancy.

NIVOLUMAB MONOTHERAPY COHORTS

These monotherapy cohorts will consist of Screening (up to 28 days), Treatment (up to 2 years), and Clinical Follow-up (up to 12 months) and Survival Follow-up (up to 2 years). There is also the possibility of Retreatment (up to 1 year) and Follow up (up to 120 days). The first dose administered will be followed by a three-week period for pharmacokinetic and pharmacodynamic assessment of nivolumab. A response assessment following administration of the first dose will be obtained. Therapy will be given on an every two week schedule thereafter with response assessments performed at Weeks 8, 16, 24 and then every 16 weeks thereafter. The scheduled response assessments must be completed before the next dose of therapy.

IPILIMUMAB/NIVOLUMAB COHORTS

These combination cohorts will evaluate the combination of nivolumab and ipilimumab.

These combination cohorts will consist of Screening (up to 28 days), Treatment (up to 2 years), and Follow-up.

LIRILUMAB/NIVOLUMAB COHORTS

These combination cohorts will evaluate the combination of nivolumab and lirilumab.

These combination cohorts will consist of Screening (up to 28 days), Treatment (up to 2 years), and Follow-up.

NIVOLUMAB/DARATUMUMAB COHORTS

Cohort A will evaluate the combination of nivolumab and daratumumab with or without pomalidomide and dexamethasone in subjects with relapsed/refractory MM that received at least 2 prior regimens including at least 2 consecutive cycles of IMID and PI alone or in combination, and were refractory to their last treatment, and pomalidomide, nivolumab, and daratumumab naïve.

Cohort B will evaluate the combination of nivolumab and daratumumab in relapsed/refractory MM subjects that either received at least 3 prior lines of therapy (including an IMID or PI) or are double refractory to IMID and PI, and were nivolumab and daratumumab naive.

The design of the combination cohorts will consist of Screening (up to 28 days), Treatment (until disease progression), and Follow-up (i.e., safety follow-up Visit 1 and 2, and long-term survival follow-up).

2.1.1 Study Design

2.1.1.1 Nivolumab Monotherapy Dose Escalation

Dose Limiting Toxicity

NIVOLUMAB MONOTHERAPY COHORTS

Dose limiting toxicity (DLT) will be determined based on the incidence and intensity of drug related adverse events (AEs) occurring up to two weeks after the administration of the third dose of nivolumab or 7 weeks after initiation of therapy whichever is longer.

Dose Limiting Hematologic Toxicity

DLT will be Grade 4 neutropenia that does not resolve to Grade 3 or less within 5 days of initiation of filgrastim (G-CSF), the need for platelet transfusion or a platelet count < 10,000/μL. The development of a transfusion requirement or an increase in transfusion requirement of more than two units of blood every two weeks over a six week period will also be considered dose limiting unless an alternative cause is identified.

Dose Limiting Non-hematologic Toxicity

Grade 2 or greater eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy or requires systemic treatment.

Clinically relevant Grade 3 or greater non-hematologic toxicity excluding lymphopenia, asymptomatic lipase or amylase or laboratory abnormalities that correct to grade 1 within 72 hours after treatment. Toxicity will be graded by CTCAE v 4.0.

DLTs that occur after the decision to dose escalate will be used to determine the recommended phase II dose for this population.

No dose escalations or de-escalations are permitted within each subject's treatment. A subject who is withdrawn from the study before the completion of the first seven weeks of treatment for a reason other than a DLT may be replaced. Subjects who experience dose limiting toxicity may resume treatment as per Section 4.1.7 of the protocol upon resolution, providing that criteria for permanent discontinuation are not met (Section 4.1.9 of the protocol).

2.1.2 Expansion Cohorts

NIVOLUMAB MONOTHERAPY COHORTS

To further characterize safety and efficacy 4 expansion cohorts will be enrolled. The diseases that will be explored are Hodgkin Lymphoma (HL)/ primary mediastinal B cell Lymphoma (PMBL), T cell lymphoma, B cell lymphoma, and multiple myeloma. A total of 6 or 9 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 or ≤ 2 of 9 subjects experiences a DLT if the MTD is not identified) before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of seven weeks of treatment in the dose escalation phase of the study, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

IPILIMUMAB/NIVOLUMAB COHORTS

To further characterize safety and efficacy, 4 tumor cohorts will be enrolled. The diseases that will be explored are HL/PMBL, T cell lymphoma, B cell lymphoma (diffuse large B cell lymphoma and follicular lymphoma only), and multiple myeloma.

LIRILUMAB/NIVOLUMAB COHORTS

To characterize safety and efficacy, four tumor cohorts will be enrolled. The diseases that will be explored are HL/PMBL, T cell lymphoma, B cell lymphoma (diffuse large B cell lymphoma and follicular lymphoma only), and multiple myeloma.

NIVOLUMAB/DARATUMUMAB COHORTS

Cohort A (ND, ND-Pd): 60 subjects will be randomized at a 1:1 ratio to the ND arm or the ND-Pd arm, respectively.

Cohort B (ND, D): 60 subjects will be randomized in a 2:1 ratio to the ND and D arms, respectively.

2.2 Treatment Assignment

For patients receiving monotherapy nivolumab, nivolumab ill be administered as an IV infusion on treatment day 1 followed by a 3 week interval to evaluate pharmacokinetics and duration of pharmacodynamics effects and then every two weeks for up to 2 years. Two dose levels will be explored, 1 mg/kg or 3 mg/kg, which will be administered at Week 1 and Week 3, then every 2 weeks. Therapy will be continued for up to 2 years with the potential for one additional year of therapy for retreatment eligible subjects in follow up.

For patients receiving nivolumab in combination with ipilimumab therapy, nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg will be administered every three weeks for four doses followed by nivolumab alone at 3 mg/kg every 2 weeks for a total of two years of therapy.

For patients receiving nivolumab in combination with lirilumab therapy, nivolumab 3 mg/kg will be administered every 2 weeks, and lirilumab 3 mg/kg will be administered every 4 weeks for a total of two years of therapy.

For subjects in Cohort A, nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 30 minutes on Day 15 during Cycle 1, and on Days 1 and 15 during Cycles 2 through 6 (ie, every 2 weeks of each 28-day cycle). Starting Cycle 7 and beyond, nivolumab will be administered at a dose of 480 mg as an IV infusion over 30 minutes every 4 weeks (Day 1 of each 28-day cycle). Daratumumab will be administered at a dose of 16 mg/kg as an IV infusion every week (Days 1, 8, 15, and 22 of each 28-day cycle) during Cycles 1 and 2. During Cycles 3 through 6 daratumumab will be administered every 2 weeks (Days 1 and 15 of each 28-day cycle), then starting Cycle 7 and beyond, daratumumab will be administered every 4 weeks (Day 1 of each 28-day cycle). Pomalidomide in the ND-Pd treatment arm will be administered orally at the dose of 4 mg daily on Days 1 - 21 of each 28-day cycle. Dexamathesone in the ND-Pd treatment arm will be administered as described in section 4.1.4.4. of the protocol.

For subjects in Cohort B, those randomized to ND treatment will receive nivolumab at a dose of 240 mg as an intravenous infusion over 30 minutes on Day 15 of Cycle 1. Starting Cycle 2 and beyond, nivolumab will be administered at a dose of 480 mg as an intravenous infusion over 30 minutes every 4 weeks (Day 1 of each 28 day cycle). Daratumumab will be administered at a dose of 16 mg/kg as an IV infusion every week (Days 1, 8, 15, and 22 of each 28-day cycle) during Cycles 1 and 2. During Cycles 3 through 6 daratumumab will be administered every 2

weeks (Days 1 and 15 of each 28-day cycle), then starting Cycle 7 and beyond, daratumumab will be administered every 4 weeks (Day 1 of each 28-day cycle).

Nivolumab should be administered before daratumumab on the days when both nivolumab and daratumumab are administered.

After informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number.

2.3 Blinding and Unblinding

This is an open label study.

2.4 Protocol Amendments

Revised protocol 01 (21-Dec-2012) incorporated Administrative Letter 01 and Amendment 01 and 02.

Amendment number 02 (21-Dec-2012) eliminated the highest (10 mg/kg) of three dose levels scheduled to be examined; it required that 8 of 16 subjects with multiple myeloma be required to undergo bone marrow biopsy while on therapy, and modified the discontinuation criteria to be more stringent.

Amendment number 03 (6-Mar-2013) updated the Summary of Safety section in the protocol to include new preliminary reproductive toxicology data.

Amendment number 04 (25-Jun-2013) eliminated the CML cohort in the expansion phase and increased the size of remaining four cohorts from 16 to 23.

Amendment number 05 (10-Oct-2013) corrected some minor errors and inconsistencies in the protocol.

Amendment number 06 (19-Dec-2013) added cohorts using a combination of ipilimumab and nivolumab in order to determine if the combination results in increased efficacy with tolerable safety, compared to monotherapy with nivolumab alone.

Amendment number 07 (20-Aug-2014) Adds an additional set of cohorts (approximately 80 additional subjects) for dose expansion with combination of lirilumab and nivolumab

Amendment number 08 (02-Dec-2014) Revises protocol to meet FDA guidance.

Amendment number 09 (05-Feb-2015) Removes exploratory cohorts from the nivolumab/ipilimumab cohorts.

Amendment number 10 (15-Apr-2015) Retrospectively collect radiographic images for blinded independent central review.

Amendment number 11 (01-Oct-2015) Update follow up requirements.

Amendment number 12 (09-Aug-2016) Adds an additional set of cohorts (approximately 60 additional subjects) for dose expansion in multiple myeloma patients treated with nivolumab and daratumumab with or without pomalidomide and dexamethasone.

Amendment number 13 (04-Aug-2017) Corrected and updated nivolumab/daratumumab cohorts.

Amendment number14 (15-Feb-2018) Remove nivolumab + ipilimumab cohorts and update corresponding sections. Add Cohort B (nivolumab+daratumumab) vs daratumumab monotherapy [ND, D])

Amendment number 15 (23-Apr-2019): Removed nivolumab+lirilumab and nivolumab monotherapy cohort.

2.5 Data Monitoring and Other External Committees

A post-hoc IRRC will be utilized in this study for determination of IRRC-assessed endpoints, ORR duration of response (DOR), CR and PR rates, time to CR and PR, and duration of CR and PR for cHL subjects in the nivolumab monotherapy cohort only. The IRRC reviews all available tumor assessment scans for all treated cHL subjects receiving nivolumab monotherapy only. Details of IRRC responsibilities and procedures were specified in the IRRC charter.

3 OBJECTIVES

3.1 Primary

Nivolumab monotherapy cohorts: To establish the dose limiting toxicities, maximum tolerated dose and recommended phase 2 dose for nivolumab up to a maximum of 3 mg/kg administered every 2 weeks to subjects with relapsed/refractory hematologic malignancy.

Ipilimumab/nivolumab cohorts: To establish the dose limiting toxicities and a tolerated dose of the combination of nivolumab and ipilimumab in subjects with select relapsed or refractory hematologic malignancies.

Lirilumab/nivolumab cohorts: To establish the tolerated dose of the combination of nivolumab and lirilumab in subjects with select relapsed/refractory hematologic malignancies.

Nivolumab/daratumumab cohorts: To establish the tolerability of the combination of nivolumab and daratumumab, with or without pomalidomide and dexamethasone, in subjects with relapsed/refractory MM.

3.2 Secondary

3.3 NON-NIVOLUMAB/DARATUMUMAB COHORTS

- To characterize the pharmacokinetics of nivolumab when administered as a single agent, nivolumab and ipilimumab when administered in combination, and nivolumab and lirilumab when administered in combination.

- To assess the preliminary antitumor activity of monotherapy nivolumab, the combination of nivolumab and ipilimumab, and the combination of nivolumab and lirilumab in subjects with relapsed/refractory hematologic malignancy.
- To characterize the immunogenicity of nivolumab when administered as a single agent, nivolumab and ipilimumab when administered in combination, and nivolumab and lirilumab when administered in combination.
- To assess the potential association between PD-L1 expression on tumor cells by immunohistochemistry and clinical efficacy measures

NIVOLUMAB/DARATUMUMAB COHORTS

- To assess the minimal residual disease (MRD) status for MM subjects in each treatment regimen group
- To assess overall response rates (ORR) and duration of response (DOR) for MM subjects in each treatment regimen group
- To assess progression free survival (PFS) for MM subjects in each treatment regimen group
- To characterize the immunogenicity of nivolumab when administered in combination with daratumumab
- To characterize the pharmacokinetics of nivolumab when administered in combination with daratumumab

4 ENDPOINTS

4.1 Primary

The primary objective to characterize the safety and tolerability of nivolumab monotherapy and combination therapy will be measured by the following endpoints:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

4.2 Secondary

4.2.1 Pharmacokinetics

The following pharmacokinetic parameters of nivolumab, ipilimumab, and lirilumab, will be derived from serum concentration time profiles of subjects and used to measure the secondary objective related to pharmacokinetics at time points specified in section 5.1 of the protocol:

Cmax - Maximum observed serum concentration

Tmax - Time of maximum observed serum concentration

Cmin - Serum concentration achieved at the end of dosing interval (trough concentration)

AUC(0-T) -Area under the plasma concentration-time curve from time zero to the last time of the last quantifiable concentration

AUC(TAU) - Area under the concentration-time curve in one dosing interval

Ceoinf - Serum concentration achieved at the end of study drug infusion

4.2.2 Efficacy

The secondary objective relating to efficacy is to assess the preliminary antitumor activity of monotherapy nivolumab, the combination of nivolumab and ipilimumab, the combination of nivolumab and lirilumab across select relapsed or refractory hematologic malignancies. This objective will be measured by tabulations of individual BOR and analyses of the ORR, duration of response, Progression Free Survival Rate (PFS Rate), and Progression Free Survival (PFS). The BOR outcomes will be based on the disease specific criteria (specified in Appendices 1, 2, and 5 of the protocol) for lymphoma, Cutaneous T-Cell and MM, respectively. Response will be based on efficacy assessments per section 5 of the protocol.

Following protocol amendment 10 which allowed for radiological images to be collected for independent central review, subjects with cHL receiving monotherapy nivolumab were retrospectively evaluated by an IRRC (2007 IWG criteria). Unless otherwise specified, the efficacy endpoints will be derived based on both investigator assessment per the International Workshop to Standardized Response Criteria for Lymphoma per protocol appendix 1 and IRRC assessment according to the 2007 IWG criteria. The investigator-based efficacy endpoints would

be the primary efficacy endpoints, and the IRRC-based efficacy endpoints would be the secondary efficacy endpoints.

In addition, the preliminary antitumor activity of nivolumab in combination with daratumumab will be evaluated in subjects with relapsed/refractory MM in Cohorts A and B. This endpoint will be measured by MRD, ORR, DOR and PFS in each treatment regimen group.

Best Overall Response (BOR)

The Investigator-reported BOR is defined as the investigator determined best response designation over the study as a whole (or at specific landmark interim analyses), recorded between the date of first dose and the date of objectively documented progression, whichever occurs first. The Investigator-reported BOR is captured in CRF form.

The IRRC-assessed BOR for cHL nivolumab monotherapy patients is defined as the best response designation recorded between the date of first dose and the date of initial documented progression per the 2007 IWG criteria or the date of subsequent anticancer therapy, whichever occurs first. Allogeneic SCT and ASCT will be considered as subsequent anticancer therapy. For subjects without documented progression or subsequent anticancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial 2007 IWG defined progression. The IRRC-assessed BOR is applicable only to cHL subjects receiving nivolumab monotherapy.

Progression Free Survival Rate (PFS Rate)

The PFSR is defined as the probability of a subject remaining progression free or surviving to time t, where t = 6, 12, 18 and 24 months This probability will be calculated by the product limit method (Kaplan-Meier estimate) which takes into account censored data.

Progression Free Survival (PFS)

The primary definition of PFS is defined as the time from the date of first dose of study medication to the date of first confirmed disease progression or death, or the time between date of randomization and the date of first documented progression or death for nivolumab/daratumumab cohorts. Subjects who remain alive and have not progressed will be censored on the last adequate tumor assessment date on or prior to the date of subsequent therapy. Allogeneic SCT and ASCT will be considered as subsequent therapy. Subjects who did not have any post-baseline efficacy assessment and did not die will be censored on the date of first dose of study medication or date of randomization for nivolumab/daratumumab cohorts.

The secondary definition of PFS (ITT definition) is defined as the time from the date of first dose of study medication to the date of first disease progression or death, or the time between date of randomization and date of progression or death. Subjects who remain alive and have not progressed will be censored on the last adequate tumor assessment date. Subjects who did not have any post-baseline efficacy assessment and did not die will be censored on the date of first dose of study medication or date of randomization for nivolumab/daratumumab cohorts.

For MM subjects, an adequate tumor assessment visit for ruling out progression will require the following information: Serum monoclonal paraprotein results, if measurable at baseline and Urine monoclonal paraprotein results, if measurable at baseline, or for subjects who do not have measurable serum and urine monoclonal paraprotein results, serum free light chain results, if measurable at baseline.

Sensitivity analyses will be performed based on an alternate censoring scheme to account for non-uniform and infrequent tumor assessment schedules. For this analysis, subjects will be censored on their last visit date, defined as the last date of dosing, tumor assessment or lab assessment, whichever occurs last.

Table 1: Censoring Scheme for Primary and Sensitivity Analysis PFS

Situation	Primary	Sensitivity
No progression per response criteria, no death and no subsequent anticancer therapy	Censored on the date of last tumor assessment	Censored on the date of last visit date
No progression per response criteria, no death and with subsequent anticancer therapy	Censored on the date of last tumor assessment prior or on the date of initiation of the subsequent anticancer therapy	Censored on the date of last visit prior or on the date of initiation of the subsequent anticancer therapy
Progression per response criteria without a subsequent anticancer therapy started	Event on the date of the first documented tumor progression per response criteria	Event on the date of the first documented tumor progression per response criteria
Progression or death after a subsequent anticancer therapy started	Censored on the date of last tumor assessment prior or on the date of initiation of the subsequent anticancer therapy	Censored on the date of last visit prior or on the date of initiation of the subsequent anticancer therapy
Death without progression per response criteria and without subsequent anticancer therapy started	Event on the date of death	Event on the date of death

Objective Response Rate (ORR)

Objective response rate is defined as the proportion of subjects whose BOR is one of the following responses divided by the number of treated subjects or number of randomized subjects in nivolumab/daratumumab cohort.

- for lymphoma subjects whose BOR is either complete remission or partial remission
- for myeloma subjects whose BOR is stringent complete response, complete response, very good partial response, or partial response

Duration of Response

Duration of response will be only calculated for subjects with best overall response of objective response defined as above. The duration of response is defined as the time between the date of first documented objective response and the date of first documented disease progression, or death, whichever is earlier. Subjects who remain alive and have not progressed will be censored on the last adequate efficacy assessment date prior to subsequent cancer therapy. Allogeneic SCT and ASCT will be considered as subsequent therapy.

Sensitivity analyses will be performed based on an alternate censoring scheme (same as PFS censoring scheme) to account for non-uniform and infrequent tumor assessment schedules. For this analysis, subjects will be censored on their last visit date, defined as the last date of dosing, tumor assessment or lab assessment, whichever occurs last.

Duration of response will be evaluated for responders (PR or CR for lymphoma subjects; SCR, CR, VGPR, or PR for myeloma subjects) only.

Time to Response (TTR)

Time to response is defined as the time from date of first dose of study medication or date of randomization for nivolumab/daratumumab to the date of the first documented objective response. Time to response will only be evaluated in subjects with minimal objective response of PR.

Time to best response is defined as the time from date of first dose of study medication or date of randomization for nivolumab/daratumumab to the date of the best overall response.

Tumor Measurements (Lymphoma)

For Hodgkin/PMBL, T cell lymphoma, B cell lymphoma subjects, target lesion tumor burden will be derived from tumor measurements.

Serum and Urine M-Protein and Free Light Chain (Myeloma)

Serum and urine tests will be performed for Myeloma subjects. For the complete list of the serum and urine tests, please refer to section 5.1 of the protocol.

FDG-PET Assessment (HL or PMBL)

FDG-PET/CT imaging scans were performed at screening, and the end of treatment for HL or PMBL subjects. The FDG-PET endpoints are the overall assessment of the scan.

mSWAT (cutaneous T cell lymphoma)

Response in skin for subjects with cutaneous T cell lymphoma will be evaluated by the mSWAT score which is reported by investigators.

Minimal Residual Disease (MRD)

In the nivolumab/daratumumab cohorts, MRD from bone marrow aspirate will be evaluated. MRD will be assessed by Next Generational Flow Cytometry (NGF) and Next Generational Sequencing (NGS).

The timepoint MRD negativity status is a dichotomized variable for quantifiable MRD detection. MRD negativity status will be considered at 10^{-5}, as per IMWG guidelines; other sensitivity levels such as 10^{-4} and 10^{-6} will also be considered.

The first MRD negative status is defined as the first negative status designation over the study as a whole, recorded between the date of first dose and the date of objectively documented progression or the date of subsequent therapy, whichever occurs first.

The best MRD negative status is defined as the best status designation with the lowest sensitivity level over the study as a whole, recorded between the date of first dose and the date of objectively documented progression or the date of subsequent therapy, whichever occurs first.

Time to the first MRD negative status is defined as the time from the date of randomization to the date of the first MRD negative status.

The duration of the MRD negativity is defined as the time between the date of first MRD negativity to the date of the first MRD positivity, or the date of the first objectively documented progression as assessed according to IMWG criteria or death due to any cause whichever is earlier prior to the initiation of subsequent anti-cancer therapy. Subjects who didn't have MRD positivity, and didn't progress nor die will be censored on the date of their last MRD negativity prior to the initiation of subsequent anti-cancer therapy.

4.2.3 *Immunogenicity*

The immunogenicity status of nivolumab, ipilimumab, and lirilumab will be analyzed.

Refer to Core Safety SAP.[1]

[redacted]

CSR.

[redacted]

5 SAMPLE SIZE AND POWER

NIVOLUMAB MONOTHERAPY COHORTS

The sample size in the escalation phase is not based on statistical consideration, but rather depends on the number of observed toxicities; between 6 and 9 subjects are expected to be treated at each dose. At the dose expansion cohorts, approximately 23 subjects are expected to be enrolled in each of four tumor types and treated at the previously determined MTD or if no MTD is identified a maximum dose of 3 mg/kg.

In an expansion cohort, if 4 (17.4%) or 5 (21.7%) responses are observed with 23 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 7.8% and 11.0% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals.

In addition, if the true ORR in a tumor type/expansion cohort is 20% then with 23 patients in each cohort there is 86.7% chance of observing at least 3 responses or 13.3% chance of observing 0, 1 or 2 responses (false negative rate). If the true ORR in a tumor type is 5% rather than 20%, then there is 10.5% chance that there will be at least 3 responses in 23 subjects (false positive rate).

IPILIMUMAB/NIVOLUMAB COHORTS

In a tumor cohort, if 3 (21%) or 4 (29%) responses are observed with 14 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 8% and 13% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals.

In addition, if the true ORR in a tumor cohort is 20% then with 14 patients in each cohort there is 80% chance of observing at least 2 responses and 96% chance of observing at least 1 response, or 20% chance of observing 0 or 1 response (false negative rate) and 4% chance of observing 0 response (false negative rate). If the true ORR in a tumor cohort is 5% rather than 20%, then there is 15% chance that there will be at least 2 responses in 14 subjects (false positive rate).

The sample size in the exploratory schedule evaluation is not based on statistical considerations, but rather depends on the number of observed toxicities; between 3 and 9 subjects are expected to be treated in cohorts 3 and 4.

Subsequent cohorts may be tested if required.

Administration of the study drug to 9 subjects at a dose level in exploratory schedule evaluation provides 90% probability of observing at least one occurrence of any adverse event that would occur with a 22% incidence in the population from which the sample is drawn.

Approximately 6-18 subjects are expected to be enrolled in exploratory schedule evaluation and approximately 56 in tumor expansion.

LIRILUMAB/NIVOLUMAB COHORTS

In a tumor cohort, if 4 (20%) or 5 (25%) responses are observed with 20 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 9% and 13% respectively. In a tumor cohort, if 3 (10%) or 6 (20%) responses are observed with 30 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 4% and 11% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals.

In addition, if the true ORR in a tumor cohorts is 20% then with 20 patients in each cohort there is 93% chance of observing at least 2 responses, or 7% chance of observing 0 or 1 response (false negative rate). If the true ORR in a tumor type is 5% rather than 20%, then there is 26% chance that there will be at least 2 responses in 20 subjects (false positive rate). If the true ORR in a tumor cohort is 20% then with 30 patients in each cohort there is 88% chance of observing at least 4 responses, or 12% chance of observing 3 or fewer responses (false negative rate).

If the true ORR in a tumor type is 5% rather than 20%, then there is 6% chance that there will be at least 4 responses in 30 subjects (false positive rate).

Approximately 130 subjects are expected to be enrolled in tumor cohorts.

The probability (%) of observing at least a certain response rate given a true ORR (%) is presented in Table 8.1-1 of the protocol.

NIVOLUMAB/DARATUMUMAB COHORTS

Cohort A (ND ± Pd) is closed to enrollment.

The planned sample size for Cohort B (ND, D) will be approximately 60 treated subjects, randomized in a 2:1 ratio to the ND and D arms, respectively. The sample size is not powered for statistical hypothesis testing, but designed to evaluate both the safety profile and clinical benefit of nivolumab in combination with daratumumab.

If the true toxicities incidence rate in a cohort is 20% then with 20 patients in the D cohort there is a 7% chance of observing 0 - 1 toxicities (false negative rate). If the true toxicities incidence rate in a cohort is 5% rather than 20%, then there is 26% chance that there will be at least 2 toxicities in 20 subjects (false positive rate). If the true toxicities incidence rate in a cohort is 20% then with 40 patients in ND cohort there is 3% chance of observing 0 - 3 toxicities (false negative rate). If the true toxicities incidence rate in a cohort is 5% rather than 20%, then there is 14% chance that there will be at least 4 toxicities in 40 subjects (false positive rate).

In two daratumumab monotherapy studies in relapsed/refractory MM patients, including a Phase 1/2 dose escalation study (GEN501) in patients with at least 2 lines of prior therapy and a Phase 2 study (SIRIUS) in patients with at least 3 lines of prior therapy, the ORR were 36% and 29.2% respectively. In two combination studies in relapsed/refractory MM patients with at least 2 lines of prior therapy, including a Phase 1b study of daratumumab in combination with pomalidomide and dexamethasone and a Phase 1 dose-escalation study of pembrolizumab in combination with pomalidomide and dexamethasone, the ORR were 60%. At observed ORR ≥

55% with 20 subjects, the lower bound of the 95% CI exceeds 31.5%. At observed ORR ≥ 77.5% with 40 subjects, the lower bound of the 95% CI exceeds 61.5%.

At observed MRD negative rate ≥ 30% with 20 subjects and observed MRD-target negativity rates ≥ 20% with 40 subjects, the lower bound of the 95% CI are 11.9% and 9.1% respectively, compares favorably to historical MRD-target negativity rate of 8% in the target population.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

NIVOLUMAB MONOTHERAPY COHORTS

This study consists of Screening (up to 28 days), Treatment (up to 2 years), Clinical Follow-up (up to 12 months) and Survival Follow-up (up to 2 years). There is also the possibility of Retreatment (up to 1 year) and Follow up (up to 120 days).

IPILIMUMAB/NIVOLUMAB COHORTS

The study will consist of Screening (up to 28 days), Treatment (up to 2 years), and Follow-up.

LIRILUMAB/NIVOLUMAB COHORTS

The study will consist of Screening (up to 28 days), Treatment (up to 2 years), and Follow-up.
NIVOLUMAB/DARATUMUMAB COHORTS

The study will consist of Screening (up to 28 days), Treatment (until disease progression), and Follow-up.

6.2 Treatment Regimens

Table 2: Treatment Information

Regimen	Specification
Nivolumab	Nivo 1
Nivolumab	Nivo 3
Nivolumab + Ipilimumab	Nivo 3 + Ipi 1
Nivolumab + Lirilumab	Nivo 3 + Liri 3
Cohort A	
Nivolumab + Daratumumab + Pomalidomide + Dexamethasone Nivolumab + Daratumumab	Nivo + Dara + Pom + Dex Nivo + Dara
Cohort B	
Nivolumab + Daratumumab	Nivo+Dara
Daratumumab	Dara

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who sign informed consent form and were registered in IVRS.
- All Randomized MM subjects: All enrolled MM subjects who were randomized to one of nivolumab and daratumumab cohorts.
- All Treated Subjects: All subjects who signed informed consent and received at least one dose of study medication are considered treated and are included in the treated population
- Pharmacokinetic (PK) Population: All subjects who receive at least one dose of study medication and have available serum concentration data.
- Response Evaluable Subjects: All treated subjects with measurable disease at baseline and one of the following: 1) at least one on-treatment efficacy assessment, 2) clinical progression, or 3) death.
- Immunogenicity evaluable subjects:
  - Nivolumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline nivolumab immunogenicity assessment.
  - Ipilimumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline Ipilimumab immunogenicity assessment.
  - Lirilumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline Lirilumab immunogenicity assessment.
- All Treated PD-L1 Evaluable Subjects: All treated subjects with quantifiable PD-L1 expression (ie excludes indeterminate and unknown).
- All MRD Evaluable Subjects: All subjects in Cohorts A and B with available MRD status data.

7 STATISTICAL ANALYSES

7.1 General Methods

All analysis will be performed in SAS using version 8.2 or higher. Some figures will be generated using S-Plus.

Continuous variables will be summarized using descriptive statistics, i.e. medians, minimums, maximums and means with standard deviations. Categorical variables will be summarized by frequencies and percents. Percentages will be rounded and, therefore, may not always add up to 100.

Unless specified otherwise, analyses will be performed by disease type within each treatment group.

7.2 Study Conduct

7.2.1 Accrual

Number (%) of subjects accrued by country and investigational site will be presented on the all enrolled subjects. The corresponding listing will be provided.

7.2.2 Protocol Deviation

Deviation from protocol inclusion and exclusion criteria will be listed for all treated subjects for nivolumab monotherapy cohorts, nivolumab/lirilumab cohorts, nivolumab/Ipilimumab cohorts and all randomized MM subjects for nivolumab/daratumumab cohorts.

7.3 Study Population

7.3.1 Subject Disposition

The number of subjects enrolled into the study, the number of subjects entering the treatment period or the number of subjects randomized and the number of subjects enrolled but not randomized/treated together with the reasons for not being dosed will be summarized.

The number of treated subjects, the number of subjects discontinuing during treatment period along with the reasons for discontinuation, and the number of subjects continued to be followed after discontinuing will be summarized by dose level or by treatment arm for nivolumab/daratumumab cohorts.

All related data will be listed.

7.3.2 Demographics and Other Baseline Characteristics

Subject demographics and baseline characteristics will be summarized for all treated subjects for nivolumab monotherapy cohorts, nivolumab/lirilumab cohorts, nivolumab/Ipilimumab cohorts and all randomized MM subjects for nivolumab/daratumumab cohorts.

Demographic characteristics include age in years, age category (<65 vs. ≥ 65; ≥ 75), gender, race, ethnicity, ECOG, and weight.

Baseline characteristics include: baseline disease characteristics (disease diagnosis, stage), prior therapy surgery, radiotherapy and systemic cancer therapy), general medical history, and baseline cytogenetic status.

For multiple myeloma subjects, baseline disease characteristics include time to study entry from disease diagnosis, ISS stage, IMWG risk stage, prior systemic cancer therapy, prior ASCT, refractoriness to prior therapies (i.e., IMiD, PI, last treatment), type of measurable disease, percentage bone marrow plasma cells, general medical history, and cytogenetic profile at study entry.

The risk factors for potential events such as pulmonary related events will be listed by dose levels for nivolumab monotherapy cohort.

All related data will be listed.

7.3.3 Prior Anti-Cancer Therapy

For non-nivolumab/daratumumab cohorts, the following will be summarized: 1. by disease type and treatment arms, 2. by prior ASCT (subjects who were treated with prior ASCT) and ASCT

naive (subjects who weren't treated with prior ASCT) within disease type and treatment arms, and 3. by Responders vs. Non-Responders.

- Number of prior regimens
- Best response to prior systemic therapy
- Best response to the most recent prior systemic therapy
- Time from completion of the most recent prior regimen to the 1st dose of study medication

For nivolumab-daratumumab cohorts, refractoriness to prior anti-myeloma therapy is defined as progression that occurred on treatment or within 60 days of the last dose of the respective prior treatment. A subject will not be considered as refractory to a prior therapy if the date of progression to the respective prior treatment is missing. Missing/partial dates will be imputed according to the rule in Section 8.

For nivolumab/daratumumab cohorts, the following will be derived and summarized:

- Number of prior regimens
- Refractory to a IMiD
- Refractory to Proteasome Inhibitor (PI)
- Refractory to both IMiD and PI
- Refractory to most recent prior therapy

IMiD includes lenalidomide, thalidomide, and pomalidomide. PI includes bortezomib, carfilzomib, and ixazomib. Refractory status to PI or IMiD will be derived for subjects who received at least two consecutive cycles (2 months) of PI or IMiD,

7.4 Extent of Exposure

Summaries of exposure will be based on all treated subjects.

7.4.1 Study Therapy

For nivolumab, ipilimumab, lirilumab, daratumumab, pomalidomide and dexamethasone, the following parameters will be listed and summarized.

- Number of doses
- Duration of therapy
- Cumulative dose per subject
- Dose intensity per subject (/week)
- Relative dose intensity per subject

Cumulative dose (mg/kg) is defined as: the sum over the duration of the study of all delivered doses (mg/kg) per subject.

Dose intensity per subject (/week) is calculated as the cumulative dose (mg/kg) divided by the duration of therapy (weeks).

Relative dose intensity is defined as dose intensity divided by planned dose per week (relative dose (%) = dose intensity / planned dose per week) * 100).

Duration of therapy (weeks) is defined as: (last dose date - first dose date + 1)/7.

A listing of study drug administered will be provided. Duration of therapy, cumulative dose, dose intensity and relative dose intensity of relative study drugs will be listed. A listing of study medication by batch (or vial) number will be provided.

7.4.2 Dose Change of Study Therapy

Dose change (interrupted, dose omission, delayed or discontinued) with associated reason will be listed for each subject and summarized by dose levels and overall or by treatment group for nivolumab/daratumumab cohorts. The number of subjects with infusion interruptions, reason for first interruption and duration of first interruption of study medication will be summarized by dose levels and overall or by treatment group for nivolumab/daratumumab cohorts. Dose delays and discontinuation (with associated reason, retrieved from CRF dosing pages) of study medication will be summarized.

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7.5 Efficacy

The summary of efficacy measures will be grouped by treatment arm and dose level within each disease type and/or within each sub-disease type by histology.

Efficacy analyses will be performed for all treated subjects for the nivolumab monotherapy cohort, nivolumab/lirilumab cohort, nivolumab/ipilimumab cohort and all randomized MM subjects for nivolumab/daratumumab cohorts. The ORR, time to response, duration of response, PFSR, and PFS, as assessed by the IRRC (only for cHL subjects receiving nivolumab monotherapy) and the investigator will be analyzed. ORR in the nivolumab/daratumumab cohorts will be assessed by investigator only.

Best Overall Response

BOR outcomes will be tabulated. A frequency distribution of the BOR outcomes together with ORR with corresponding 2-sided 95% exact confidence interval will be tabulated.

Objective Response Rate

The objective response rate (ORR) and corresponding two-sided 95% exact confidence interval will be provided by within each treatment cohort by disease type, and by treatment arm within each nivolumab/daratumumab cohorts based on the Clopper-Pearson method.

Duration of Response

The median duration of response will be estimated by Kaplan-Meier methodology depending on data availability. The corresponding 95% confidence interval will be derived based on Greenwood formula and log-log transformation. The number of subjects still in response at the time of database lock will be indicated. If number of responders is small, the above analysis may not be performed. Duration of response will be listed.

Progression Free Survival

Kaplan-Meier plots of PFS will be provided. PFS Rate at select time points will be estimated by Kaplan-Meier methodology, and the corresponding two-sided 95% confidence interval will be derived based on Greenwood formula depending on data availability.

Time to Response

TTR will be derived and listed. TTR will be summarized in a swimmer plot. Time to best response will be derived and listed for nivolumab/daratumumab cohorts.

Tumor Measurements (Lymphoma)

For lymphoma subjects, tumor measurements, target lesions tumor burden (the sum of the products of the greatest diameters) at each visit, along with corresponding percent change from baseline, will be listed.

Individual percent changes in the target lesion tumor burden over time may be presented graphically (a.k.a spider plot) (Hodgkin/PMBL, T-cell lymphoma, B-cell lymphoma) based on data availability within a disease type.

The individual maximum tumor reduction from baseline may be presented graphically (a.k.a waterfall plot) based on data availability within a disease type.

Spider plot and waterfall plot will exclude multiple myeloma and cutaneous T-cell Lymphoma patients.

Tumor measurements for subjects received treatment beyond progression will be listed.

Overall Survival

Median overall survival and corresponding two-sided 95% confidence interval will be estimated by K-M method. Kaplan-Meier plots of OS will be provided.

Duration of Follow-up

The descriptive median, minimum and maximum will be calculated for the duration of follow-up.

Serum and Urine M-Protein and serum Free Light Chain (Myeloma)

Summary statistics for serum and urine test results, and corresponding changes (or percent changes) from baseline will be tabulated.

For patients with measurable disease in serum M-protein (=>0.5 g/dL) and/or measurable disease in urine M-protein (=>200 mg/24 hours), the individual percent changes in the M-protein over time will be presented graphically (a.k.a spider plot). If the disease is not measurable by either serum M-Protein (<0.5 g/dL) or urine M-protein (<200 mg/24 hours), the individual percent changes in the serum free light chain over time will be presented graphically (a.k.a spider plot).

FDG-PET Assessment (HL or PMBL)

The number and percentage of subjects with PDG-PET scan performed will be summarized by visit for HL and PMBL subjects. Among subjects with PDG-PET scan performed, the number and percentage of subjects with abnormal findings will be summarized by visit.

All related data will be listed.

mSWAT Score

To evaluate the response in skin for subjects with cutaneous T cell lymphoma, the percentage change from baseline on the mSWAT score will be derived and listed at subject level.

MRD (nivolumab-daratumumab)

Analyses of MRD status will be based on all evaluable MRD subjects and performed at each sensitivity level. Both molecular and cytometry MRD status from bone marrow aspirate will be evaluated. MRD negativity status will be evaluated by timepoints. Summary statistics of time to the first MRD negativity will be provided by treatment group for subjects achieving MRD negative status. Cumulative MRD negativity rates will be tabulated at the first on-study assessment (i.e, C4D1 or ≥VGPR, whichever occurs first) and every 6 months thereafter depending on the data availability. Median duration of the MRD negativity and corresponding two-sided 95% CI will be analyzed by KM product limit method for subjects who achieved MRD negative status depending on the data availability. A plot of individual time course of abnormal bone marrow plasma cells will be produced.

7.6 Safety

Safety summary tables will be generated for all treated subjects. Listings will include all available data.

7.6.1 Death

See CORE Safety SAP.[1]

7.6.2 Serious Adverse Events

See CORE Safety SAP.[1]

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See CORE Safety SAP.[1]

7.6.4 Adverse Events Leading to Dose Modification

See CORE Safety SAP.[1]

7.6.5 Adverse Events

See CORE Safety SAP.[1]

7.6.6 Select Adverse Events

See CORE Safety SAP.[1]

7.6.7 Immune Modulating Medication

See CORE Safety SAP.[1]

7.6.8 Multiple Events

See CORE Safety SAP.[1]

7.6.9 Laboratory Parameters

See CORE Safety SAP.[1]

7.6.10 Vital Signs

See CORE Safety SAP.[1]

7.6.11 Immunogenicity Analysis

Immunogenicity analyses will be performed separately for Nivolumab ADA Evaluable Subjects. See CORE Safety SAP.[1]

7.6.12 Pregnancy

See CORE Safety SAP.[1]

7.6.13 Clinical Safety Program (CSP)

See CORE Safety SAP.[1]

7.7 Pharmacokinetics

Summary statistics will be tabulated for the pharmacokinetic parameters of nivolumab when administered as a single agent, nivolumab and ipilimumab when administered in combination, nivolumab and lirilumab when administered in combination and nivolumab when administered in combination with daratumumab by treatment arm and dose level in each study week as appropriate. To describe the dependency on dose, scatter plots of Cmax and AUC(0-T) versus dose will be provided for each day measured. To assess attainment of steady state, plots of Cmin versus time will be provided. Pharmacokinetic concentrations from all samples will be listed (including the limited samples collected but not included in parameter calculations), and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report.

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8 CONVENTIONS

In general, EmBARC standard time windowing, imputation rules, and counting rules will be applied.

- For death dates, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
  - If the month or the year is missing, the death date will be imputed as the last known alive date.
  - If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive.
- For date of progression after start of study therapy, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. In case of the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
  - For date of progression to prior therapies, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For date of progression to prior therapies, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For other partial/missing dates, the following conventions were used:
  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, “July 1” will be used to replace the missing information.
  - If a date is completely missing, it will be considered as missing.

8.1 Safety Data Conventions

Safety data will be handled according to the BMS safety data conventions (described in "Analysis of Safety Data"). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

8.2 Baseline Measurements

For laboratory measures the following will be used, in a hierarchical sequence, to select the baseline (if a criterion does not apply it would be skipped in the sequence):

- The baseline value corresponds to the last lab drawn prior to first dose of study drug;
- If both local and central laboratory values qualify as baseline according to the above criterion, the central laboratory value will be used as the baseline value.

For all other measures (tumor, vital etc.) the baseline value is the last value prior to the first dose of study drug.

8.3 Multiple Measurements

Laboratory Measures

For tabulations of changes from baseline the following will be used, in a hierarchical sequence, to select the post-treatment measurement included in the analysis (if a criterion does not apply it would be skipped in the sequence):

- If multiple laboratory measurements are obtained within the same scheduled time frame, then the measurement obtained on the time closest to the target time/day will be used;
- If more than one value meets the above criterion, then the measurement obtained on the earlier time will be used;
- If both local and central laboratory values qualify as baseline according to the above criterion, the central laboratory value will be used as the baseline value;
- If more than one value meets the above criterion, then the average value will be used.

For tabulations by CTC grade and summarized by worst toxicity grade, if multiple laboratory measurements are obtained within a analysis period (post-baseline), then the worst measurement within the analysis period, respectively, will be used.

Vital Signs

The following criteria will be used, in a hierarchical sequence, to select the post-treatment measurement included in the analysis:

- If multiple vital sign measurements are obtained within the same scheduled time frame, then the measurement obtained on the time closest to the target time/day will be used;

- If more than one value meets the above criterion, then the measurement obtained on the earlier time will be used;
- If more than one value meets the above criterion, then the average value will be used.

9 CONTENT OF REPORTS

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