Official Title: NON-COMPARATIVE, MULTI-COHORT, SINGLE ARM, OPEN-LABEL, PHASE 2 STUDY OF NIVOLUMAB (BMS-936558) IN CLASSICAL HODGKIN LYMPHOMA (CHL) SUBJECTS AFTER FAILURE OF AUTOLOGOUS STEM CELL TRANSPLANT (ASCT)

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

NON-COMPARATIVE, MULTI-COHORT, SINGLE ARM, OPEN-LABEL, PHASE 2 STUDY OF NIVOLUMAB (BMS-936558) IN CLASSICAL HODGKIN LYMPHOMA (CHL) SUBJECTS AFTER FAILURE OF AUTOLOGOUS STEM CELL TRANSPLANT (ASCT)

PROTOCOL(S) CA209205

VERSION # 3.1

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[redacted]

Research Hypothesis:

Cohorts A, B and C: Treatment with nivolumab will lead to clinical benefit, as demonstrated by a clinically meaningful objective response rate, including durable responses with substantial magnitude of tumor burden reduction in heavily treated cHL subjects.

Cohort D: A new regimen, consisting of nivolumab monotherapy followed by the combination of nivolumab and chemotherapy (AVD; a combination of doxorubicin, vinblastine and dacarbazine), will be safe and tolerable in previously untreated cHL subjects with newly diagnosed advanced stage (Stage IIB, III and IV) disease.

Schedule of Analyses:

Cohorts A, B and C: The objective response rate (ORR) based on independent radiologic review committee (IRRC) assessment is the primary endpoint of this study. Primary analysis will be performed separately for each cohort (i.e. at separate time points) upon completion of a pre-specified amount of follow-up after last patient first treatment (LPFT) as follows:

- Cohort A: Primary ORR analysis after 1 year minimum follow-up in all Cohort A subjects.
- Cohort B: Primary ORR analysis after 6 months minimum follow-up in all Cohort B subjects.
- Cohort C: Primary ORR analysis after 1 year minimum follow-up in all Cohort C subjects.

In addition, safety analyses will be performed on combined cohorts. Additional survival analysis will be conducted for up to 5 years beyond analysis of the primary endpoint. Analysis schedules were chosen based on a median duration of response (6.7 months) and a median duration of CR (20.5 months) observed from a pivotal Ph 2 study testing brentuximab vedotin in a similar patient population[2].

Cohort D: The primary analysis for Cohort D will be conducted when all treated patients for Cohort D have completed Follow-up visit 1 and end-of-therapy response assessment. All analyses for Cohort D will be performed separately from other cohorts.

2 STUDY DESCRIPTION

2.1 Study Design

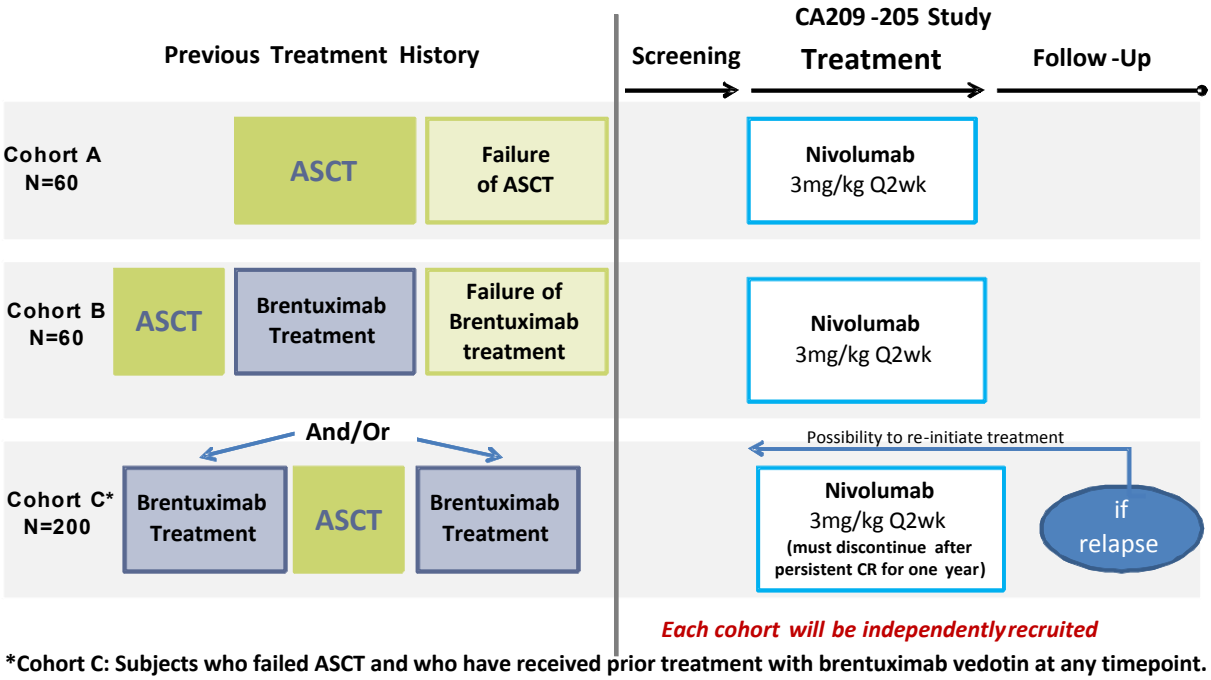
2.1.1 Cohorts A, B and C

This is a non-comparative, parallel cohort, single-arm Phase 2 study in cHL subjects ≥ 18 years old who failed ASCT. Subjects may be brentuximab vedotin-naïve (Cohort A), or may have had prior brentuximab vedotin treatment as a salvage therapy after failure of ASCT (Cohort B). In addition to Cohorts A and B, a third cohort (Cohort C) allows subjects with broader eligibility criteria. Subjects with a treatment history of brentuximab vedotin before first ASCT will not be eligible, except in Cohort C. Approximately 320 subjects with failure after ASCT will be treated with nivolumab 3mg/kg IV every 2 weeks until disease progression or unacceptable toxicity; Cohorts A and B consist of approximately 60 subjects each, whereas approximately 200 subjects will be treated in Cohort C. Subjects will be independently enrolled for each cohort. When one cohort completes enrollment, the other cohort will remain open until its complete accrual is reached.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 14-day dosing period will constitute a cycle.

The study design schematic is presented in Figure 2.1.1-1.

Figure 2.1.1-1: Study Design Schematic (Cohorts A, B and C)

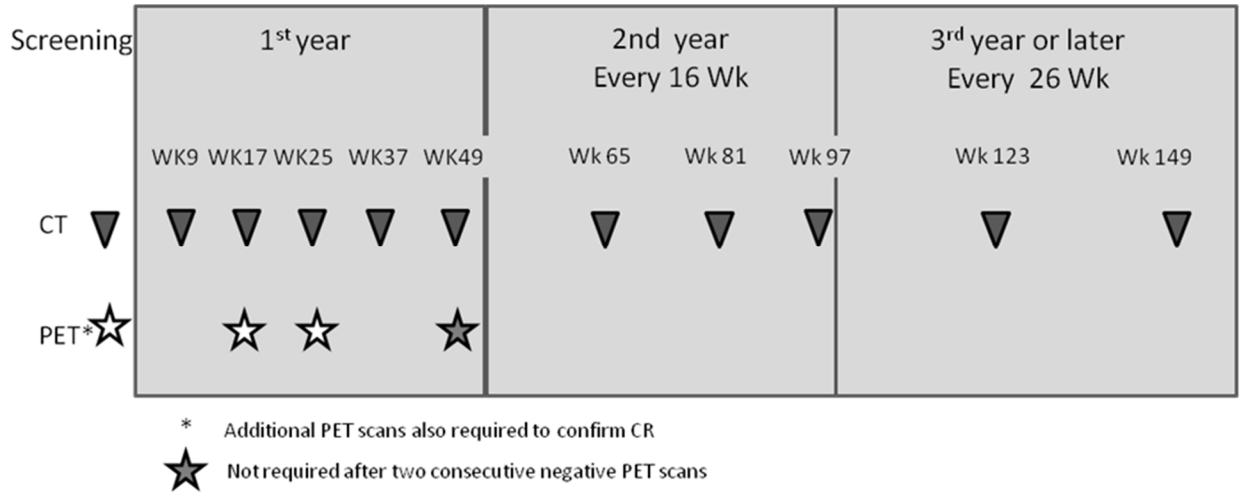


***Cohort C: Subjects who failed ASCT and who have received prior treatment with brentuximab vedotin at any timepoint. Patients may have brentuximab treatment only before ASCT and failure of ASCT. Patients may have failure of ASCT, and failure of post-ASCT brentuximab treatment. Or, patients may have brentuximab treatment before and after ASCT, and failure of brentuximab at enrollment.**

Radiographical tumor assessments by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI) will begin at screening, then at Week 9 (± 7 days) after the start of therapy and will continue at Weeks 17, 25, 37 and 49 for the first year of treatment. CT (preferred) or MRI will continue every 16 weeks (± 14 days) for the second year of treatment. CT (preferred) or MRI will be performed every 26 weeks (± 21 days) for the third year or beyond of treatment. [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scan will be required in all subjects at screening and at Weeks 17 and 25 (± 7 days).

Additionally, a FDG-PET scan at Week 49 (± 7 days) is required for subjects who do not have two consecutive negative FDG-PET scans after Week 1 and prior to Week 49. FDG-PET scan will also be required for confirmation of radiographic CR after initiation of the study drug at other timepoints when FDG-PET is not otherwise scheduled; this FDG-PET scan should be performed within 4 weeks of the CT scan. Tumor assessments will follow the above schedule until disease progression is documented or until the subject initiates a preparative regimen for allogeneic stem cell transplantation (SCT) or autologous stem cell transplant (ASCT), whichever occurs earlier. If the subject discontinues treatment prior to disease progression, tumor assessment will continue in the follow-up phase.

Figure 2.1.1-2: CT or MRI and FDG-PET Scans Schedule (Cohorts A, B and C)



If the subject discontinues study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo IRRC radiographic assessments described here. Instead, they will be evaluated using the following schedule. Tumor assessment (CR or non-CR) will be assessed by the investigator according to the 2007 IWG criteria and will be required on Day 100, at 6 months, 1 year and every year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented. Investigators will make telephone contacts with the subject's referring hematologist/oncologist/transplant physician to obtain CR or non-CR status and document the status if subject is being followed by another physician.

Nivolumab will be administered until unacceptable toxicity or disease progression which is defined by relapsed disease (after CR achieved during the study) or progressive disease (after PR, SD attained during the study) according to the 2007 IWG criteria. In addition, subjects in Cohort C are to discontinue treatment following a 1 year persistent CR, with the possibility to reinitiate therapy upon relapse.

Treatment beyond investigator-assessed progression is permitted in the circumstances specified in the protocol.

2.1.2 Cohort D

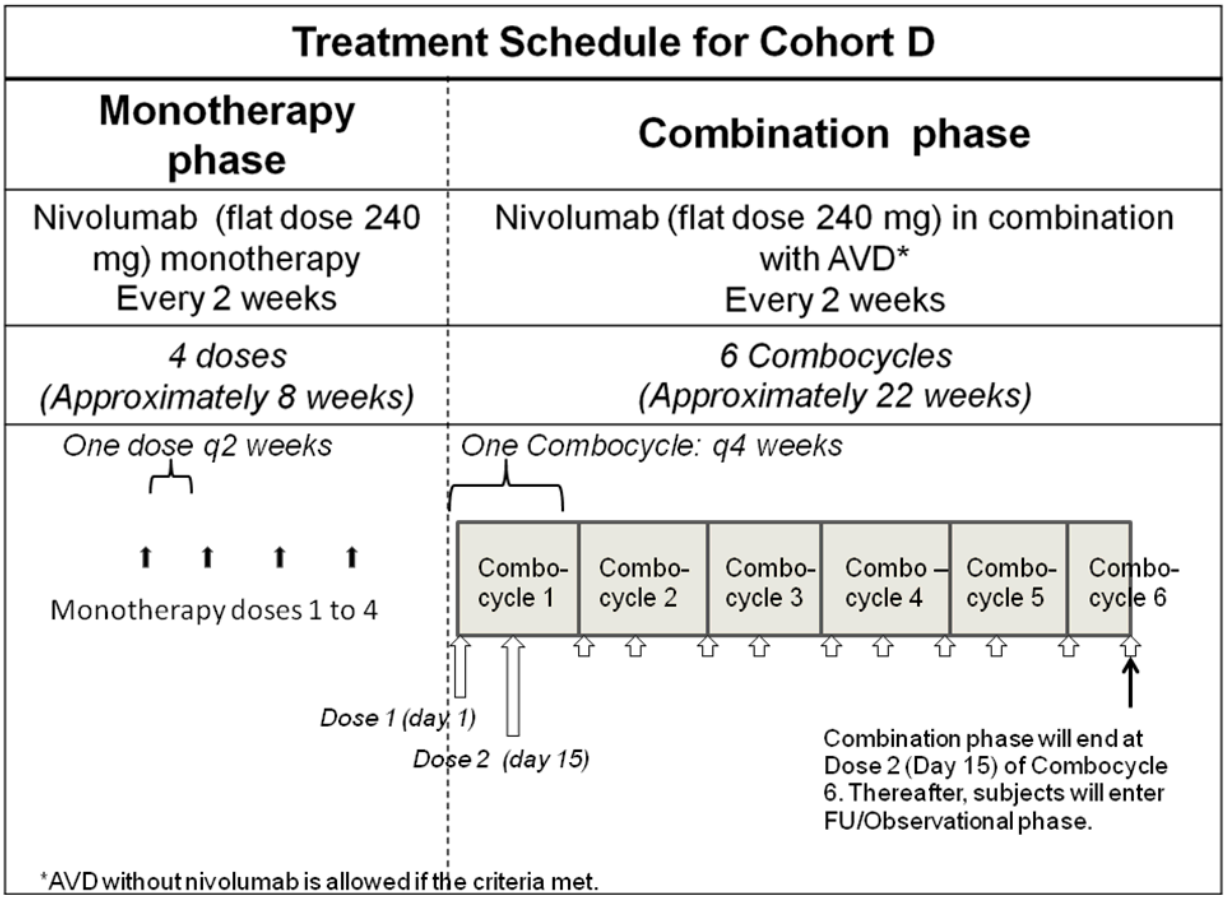
Cohort D is a non-comparative single-arm cohort in subjects ≥ 18 years old who are newly diagnosed, previously untreated cHL with advanced stage (Stage IIB, III and IV). Treatment for Cohort D consists of two phases: monotherapy and combination phases. Subjects will be treated with four doses of nivolumab flat dose 240mg IV every 2 weeks (monotherapy phase), followed by twelve doses of the combination of AVD chemotherapy (doxorubicin, vinblastine, and dacarbazine) (combination phase).

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Subjects will be enrolled independently from other cohorts.

Cohort D consists of approximately 50 subjects.

The study design schematic is presented in Figure 2.1.2-1.

Figure 2.1.2-1: Treatment Schedule for Cohort D



Treatment consists of two phases: monotherapy phase (approximately 8 weeks) and Combination phase (approximately 22 weeks). The monotherapy phase begins from the first dose of nivolumab (flat dose 240mg) until the first dose of the combination therapy. Nivolumab monotherapy is administered every 2 weeks for four doses. After subjects complete all four doses of nivolumab monotherapy, they will enter the combination phase, and will be treated with the combination of AVD chemotherapy and nivolumab. As exceptions, before completing all four doses of nivolumab monotherapy, subjects who meet discontinuation criteria (Section 4.5.5 of the protocol), or subjects who meet dose delay criteria (Section 4.5.2 of the protocol) and the dose delay is > 4 weeks from previous dose are allowed to discontinue monotherapy phase and enter combination phase when the criteria are met as described in Table 3.1.2-1 of the protocol.

The combination phase (approximately 22 weeks) begins from the first dose of the combination therapy. The first dose of combination therapy should be dosed no less than 12 days and no more than 17 days after the last dose of nivolumab monotherapy. The combination therapy is administration of nivolumab (flat dose 240mg) and AVD (Adriamycin/ doxorubicin 25mg/m^2, vinblastine 6mg/m^2, dacarbazine 375mg/m^2) on the same day. Use of AVD only (without

nivolumab) is permitted as an alternative regimen only when the conditions are met as described in Table 3.1.2-1 of the protocol. Each 28-day dosing period will constitute a Combocycle: two doses of the combination therapy per cycle, except for Combocycle 6, which will only be a 15-day cycle. The combination therapy is administered every 2 weeks for 12 doses (two doses, Dose 1 on Day 1 and Dose 2 on Day 15, of each Combocycle x 6 cycles). The combination phase will end at Dose 2 (Day 15) of Combocycle 6. Thereafter, subjects will enter the Follow-up (FU)/Observational phase. Subjects who discontinue combination treatment before completing Combocycle 6 Dose 2 (Day 15) and who have not started subsequent anti-lymphoma therapy will also enter the FU/Observational phase.

Table 2.1.2-1: Selection of Combination Therapy for Cohort D

During Monotherapy Phase	Regimen to be Used During Combination Phase
Subjects who have completed all 4 doses of nivolumab monotherapy (4 monotherapy doses)[a,b]	The combination of nivolumab and AVD
Subjects who have discontinued monotherapy before completing four doses of nivolumab because Nivolumab Discontinuation criteria (Section 4.5.5 of the protocol) are met	AVD
Subjects who have discontinued monotherapy before completing four doses of nivolumab because Nivolumab Delay Criteria (Section 4.5.2.1 of the protocol) are met, and the dose delay was > 4 weeks from a previous dose	AVD
Subjects who discontinued nivolumab monotherapy due to disease progression meeting 2007 IWG criteria based on investigators' assessment (but have not met safety criteria for discontinuation)	The combination of nivolumab and AVD or AVD alone

[a] If a subject subsequently meets Criteria to Resume Nivolumab Dosing (Section 4.5.4 of the protocol), the combination of nivolumab and AVD can be used

[b] Subjects who underwent treatment beyond progression during the Monotherapy phase can use the combination of nivolumab and AVD if all 4 doses of nivolumab monotherapy are completed

For Cohort D, radiographical tumor assessments by CT (preferred) or MRI, and FDG-PET scans will be required at screening. Mandatory radiographical tumor assessments during the treatment are as follows:

- **Post-Monotherapy dose 4 assessments**: FDG-PET scan and CT (preferred) or MRI after Monotherapy dose 4 and before entering the Combination phase.
- **Post-Combocycle 2 assessments**: FDG-PET scan* and CT (preferred) or MRI after Combocycle 2 and before Combocycle 3.

  *Interim FDG-PET scans are optional if a previous scheduled or unscheduled FDG-PET scan after the first dose of nivolumab monotherapy was negative based on investigator's assessment.

The end-of-therapy radiographic tumor assessments should be done at 9 weeks (± 14 days) from the last treatment). End-of-therapy FDG-PET, and CT (preferred) or MRI scans are mandatory in all subjects. When end-of-therapy FDG-PET scans are positive based on investigator's assessment, tumor biopsy for FDG-avid lesion is strongly encouraged whenever possible. Bone marrow assessment is not required for CR determination as FDG-PET can be used in lieu of bone marrow aspirate/ biopsy.

After the end-of-therapy radiographic tumor assessments, no FDG-PET scan is required unless clinically indicated. CT (preferred) or MRI scans should be conducted at 39 weeks (± 21 days), 65 weeks (± 21 days), and 104 weeks (± 21 days) from the last dose for the subjects who enter the FU/Observational phase. Thereafter, no radiographic tumor assessment is required. Treatment beyond investigator-assessed progression is permitted in the circumstances specified in the protocol.

2.2 Treatment Assignment

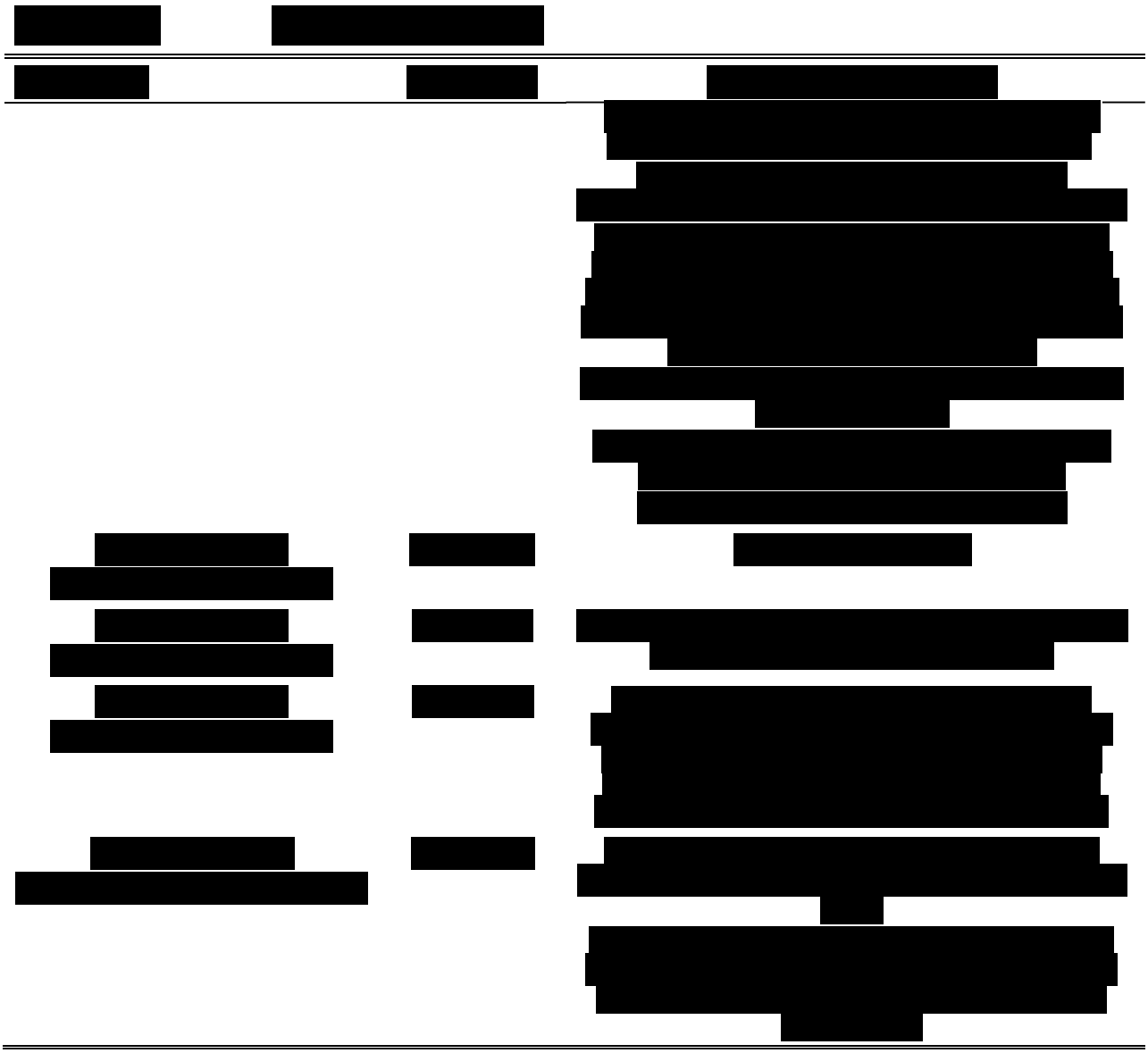
After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. All enrolled subjects from Cohorts A, B or C who meet eligibility criteria will be treated with nivolumab at 3mg/kg IV every 2 weeks. All enrolled subjects from Cohort D who meet eligibility criteria will be treated with four doses of nivolumab 240mg IV every 2 weeks followed by 12 doses of Nivolumab 240mg combined with AVD (Adriamycin/ doxorubicin 25mg/m^2, vinblastine 6mg/m^2, dacarbazine 375mg/m^2) every 2 weeks.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

This SAP incorporates the following protocol amendments.



2.5 Data Monitoring and Other External Committees

An IRRC will be utilized in this study for determination of IRRC-assessed primary endpoints (ORR), secondary endpoints (DOR, CR and PR rates and durations) endpoints and exploratory endpoints (PFS). The IRRC will review all available tumor assessment scans for all treated subjects. Details of IRRC responsibilities and procedures will be specified in the IRRC charter.

3 OBJECTIVES

3.1 Primary

3.1.1 Cohorts A, B and C

To assess the clinical benefit of nivolumab, as measured by objective response rate (ORR) based on independent radiologic review committee (IRRC) assessment, and defined as proportion of subjects achieving either a partial remission (PR) or complete remission (CR) according to the revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria).

3.1.2 Cohort D

To assess the overall safety and tolerability of nivolumab monotherapy (flat dose 240 mg), followed by the combination of nivolumab and doxorubicin, vinblastine and dacarbazine (AVD) chemotherapy in previously untreated cHL subjects who are newly diagnosed with advanced stage (Stage IIB, III and IV) disease , as measured by the proportion of subjects who experienced at least one treatment-related Grade 3-5 AEs with an onset date after or on the first dose date and no later than 30 days after the last study dose date, among subjects receiving at least one dose of study treatment.

3.2 Secondary

3.2.1 Cohorts A, B and C

- To assess the duration of objective response (DOR) based on IRRC assessments
- To assess the CR rate and the duration of CR based on IRRC assessment
- To assess the PR rate and the duration of PR based on IRRC assessment
- To assess the ORR and DOR based on investigator assessments

3.2.2 Cohort D

- To evaluate the safety and tolerability of nivolumab monotherapy during the monotherapy phase
- To evaluate the safety and tolerability of nivolumab in combination with AVD during the combination phase
- To evaluate the treatment discontinuation rate of the study therapy during the monotherapy phase, combination phase, and overall (the entire course of study treatment consisting of both phases)
- To assess the clinical activity of study therapy, as measured by the CR rate at the planned end of therapy, based on IRRC assessments.

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint

4.1.1 Cohort A, B, C

The primary objective will be measured by the primary endpoint of ORR based on IRRC assessment. It is defined as the number of subjects with a Best Overall Response (BOR) of CR or PR, according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The BOR is defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the date of subsequent therapy, whichever occurs first. Allogeneic SCT and ASCT will be considered as subsequent anti-cancer therapy. For subjects without documented progression or subsequent 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. For purposes of analysis, if a subject receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this subject will be counted in the denominator (as non-responder).

Analysis of the primary endpoint of each Cohort will occur separately at least 1 year (Cohorts A and C) or 6 months (Cohort B) after last patient first treatment in each respective Cohort.

The objective response will be further characterized by the time to response (TTR). TTR is defined as the time from first dosing date to the date of the first response, based on IRRC assessment.

4.1.2 Cohort D

The primary objective for Cohort D will be measured by the proportion of subjects who experienced at least one treatment-related Grade 3 - 5 AEs (per NCI CTCAE version 4.0 criteria, any PT term) with an onset date after or on the first dose date and no later than 30 days after the last study dose date, among subjects receiving at least one dose of study treatment.

4.2 Secondary Endpoints

4.2.1 Cohorts A, B and C

4.2.1.1 Duration of Objective Response Based on IRRC Assessment

DOR is defined as the time from first response (CR or PR) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy. Sensitivity analyses will be performed based on an alternate

censoring scheme to account for infrequent tumor assessments. See Table 4.2.1.1-1 for censoring details. This endpoint will only be evaluated in subjects with objective response of CR or PR.

Table 4.2.1.1-1: Censoring Scheme for Primary and Sensitivity Analysis of DOR (Cohorts A, B and C)

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
Subsequent anticancer therapy started without a reported progression per response criteria	Censored on date of last tumor assessment prior or on the date of initiation of the subsequent anticancer therapy	Censored on 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

Censoring scheme for primary analysis of DOR aligns with censoring scheme for PFS analysis.
Last visit is defined as the last date of dosing, tumor assessment or lab assessment, whichever occurs last.

4.2.1.2 Complete Remission Rate and Duration Based on IRRC Assessment

The CR rate is defined as the number of subjects with a BOR of CR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The duration of CR will only be evaluated in subjects with BOR of CR and is defined as the time from first documentation of CR (the date of first negative FDG-PET scan or the date of first documentation of no disease involvement in the bone marrow (if required), whichever occurs later) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition. This endpoint will be further characterized by the time to CR, defined as the time from first dosing date to the date of first documentation of CR.

4.2.1.3 Partial Remission Rate and Duration Based on IRRC Assessment

The PR rate is defined as the number of subjects with a BOR of PR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The duration of PR will only be evaluated in subjects with BOR of PR and is defined as the time from first documentation of PR to the date of initial objectively documented progression as determined using

the 2007 IWG criteria or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition.

4.2.1.4 Objective Response Rate and Duration Based on Investigator Assessment

Investigator-assessed ORR and DOR are defined similarly as described for ORR and DOR per IRRC assessment above (Section 4.1), but will be assessed per investigator based on 2007 IWG criteria. It will be further characterized by TTR, time to CR and duration of CR.

4.2.2 Cohort D

4.2.2.1 Treatment discontinuation rate

- The treatment discontinuation rate, defined by the number of subjects who were treated with fewer than 12 doses (2 doses per cycle x 6 cycles) of combination regimen (AVD ± nivolumab), divided by the number of subjects who have received at least one dose of nivolumab monotherapy. Discontinuation can be due to any reason including, but not limited to, drug-related toxicity, diseases progression, or death. The numerator includes subjects who discontinued nivolumab monotherapy and were unable to start combination regimen (AVD ± nivolumab), as a part of study, and subjects who discontinued nivolumab monotherapy and were treated with fewer than 12 doses of combination regimen (AVD ± nivolumab). The numerator does not include subjects who discontinued nivolumab monotherapy and were able to complete all 12 doses of the combination regimen (AVD ± nivolumab).
- The treatment discontinuation rate of nivolumab monotherapy is equal to one minus the completion rate of nivolumab monotherapy phase. The completion rate of nivolumab monotherapy is defined as the number of subjects who have received four nivolumab monotherapy doses, divided by the number of subjects who have received at least one dose of nivolumab monotherapy.
- The treatment discontinuation rate of the Nivolumab-AVD combination therapy is equal to one minus the completion rate of Nivolumab-AVD combination therapy. The completion rate of Nivolumab-AVD combination therapy is defined as the number of subjects who have received 12 doses of Nivolumab-AVD therapy, divided by the number of subjects who received at least one dose of Nivolumab-AVD therapy.
- The treatment discontinuation rate of combination therapy (AVD ± nivolumab) is equal to one minus the completion rate of combination therapy (AVD ± nivolumab). The completion rate of combination therapy (AVD ± nivolumab) is defined as the number of subjects who have received 12 doses of any combination therapy (AVD ± nivolumab), divided by the number of subjects who received at least one dose of any combination therapy (AVD ± nivolumab).

4.2.2.2 Treatment-related Grade 3-5 AEs in each therapy phase

- The proportion of subjects who experienced at least one treatment-related Grade 3-5 AEs during the monotherapy phase (per NCI CTCAE version 4.0 criteria, any PT term) with an onset date after or on the first dose date and before the first dose of combination therapy, or no later than 30 days after the last dose of Nivolumab monotherapy whatever comes first. This

proportion will be calculated among subjects receiving at least one dose of nivolumab monotherapy.

- The proportion of subjects who experienced at least one treatment-related Grade 3-5 AEs during the combination phase (per NCT CTCAE version 4.0 criteria, any PT term) with an onset date after or on the first dose of nivolumab combined with AVD and no later than 30 days after the last dose of combination therapy. This proportion will be calculated among subjects receiving at least one dose of nivolumab combined with AVD.

4.2.2.3 Complete remission rate at the end of study therapy per IRRC

- The CR rate at the planned end of study therapy (IRRC-assessed) is defined as the number of subjects who are CR according to the 2007 IWG criteria at the planned end of study therapy radiographic tumor assessment, divided by the number of subjects who have received at least one dose of nivolumab monotherapy.

For our main analysis on all treated subjects, the following definitions will be used to identify the planned response assessments:

- The End of Monotherapy assessment is the first assessment performed on or after the last nivolumab monotherapy dose date (regardless of its dose number) and before or on the day of the first combination therapy dose date (if any). The End of Monotherapy assessment must be prior or on the first subsequent therapy date if any.

- The After 2 combocycles assessment is the first assessment performed on or after dose 2 of combo cycle 2 and before or on the first dose of combo cycle 3. The After 2 combocycles assessment must be prior or on the first subsequent therapy date if any.

- The End of Therapy assessment is the closest assessment to last dose date + 9 weeks which is prior or on the first subsequent therapy date (if any) and which is within [last dose date + 2 weeks; last dose date + 24 weeks].

[redacted]

4.3.1.2 Overall Survival

Overall Survival (OS) is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive. The overall survival rate at time T is defined as the probability that a subject is alive at time T following first dosing date.

4.3.1.3 Safety and Tolerability

Safety will be analyzed through the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See details in the Core Safety SAP[1].

For cohorts A, B and C, safety of subjects who undergo a subsequent allogeneic transplant will also be analyzed through cumulative incidence rate of transplant related deaths and acute gvhd. Other transplant-related complications will also be reported. Subjects with missing worst acute gvhd grade will be imputed grade 4. Subjects with missing acute gvhd onset dates will be imputed to the first subsequent allogeneic transplant date.

For cohort D, safety of subjects will be analyzed per treatment phase (monotherapy phase, combination therapy phase) and overall. Change from baseline of pulmonary function after treatment will also be reported.

4.3.1.4 Immune-Mediated Adverse Events

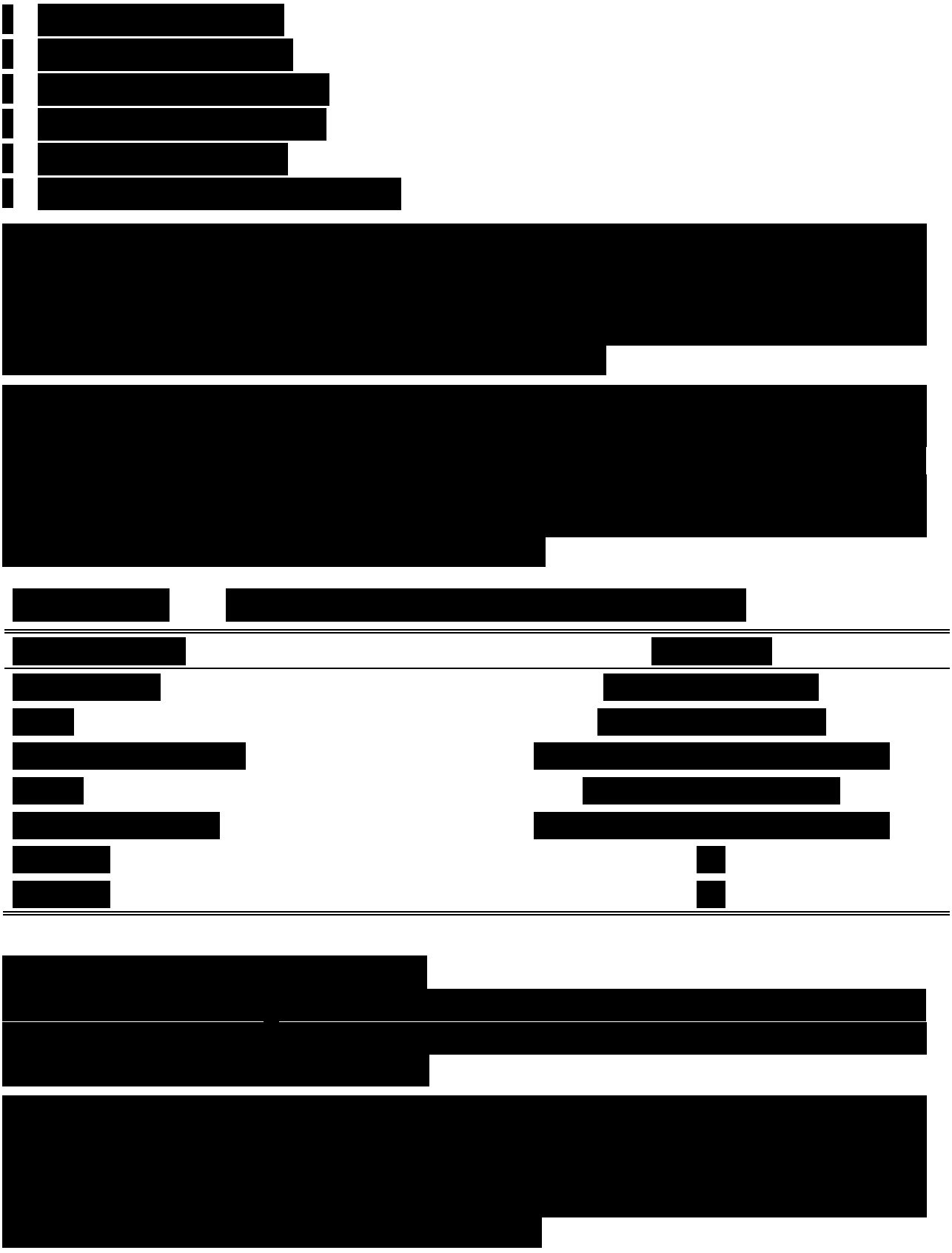
In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (imAEs) will be conducted. Immune-mediated AEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis). The imAE categories and terms are defined by the Sponsor and the list that is the most current at the time of analysis will be used. This list will be based on the most current version of MedDRA at the time when database will be built. The final list used for the CSR will be included in an Appendix of the CSR.

[redacted]

4.3.1.6 Immunogenicity to Nivolumab

Refer to Core Safety SAP[1].

[redacted]



[redacted]

5 SAMPLE SIZE AND POWER

The planned sample size for this study will be approximately 270 treated subjects, placed into four cohorts of subjects: brentuximab vedotin-naïve [n = 60; Cohort A], treatment with brentuximab vedotin after failure of ASCT [n = 60; Cohort B], treatment with brentuximab vedotin at any timepoint [n = 100; Cohort C] and first-line subjects [n = 50; Cohort D].

Cohorts A and B

The sample size from both cohorts was determined based on two considerations: the ability to produce a CI which would exclude an ORR of 20%, which is not considered clinically relevant and provide sufficient information for a reliable understanding of the safety profile[2].

Assuming the true ORR is 40%, each cohort has approximately 93% power to reject the null hypothesis that the true ORR is ≤ 20%, considering a 2-sided alpha of 5%. In addition, Table 5-1 summarizes the 95% exact CI for the target ORRs ranging from 35% to 70% with sample size of 60. At observed ORR ≥ 35%, the lower bound of the 95% CI excludes 20%.

Table 5-1: Observed ORR with Exact 95 % CI

ORR	95% Exact CI
35%	[23.1%-48.4%]
40%	[27.6%-53.5%]
50%	[36.8%-63.2%]
60%	[46.5%-72.4%]
70%	[56.8%-81.2%]

Cohort C

The sample size for Cohort C was empirically determined to support expanded assessment of the benefit-risk profile of nivolumab in cHL through observation of less common safety events. In particular, administration of nivolumab to 100 subjects provides 87% probability of observing at least one occurrence of any adverse event that would occur with 2% incidence in the population from which the sample is drawn. Benefit in this cohort will be measured by the ORR and DOR.

Cohort D

The sample size for Cohort D was empirically determined to provide sufficient information for understanding the safety profile and estimating the proportion of subjects who experience at least one treatment-related grade 3-5 adverse events.

In a randomized study comparing ABVD and BEACOPP in previously untreated and unfavorable Hodgkin's lymphoma, 43% of the subjects from the ABVD arm experienced at least one Grade 3 or 4 acute hematologic adverse event and 7% of subjects experienced at least one acute non-

hematologic adverse event in the ABVD arm. Table 5-2 summarizes the 95% exact CI for a range of incidence rates.

Table 5-2: Observed Percentage of Subjects with Treatment-Related Grade 3-5 AE with Exact 95%CI

Observed Incidence rate	95% Exact CI
16%	[7.17% - 29.11%]
26%	[14.63% 40.34%]
36%	[22.92% 50.81%]
46%	[31.81% 60.68%]

CI = confidence interval

Other considerations:

A discontinuation rate above 20% is not considered as acceptable because ABVD discontinuation rates due to any reasons (toxicity, disease progression or others) are consistently around 10% across previous clinical studies. Table 5-3 summarizes the 95% exact CI for a target discontinuation rate ranging from 8% to 14%. If 10% (Five out of 50 treated subjects) or fewer discontinue the treatment, the upper bound of the 95% CI will exclude 20%.

Table 5-3: Observed Discontinuation Rate with 95% CI

Observed Discontinuation Rate	95% Exact CI
8%	[2.22% 19.23%]
10%	[3.33% 21.81%]
12%	[4.53% 24.31%]
14%	[5.82% 26.74%]

CI - confidence interval

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment

- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment as defined in Table 6.1.2-1. Specifically, re-initiation nivolumab therapy is excluded for the purpose of determining the last dose of nivolumab as part of the definition of on-treatment; separate safety analyses for re-initiation therapy may be performed. Refer to Core SAP[1].

On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment. Refer to Core SAP[1].

Table 6.1.2-1: Primary On-Treatment Definition For Safety in Treated Subjects

Cohort	Option for Re-Initiation	On-Treatment Definition
Cohorts A and B	No	On or after first dose of nivolumab and within 30 (or 100) days after last dose of nivolumab
Cohort C	Yes	On or after first dose of nivolumab and within 30 (or 100) days after the last dose of nivolumab prior to re-initiation dosing
Cohort D	No	On or after first dose of nivolumab and within 30 (or 100) days after last dose of nivolumab.

For cohort D, the following phases will be considered

- the monotherapy phase: from first nivolumab dose date to the first combination therapy dose date, or for subjects who do not enter the combination therapy phase up to 30 (or 100) days after the last dose of nivolumab. All treated subjects will be considered.
- the combination therapy phase: from the first combination therapy dose date up to 30 (or 100) days after the last study dose date. All subjects who received at least one dose in the combination therapy phase will be considered.
- overall: from the first nivolumab dose date up to 30 (or 100 days depending on analysis) of the last dose of study treatment). All treated subjects will be considered.

6.2 Treatment Regimens

All subjects from cohort A, B, C will be treated with nivolumab 3mg/kg and from cohort D will be treated with Nivolumab 240mg monotherapy followed by Nivolumab 240mg combined with AVD.

6.3 Populations for Analyses

6.3.1 Study Cohorts

Cohort A: Brentuximab vedotin- naïve subjects who have failed ASCT.

Cohort B: Subjects who received brentuximab vedotin treatment as salvage following failure of ASCT.

Cohort C: Subjects who have undergone ASCT and received brentuximab vedotin, in any treatment order.

Cohort D: Previously untreated cHL subjects. Cohorts will be determined as entered in CRF.

6.3.2 Analysis Populations

Within each cohort the following populations will be defined.

- **Enrolled subjects**: All subjects who signed an informed consent form and were registered into the IVRS.
- **Treated subjects**: All subjects who received at least one dose of nivolumab. This is the primary population for efficacy and safety.
- **Response evaluable subjects**: All treated subjects who have baseline and at least one on-study evaluable tumor measurement.
- **Immunogenicity evaluable subjects**: See Core SAP[1].
- **PD-L1 per Dako tested subjects**: All subjects who had a tumor tissue sample available for assessment of PD-L1 expression.
- **PD-L1 per Dako evaluable subjects**: All treated subjects with quantifiable baseline PD-L1 expression
- **Outcomes Research subjects**: All treated subjects who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment (for EORTC QLQ-C30 and EQ-5D separately).(QLQ-C30 for Cohorts A, B and C only).
- **Nivolumab subjects treated beyond progression (Cohorts A, B and C):** All subjects who received at least one dose of nivolumab after the date of initial progression per 2007 IWG criteria based on investigator assessment.
- **Persistent CR subjects (Cohort C only):** All treated subjects in Cohort C who discontinue treatment following a CR of 1 year duration.
- **Treated Subjects who underwent a subsequent Allogeneic Transplant (Cohorts A, B and C)**: All subjects who received at least one dose of Nivolumab and who reported an allogeneic transplant date after first nivolumab dose.

The following populations will also be defined for Cohort D:

- Treated subjects with NAVD: All subjects who received at least one dose of nivolumab in the combination therapy phase.
- Treated subjects with AVD only: All subjects who received at least one dose of AVD but no nivolumab in the combination therapy phase.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum values. If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distribution (e.g. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[6] for variance derivation and on log-log transformation applied on the survivor function S(t) [7].

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[8].

All analyses will be performed separately for each cohort upon completion of follow-up for the primary endpoint in each cohort. In addition to separate analyses per cohort, safety analyses will be performed on combined cohorts.

7.2 Study Conduct

7.2.1 Accrual

The following will be summarized on the enrolled population separately for each cohort and on the pooled population:

- Number of subjects accrued by country and investigational site
- Number of subjects accrued by month

A by subject listing of accrual will be produced.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both

programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

7.2.2.1 Cohorts A, B and C

At entrance:

- Subjects without documented classical Hodgkin's lymphoma
- Subjects without prior ASCT
- Subjects with prior brentuximab vedotin treatment (Cohort A only)
- Subjects without prior brentuximab vedotin treatment (Cohorts B and C only)
- Subjects with prior treatment history of brentuximab vedotin administered before first ASCT (Cohort B only)
- Subjects without either measurable disease at baseline or FDG avid by PET
- Subject with baseline ECOG >1

On-Study:

- Any concurrent antineoplastic therapy (i.e., chemotherapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer).

A summary table will be produced separately for each cohort and pooled across cohorts in all treated subjects. A by subject listing will be produced.

7.2.2.2 Cohort D

At entrance:

- Subjects without documented classical Hodgkin's lymphoma
- Subjects with prior treatment history for classical Hodgkin's lymphoma
- Subjects without either measurable disease at baseline or FDG avid by PET
- Subject with baseline ECOG not in (0, 1)

On-Study:

- Subjects with concurrent autologous or allogeneic transplant, systemic anti-cancer therapy or non-palliative radiotherapy (curative or other).

7.3 Study Population

Except stated otherwise, analyses from this section will be produced separately for each cohort and pooled across cohorts A, B and C.

7.3.1 Subject Disposition

The total number of subjects enrolled (treated or not) will be presented along with the reason for not being treated.

Number of subjects who discontinued treatment along with corresponding reason will also be tabulated. For Cohort D, number of subjects who prematurely discontinue monotherapy treatment phase and enter combination therapy phase will also be presented.

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics will be summarized the following baseline characteristics for all treated subjects. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age categories (< 65, ≥ 65 and < 75, ≥75 and < 85, ≥ 85, ≥ 75, ≥ 65, < 30, ≥30 and < 45, ≥ 45 and < 60, ≥ 60)
- Gender (male, female)
- Race (white, black or african american, asian, american indian or alaska native, native hawaiian or other pacific islander, other)
- Ethnicity (hispanic or latino, not hispanic or latino, nor reported)
- Baseline ECOG Performance Status (0, 1)
- Weight (descriptive statistics)
- Time from initial disease diagnosis to first dose of nivolumab (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year)
- Region (US/Canada, Europe, Rest of the World)
- Smoking Status (Current\Former, Never Smoked, Unknown)
- Disease stage at initial diagnosis (Stage I-II-III-IV)
- International Prognostic Score (IPS) (0-2, 3 or higher) at initial diagnosis
- Disease stage at study entry (Stage I-II-III-IV)
- Specific B-symptoms at baseline (Fever, Night Sweats, Weight Loss)
- Bulky disease at baseline (Yes, No, Not Available)
- Extra lymphatic involvement at baseline (Yes, No, Not Available)
- Lymphoma involvement in bone marrow at baseline (Yes, No, Not Available)
- All lesions (Investigator Tumor Assessments at Baseline): sites of diseases, number of disease sites per subject
- Target Lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of product diameters of target lesions.

For Cohorts A, B and C:

- Time from the initial diagnosis to first transplant (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year)
- Time from the most recent transplant to first dose of nivolumab (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year)
- Time from the most recent transplant to first subsequent treatment (< 6 months, 6 - < 12 months, ≥ 12 months)
- B-symptoms at initial diagnosis and at study entry (absent, present)

7.3.3 Medical History

General medical history will be listed by subject and pretreatment events will be tabulated.

7.3.4 Prior therapy (Cohorts A, B and C)

The following will be summarized:

- Number of subjects by type of prior therapy received (excluding preparative regimen for ASCT): immunomodulatory derivatives (e.g. lenalidomide), other chemotherapy, immunotherapy by monoclonal antibodies (e.g. Rituximab, Brentuximab)
- Number of subjects by type of regimen for first and second lines of therapy (e.g. ABVD, ICE, BEACOPP, Stanford V)
- Number of subjects by type of regimen received for preparation to ASCT (BEAM, CBV, Other)
- Number of prior systemic regimens received (1, 2, 3, 4, ≥ 5), excluding preparative regimen for ASCT
- Number of prior systemic regimens received (1, 2, 3, 4, ≥ 5), excluding preparative regimen for ASCT, for subjects who received brentuximab prior to ASCT only, received brentuximab after ASCT only, and received brentuximab both prior to and after ASCT), Cohort C only
- Number of Prior Systemic Regimens by Administration Sequence of ASCT and brentuximab
  - Number of prior systemic regimens (1, 2, 3, 4, ≥ 5) received before ASCT and after ASCT, Cohort A only
  - Number of prior systemic regimens received (1, 2, 3, 4, ≥ 5) before ASCT, between ASCT and brentuximab and after brentuximab administration, Cohort B only
  - Number of prior systemic regimens received (1, 2, 3, 4, ≥ 5) before brentuximab, between brentuximab and ASCT, and after ASCT, Cohort C subjects who received brentuximab prior to ASCT only
  - Number of prior systemic regimens received (1, 2, 3, 4, ≥ 5) before ASCT, between ASCT and brentuximab, and after brentuximab administration, Cohort C subjects who had brentuximab only after ASCT
- Best response to regimen before most recent ASCT
- Disease Status at most recent ASCT
- Best response to most recent ASCT
- Best response to regimen post most recent ASCT

- Best response to regimen post brentuximab (post most recent ASCT), Cohort B
- Best response to regimen post most recent brentuximab but prior to most recent ASCT, Cohort C subjects who received brentuximab prior to ASCT only
- Best response to regimen post most recent brentuximab, Cohort C subjects who had brentuximab only after ASCT
- Best response to front line therapy for Cohort A subjects
- Best response to most recent Brentuximab for Cohort B and C subjects
- Time from completion of most recent prior regimen to treatment (< 3, 3 - 6, > 6 months)
- Prior radiotherapy (yes or no)

Other Prior therapy:

- Prior/current non-study medication classified by anatomic and therapeutic classes.

Medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Prior Therapy (Cohort D)

Subjects are not expected to have received prior cHL anti-cancer therapy. Note that surgeries are not considered as prohibited prior therapies. A summary table and listing of prior therapies reported will be provided.

7.3.6 Baseline Examinations

Percentage of subjects with abnormal baseline physical examination will be tabulated by examination criteria.

7.4 Extent of Exposure

Analyses from this section will be produced separately for each cohort and pooled across cohorts A, B and C. For cohort C, extent of exposure summary tables will exclude data collected in persistent CR subjects on or after the first date of re-initiation therapy. Listings will include all available exposure data.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics):

- For each drug, relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- For each drug, number of doses received (summary statistics)

  For cohort D, this will include
  - The number of subjects who received 1, 2, 3 or 4 doses of Nivolumab during the monotherapy period

  - The number of subjects who received 1, ... 12 doses for each drug during the combination period
  - The number of subjects who received 12 doses of NAVD during the combination therapy among subjects who have received at least one dose of NAVD
  - The number of subjects who received 12 doses of AVD with or without Nivolumab during the combination therapy among subjects who have received at least one dose of combination therapy (AVD with or without Nivolumab).
- For each drug, cumulative dose
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who discontinued study therapy. Subjects who are still on study therapy will be censored on their last dose date. Median duration of treatment and associated 95% CI will be provided.
- A by-subject listing of dosing of study medication (record of study medication, infusion details, dose change) and a listing of batch number will be also provided.

Table 7.4.1-1: Administration of study therapy: definition of parameters (Cohorts A, B, C)

	nivolumab
Dosing schedule per protocol	3mg/kg every 2 weeks
Dose	Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	Cum dose (mg/kg) is sum of the doses (mg/kg) administered to a subject during the treatment period.
Relative dose intensity (%)	Cum dose (mg/kg) /[(Last dose date - Start dose date + 14) x 3 / 14] x 100
Duration of treatment	Last dose date - Start dose date +1

Table 7.4.1-2: Administration of study therapy: definition of parameters (Cohort D)

	Nivolumab	**AVD**
Dosing schedule per protocol	240mg every 2 weeks	A: adriamycin/doxorubicin 25mg/m^2, V: vinblastine 6mg/m^2, D: dacarbazine 375mg/m^2
Dose	*Dose (mg)* is defined as Total Dose administered (mg). Dose administered in mg at each dosing date on the CRF	*Dose (mg/m²)* is defined as Total Dose administered (mg) / BSA. Dose administered in mg at each dosing date

Table 7.4.1-2: Administration of study therapy: definition of parameters (Cohort D)

	Nivolumab	AVD
		and BSA (computed using bsl weight and bsl height) are collected on the CRF. Dose (mg/kg) is defined as Total Dose administered (mg) /Weight. Dose adminstered in mg at each dosing date and weight (actual weight at each visit) are collected on the CRF
Cumulative Dose	*Cum dose (mg) is* sum of the doses (mg) administered to a participant during the treatment period.	*Cum dose (mg/m², mg/kg) is* sum of the doses (mg/m²) administered to a participant during the treatment period
Relative dose intensity (%)	Cum dose (mg) / [(Last dose date - Start dose date + 14) x 240 / 14] x 100	A: Cum dose (mg/m²) / [(Last dose date - Start dose date + 14) x 25 / 14] x 100 V: Cum dose (mg/m²) / [(Last dose date - Start dose date + 14) x 6 / 14] x 100 D: Cum dose (mg/m²) / [(Last dose date - Start dose date + 14) x 375 / 14] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose delays

Treatment may be delayed for up to a maximum of 6 weeks from the last dose. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date). Length of delay is defined as (duration of previous cycle in days - 14). Dose delays will be divided into following categories: 4 - < 8 days, 8 - < 15 days, 15 - < 43, ≥ 43 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized for each drug separately:

- Number of subjects with at least one dose delayed, number of dose delayed per subject, Length of Delay and Reason for Dose Delay

7.4.2.2 Infusion Interruptions and Rate Changes

The following parameters will be summarized for each drug:

- Number of subjects with at least one dose infusion interruption, number of infusion interruptions per subject and the reason for interruption.
- Number of subjects with at least one IV infusion rate reduction, number of IV infusion rate reduction per subject and the reason for reduction

7.4.2.3 Dose Reductions/Escalation

There will be no dose escalations or reductions of nivolumab allowed.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

For Cohort D, concomitant medication will be analyzed by treatment phase and overall.

The following summary tables will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term).

A by-subject listing will accompany the table.

7.5 Efficacy

Analyses from this section will be produced separately for each cohort.

For persistent CR subjects, tumor assessments taken prior to progression/relapse (including during the observational follow-up period), and thus prior to re-initiation, will contribute towards BOR, time to objective response, duration of objective response and PFS following endpoint definitions. If persistent CR subjects re-initiate study therapy for progression/relapse, tumor assessments performed after re-initiation will be identified in efficacy listings but do not contribute towards these endpoints.

7.5.1 Primary Endpoint of ORR (based on IRRC assessment) (Cohorts A, B and C)

The ORR based on IRRC assessment (using 2007 revised International Working Group Criteria for Malignant Lymphoma criteria) will be summarized using all treated subjects by a binomial response rate. The Clopper-Pearson method[8] will be used to estimate the two-sided 95% confidence interval.

The null hypothesis will be rejected if the 2-sided 95% CI lower bound is greater than 20%. This translates in observing at least 19 responders out of 60 treated subjects.

BOR will be summarized by response category.

Summary statistics of time to objective response will be provided for subjects who achieve PR or CR, as assessed by the IRRC. CR requires confirmation by PET. To assess tumor response kinetics, time to response will also be analyzed using the KM methodology for all treated subjects. Kaplan-Meier curve will represent the cumulative rate of response over time. For the non-responders, time to response will be censored at the maximum time to response + 1 day of all subjects in their

respective treatment group. Cumulative response rates will be tabulated for Week 9, Month 4, 6, 8, 12 and 18.

7.5.1.1 ORR Subgroups

- To assess consistency of ORR, IRRC-assessed ORR (primary analysis) will be summarized for the following subgroups by cohort: Age (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85, ≥ 75, ≥ 65, < 30, ≥ 30 and < 45, ≥ 45 and < 60, ≥ 60)
- Region (US/Canada, Europe, Rest of the World).
- Gender (Male, Female)
- Race (white, black, Asian, and other)
- Smoking status (yes, no)
- ECOG (0, 1)
- B-symptoms at initial diagnosis and at study entry (absent, present)Time from the initial diagnosis to transplant (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year)
- Number of prior therapies (≤ 3, 4-6, ≥7) excluding preparative regimen
- Time from the most recent transplant to first subsequent treatment (< 6 months, 6 - < 12 months, ≥ 12 months)
- Categories including less than 5 subjects may be collapsed. Analyses of subgroups of less than 5 subjects may not be provided.

7.5.1.2 Sensitivity Analyses for ORR

- As sensitivity analysis, a summary of IRRC-assessed ORR based on response evaluable subjects instead of all treated subjects will also be presented.
- To assess concordance between IRRC (primary analysis) and investigator assessments, BOR will be cross-tabulated by assessment type (Investigator vs IRRC). Concordance Rate of Responders will be computed as the frequency with which Investigator and IRRC agree on classification of a subject as responder/non responder as a proportion of the total number of subjects assessed.

The following subject-level graphics will also be provided:

- For the responders only, time courses of the following events of interest will be graphically displayed (IRRC assessed): first tumor response, tumor progression, last dose received, subsequent hematopoietic stem cell transplant and death.
- For response evaluable subjects, a waterfall plot showing the best reduction from baseline in target lesion based on IRRC assessment will be produced (excluding assessments after PD and assessments after start of subsequent anti-cancer therapy).
- Plot of Individual Time course of Tumor Burden Change, per IRRC, for all treated subjects (spider plot)

7.5.2 Secondary Endpoints

7.5.2.1 Duration of Response Based on IRRC Assessment (Cohorts A, B and C)

The DOR will be summarized by cohort for subjects who achieve PR or CR as determined by IRRC using KM product-limit method. Two-sided, 95% confidence intervals for median DOR will be constructed based on log-log transformation. Range of DOR will also be presented. Sensitivity analysis will be performed based on an alternate censoring scheme. In addition, the number of subjects with duration of response at least 3, 6, 12, 18 and 24 months will be presented.

7.5.2.2 Complete Remission Rate and Duration Based on IRRC Assessment (Cohorts A, B , C and D)

Complete remission rate (CRR) based on IRRC assessment will be summarized by cohort by a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson method[8].

To further characterize CRR, the duration of CR will be summarized by cohort for subjects who achieve CR as determined by IRRC using KM product-limit method. Two-sided, 95% confidence intervals for median duration of CR will be constructed based on log-log transformation. Range of duration of CR will also be presented. For Cohorts A, B and C, sensitivity analysis will be performed based on an alternate censoring scheme.

To assess tumor response kinetics, time to first CR will also be analyzed using the KM methodology for all treated subjects. Kaplan-Meier curve will represent the cumulative rate of CR over time. For the subjects who don't achieve CR, time to CR will be censored at the maximum time to complete response + 1 day of all subjects in their respective treatment group.

For Cohort D, response assessment after the start of subsequent therapy will be censored for the main analysis. A second analysis will be performed to keep them in the analysis. Another analysis of the (complete) response rate at each planned timepoint (end of monotherapy, after two combination therapy cycles and end of therapy assessment) will be performed on all treated subjects with an evaluable response at the considered timepoint.

7.5.2.3 Partial Remission Rate and Duration Based on IRRC Assessment (Cohorts A, B and C)

Partial remission rate (PRR) based on IRRC assessment will be summarized by cohort by a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson[8] method.

To further characterize PRR, the duration of PR will be summarized by cohort for subjects who achieve PR as determined by IRRC using KM product-limit method. Two-sided, 95% confidence intervals for median duration of PR will be constructed based on log-log transformation. Range of duration of PR will also be presented. Sensitivity analysis will be performed based on an alternate censoring scheme.

7.5.2.4 Objective Response Rate and Duration Based on Investigator Assessment (Cohorts A, B and C)

Investigator-assessed ORR will be summarized by cohort by a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson method[8].

The DOR based on investigator assessment will be summarized by cohort for subjects who achieve PR or CR as determined by investigator using KM product-limit method. Two-sided, 95% confidence intervals for median DOR will be constructed based on log-log transformation. Range of DOR will also be presented.

Time to CR and duration of CR based on investigator assessment will be summarized using the same method as for the IRRC assessment.

[redacted]

7.5.3.3 Progression Free Survival based on IRRC Assessment (Cohorts A, B and C)

PFS based on IRRC assessment will be summarized descriptively by cohort using the Kaplan-Meier (KM) product-limit method. Median values of PFS, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated.

The source of progression (death vs. progression) will be summarized.

The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated using following categories:

- Received subsequent anti-cancer therapy (Stem Cell Transplant, other)
- Still on-treatment

- Progression-free in follow-up
- Off-study: (lost to follow-up, withdrew consent, other).

KM curve of PFS will be generated. PFS rates per IRRC at 6 and 12 months will be estimated using KM estimates on the PFS curve. Associated two-sided 95% CIs will be calculated.

Subject listings of PFS will be produced.

7.5.3.4 Modified Progression Free Survival (Cohort D)

Modified PFS based on IRRC assessment/investigator assessments will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. Median values of modified PFS, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated.

The source of progression (death vs. progression vs start of subsequent therapy) will be summarized.

The status of subjects who are censored in the modified PFS Kaplan-Meier analysis will be tabulated using following categories:

- Still on-treatment
- Progression-free in follow-up
- Off-study: (lost to follow-up, withdrew consent, other).

KM curve of modified PFS will be generated. ModifiedPFS rates at 6, 12,... months will be estimated using KM estimates on the modified PFS curve. Associated two-sided 95% CIs will be calculated.

By-subject listings of modified PFS will be produced.

7.5.3.5 Overall Survival

OS will be summarized by the Kaplan-Meier product-limit method. Median values of OS, along with two-sided 95% CIs (based on the log-log transformation), will be calculated. Survival rates at 6, 12, 18 and 24 months (minimum follow-up must be longer than timepoint to generate the rate) will also be estimated using KM estimates from the OS curve. The associated two-sided 95% CIs will be calculated based on the log-log transformation. Additional follow-up may be up to 5 years and updated OS analysis may be performed.

The status of subjects who are censored in the OS Kaplan-Meier analysis will be tabulated using the following categories:

- On-study (on-treatment and not progressed, on-treatment progressed, in follow-up);
- Off-study: (lost to follow-up, withdraw consent, etc.).

Subject Follow-up

The extent of follow-up for survival defined as the time between first dose date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (mean, standard deviation, median, first and third quartiles, minimum, maximum) for all treated subjects.

The currentness of follow-up for survival, defined as the time between last contact for overall survival (i.e., last known date alive or death date) and cutoff date (defined by last patient last visit date), will be summarized for all treated subjects. Subjects who died before cut-off date or subjects whose last known date alive is on or after data cut-off date will have currentness of follow-up set to zero. The currentness of follow-up will be categorized into the following categories: 0 day, 1day-3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.

Follow-Up Therapy

The following information pertaining to subsequent therapies will be summarized:

Number and percentage of subjects receiving subsequent therapies including:

- Chemotherapy by drug name
- Antibody by drug name (e.g. brentuximab)
- Immunotherapy by drug name (including anti-PD1 or anti-CTLA4 agents)
- Other investigational agent by drug name
- Hematopoietic stem cell transplantation (Allogeneic, Autologous)
- Radiotherapy

A subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

[redacted]

7.5.4.2 Efficacy for Subjects Treated Beyond Progression (Cohorts A, B and C)

Individual time course of tumor burden change from baseline in target lesions, per investigator, will be generated for nivolumab subjects treated beyond progression (spider plot).

By subject listing of efficacy and per timepoint tumor response per investigator will also be produced.

7.6 Safety

For Cohort A, B and C, all analyses from the Core Safety SAP[1] will be produced separately for each cohort and on combined cohorts following the definition of on-treatment described in Table 6.1.2-1. Additional analyses examining the discontinuation schedule and subsequent potential re-initiation of therapy in persistent CR subjects may be performed. Listings will include all available data.

For Cohort D, all analyses from the Core Safety SAP will be produced for this cohort separately, for the monotherapy phase, combination phase and overall, except the following list of outputs which will not be produced:

- Summary of Any Adverse Events That Required Immune Modulating Medication by Worst CTC Grade with Extended Follow-Up (Any Grade, Grade 3-4, Grade 5)
- Summary of Late Emergent Drug-Related Adverse Events by Worst CTC Grade
- Summary of Any Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) by Gender, Race, Age Category, Region
- Summary of Drug-Related Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) by Gender, Race, Age Category, Region
- Summary of Any Select Adverse Events by Worst CTC Grade with Extended Follow-Up
- Summary of Any Drug-Related Select Adverse Events by Worst CTC Grade with Extended Follow-Up
- Summary of Any Select Endocrine Adverse Events by Worst CTC Grade with Extended Follow-Up
- Summary of Any Drug-Related Endocrine Select Adverse Events by Worst CTC Grade with Extended Follow-Up
- Summary of Drug-Related Serious Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
- Summary of Time to Onset of Drug-Related Select Adverse Events by Category for Treated Subjects Who Experienced at Least One Drug-Related Select Adverse Event from the Category
- Summary of Time to Onset of Drug-Related Select Endocrine Adverse Events by Subcategory for Treated Subjects Who Experienced at Least One Drug-Related Select Adverse Event from the Subcategory
- Summary of Time to Resolution of Drug-Related Select Adverse Events by Category for Treated Subjects Who Experienced at Least One Drug-Related Select Adverse Event from the Category
- Summary of Time to Resolution of Drug-Related Select Adverse Events where Immune Modulating Medication Was Initiated by Category for Treated Subjects Who Experienced at Least One Drug-Related Select Adverse Event from the Category

- Summary of Time to Resolution of Drug-Related Select Endocrine Adverse Events by Subcategory for Treated Subjects Who Experienced at Least One Drug-Related Select Adverse Event from the Subcategory
- Summary of Time to Resolution of Drug-Related Select Endocrine Adverse Events where Immune Modulating Medication Was Initiated by Subcategory for Treated Subjects Who Experienced at Least One Drug-Related Select Adverse Event from the Subcategory
- By Subject Listing of Time to Resolution for Longest Any Grade Immune-Mediated Adverse Event Cluster for Treated Subjects Who Experienced at Least One Immune-Mediated Adverse Event in the Category
- By Subject Listing of Time to Resolution for Longest Grade 3-5 Immune-Mediated Adverse Event Cluster for Treated Subjects Who Experienced at Least One Grade 3-5 Immune-Mediated Adverse Event in the Category

7.6.1 Deaths

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] with the exception that most of the analyses of select adverse events will be limited to the 30 days safety windows and will not be repeated with the 100 days safety windows. Plots of time to onset of select adverse events and tables of rates by timepoint of select adverse events will not be produced. Summary of any select, drug-related select, select endocrine, drug-related select endocrine AE by worst CTC grade will be produced. Summary of any select, drug-related select, select endocrine and drug-related select endocrine AE leading to discontinuation by worst CTC grade will also be produced.

7.6.7 Immune modulating medication

See Core Safety SAP[1]

7.6.8 Multiple Events

See Core Safety SAP[1]

7.6.9 Clinical laboratory evaluations

See Core Safety SAP[1]

7.6.10 Vital Signs and Pulse Oximetry

See Core Safety SAP[1]

7.6.11 Immunogenicity Analysis

See Core Safety SAP[1]

7.6.12 Pregnancy

By-subject listing of pregnancy tests results will be provided

7.6.13 Clinical Safety Program (CSP)

See Core Safety SAP[1]

7.6.14 Adverse Events by Subgroup

See Core Safety SAP[1]

7.6.15 Immune-mediated Adverse Events Analysis

IMAE analyses will include events, regardless of causality, occurring within 100 days of the last dose. These analyses are limited to subjects who received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which will be included in the analysis regardless of treatment since these events are often managed without immunosuppression.

IMAEs, serious IMAEs, IMAEs leading to discontinuation, and IMAEs leading to dose delay or reduction will be summarized by worst CTC grade and presented by IMAE Category/PT.

Time to onset, time to resolution, time to resolution with completion of immunosuppressive medication will be defined and summarized by IMAE category in the same manner as for select AEs (see Section 7.6.6) except that, other than for the endocrine category, the longest duration of

IMAEs has to be associated with the use of an immune-modulating medication. Time to Resolution for Longest Any Grade or Grade 3-5 IMAE cluster per subject will be listed.

Use of immune-modulating medications for IMAE management will be summarized by IMAE category in a similar manner as for the select AEs (see Section 7.6.7).

IMAE rechallenge will be also summarized.

7.6.16 Other Events of Special Interest

In addition to select AE and immune-mediated AE, categories of other events of special interest (OESI) have been defined (i.e. myasthenic syndrome, Guillain-Barre syndrome, demyelination, pancreatitis, uveitis, encephalitis events). Worst CTC grade of any and drug-related OESI (both safety windows) will be summarized along with the time to onset and resolution. In addition, worst CTC grade of serious OESI and OESI leading to discontinuation will be summarized (both safety windows). Lastly, OESI occurring within 100 days of the last dose in subjects who received immunosuppressive medication for treatment of the events will be tabulated by worst CTC grade and the time to onset and resolution will be provided.

7.6.17 Safety of subjects who undergo subsequent Allogeneic Transplant (Cohorts A, B and C)

Summary of baseline characteristics for subjects who undergo subsequent Allogeneic Transplant will be provided by cohort and overall (age, age categorisation, gender, race, ethnicity, number of prior systemic cancer therapies).

Summary of Allogeneic Transplant characteristics will be also provided by cohort and overall (Number of Nivolumab doses prior subsequent allogeneic transplant, Time between last nivolumab dose and allogeneic transplant, transplant source, donor type and relationship, type of preparative stem cells regimen).

The extent of post allogeneic transplant (time from allogeneic transplant to last known alive date or death), will be summarized for each cohort and overall. Number and percentage of subjects with at least 100 days, 6 months and 1 year extent of post-allogeneic transplant follow-up will be provided.

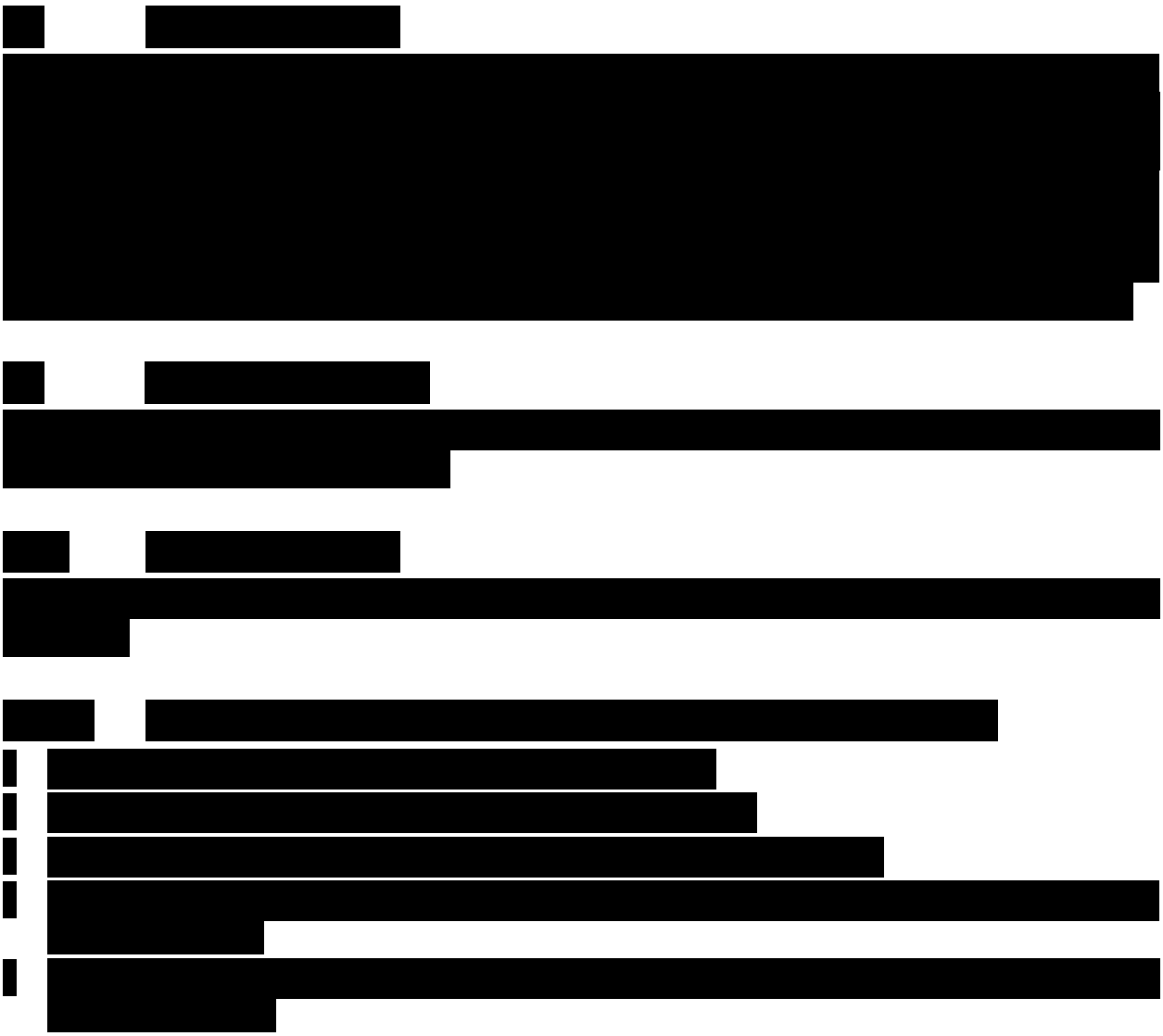
The incidence of subjects who progress post allogeneic transplant, the incidence of transplant related deaths, acute gvhd (any grade, grade 2-4, grade 3-4) or other potential complications will be summarized by cohort and overall. The time from transplant to these events will be summarized as well. Cumulative incidence rate will be plotted for cohort A+B+C. A multivariate Cox model analysis may be performed on cohort A+B+C to model the occurrence of transplant related deaths, acute gvhd grade 2-4, acute gvhd 3-4 with a set of covariates which may include a set of relevant factors such as age at the time of transplant, number of therapies prior Nivolumab, number of nivolumab doses, time from last nivolumab dose to allogeneic transplant, transplant source, donor type and relationship or other transplant characteristics. As post-transplant disease progression can be seen as a competing risk to transplant-related death or acute gvhd, competing risk modeling

methods such as Fine-Clay model may be used instead of the Cox model if competing risks are observed.

By-subject listings of transplant-related characteristics, transplant-related complications and extent of post-transplant follow-up will also be provided.

7.6.18 Other safety analyses

For cohort D, a by-subject listing of electrocardiograms results and pulmonary functions data will be provided. A summary table of the change from baseline in pulmonary functions (such as percentage of the predicted forced expiratory volume in one second (FEV1), percentage of the predicted forced vital capacity (FVC) and the percentage of the predicted ratio of FEV1/FVC) after study therapy will also be provided.



[redacted]

[redacted]

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[9]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non-Study Medication Domain Requirements Specification[10].

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 alive date

For date of progression, 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.
- In case, 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.

For other partial/missing dates, the following conventions will be 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.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

Table 10-1: Document History

[redacted]	[redacted]	[redacted]
[redacted]		