Official Title of Study:

Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects

(CheckMate 205: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 205)

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Clinical Protocol CA209205

Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects

(CheckMate 205: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 205)

Revised Protocol Number: 04c

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04c	22-Aug-2019	In this protocol revision, subjects will switch from a dose of 3 mg/kg every 2 weeks to a flat dose of 480 mg every 4 weeks or a flat dose of 240 mg every 2 weeks by IV infusion over 30 minutes.
Revised Protocol 04b	14-Sep-2018	This protocol revision clarifies timing of sample collection.
Revised Protocol 04a	08-Sep-2016	Incorporates Amendment(s) 8 & 12
Amendment 12	08-Sep-2016	This amendment is introducing a Data Monitoring Committee for Cohort D, a revised protocol Appendix 1 Management Algorithms and a few other minor updates.
Amendment 8	24-Mar-2016	This amendment is documenting the revised timing of primary endpoint analysis for cohorts A and C
Revised Protocol 04	21-Oct-2015	Incorporates Amendment(s) 07
Amendment 07	21-Oct-2015	This global amendment is introducing a new cohort (Cohort D) into the study.
Revised Protocol 03	23-Jun-2015	Incorporates Amendment(s) 06
Amendment 06	23-Jun-2015	This amendment is clarifying the timing of analysis for each study cohort.
Administrative Letter 01	20-May-2015	This administrative letter is announcing a change of duration of follow-up for primary endpoint analysis.
Revised Protocol 02	04-Dec-2014	Incorporates Amendment(s) 05
Amendment 05	04-Dec-2014	This global amendment is introducing a new cohort (Cohort C) into the study.
Revised Protocol 01	10-Jul-2014	Incorporates Amendment(s) 03
Amendment 03	10-Jul-2014	This global amendment is introducing the following changes or clarifications: • [redacted] • Study drug administration may begin before the results of a bone marrow biopsy (pathological reports) become available. The purpose of a bone marrow biopsy/aspirate is to determine the extent of disease (lymphoma) involvement in the bone marrow and because bone marrow biopsy results will not change the eligibility of the subject, it is acceptable that sites cannot confirm those results prior starting study drug as long as sites can verify the documentation that a bone marrow

Document	Date of Issue	Summary of Change
		biopsy was performed. Those results can be confirmed later. • Immunotherapeutic agents produce atypical clinical response patterns, which are not usually observed in conventional chemotherapy. Two distinct non-conventional patterns have been reported: 1) a reduction in total tumor burden despite of the appearance of new lesion(s), and 2) responses after a transit increase in total tumor burden in an initial phase, followed by subsequent tumor shrinkage. Therefore, it is important to avoid premature discontinuation of the study drug as nivolumab might induce non-conventional response patterns in some patients. Under the current discontinuation criteria (Section 3.5), subjects must stop the study drug when investigator assessment determines disease progression using the 2007 IWG criteria. The change in this amendment will permit the subjects to continue on the study drug beyond investigator-assessed disease progression in certain cases. • Exclusion criteria of history of severe hypersensitivity reaction to any monoclonal antibody is reworded to allow for subjects who experienced Grade 3 – 4 infusion-related reaction with the first dose of rituximab, but who were able to receive subsequent rituximab without recurrence of Grade 3 or 4 infusion-related reaction to be eligible. • A clarification note is being added with regard to disease response evaluation. • A section is introducing guidelines for assessment and initial management of tumor lysis syndrome. • A few editorial or administrative corrections.
Original Protocol	25-Apr-2014	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 04C:

The purpose of this revision is to allow subjects in Cohorts A, B, and C to have access to a more convenient dosing schedule, 480 mg (flat dose) every 4 weeks, based on feedback from investigators. Also, to simplify the dosing regimen, those subjects that prefer to remain on an every 2-week dosing schedule, a switch to 240 mg (flat dose) will be required.

Revisions apply to all participants currently enrolled.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04C		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis; 1.4.3.5, Nivolumab Monotherapy Clinical Pharmacology Summary; 3.1.1, Study Design and Duration for Cohorts A, B, and C; 4.5, Selection and Timing of Dose for Each Subject; Table 5.1.1-2, On-Treatment Assessments for Cohorts A, B, and C Table 5.1.1-5, Re-Initiation of Treatment Assessments for Cohort C Subjects	• Subjects will switch from a dose of 3 mg/kg every 2 weeks to a flat dose of 480 mg every 4 weeks or a flat dose of 240 mg every 2 weeks by IV infusion over 30 minutes. • Subjects must sign an informed consent document prior to switching the dosing schedule.	To align with recommended dosing in nivolumab label.
1.1.2.2, Justification for Doses in Cohorts A, B, and C	Section added for justification of new doses/dosing frequencies.	To align with the current nivolumab IB.
Table 4-1, Study Drugs for CA209205 - Treatment Period 4.3, Storage and Dispensing	Detailed text around packaging and storing conditions made more general and pharmacy manual is referenced.	To allow for change in dosing.
Table 5.1.1-3, Follow-Up Assessments for Cohorts A, B, and C Table 5.5-1, Sampling Schedule for Cohorts A, B, and C	Collection of pharmacokinetic and immunogenicity samples at follow-up visits were removed.	To align with current nivolumab protocol standards, as immunogenicity and PK is already well-characterized in many subjects across multiple tumor types.
Appendix 1, Nivolumab Management Algorithms	New Myocarditis Adverse Event Management Algorithm was added.	To align with current nivolumab standards.
All	• Minor formatting and typographical corrections. • "Patients" changed to "subjects" when referring to study participants.	To improve readability and understanding.

SYNOPSIS

Clinical Protocol CA209205

Protocol Title: Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (BMS-936558) administered IV over 60 minutes at 3 mg/kg (Cohorts A, B and C) or flat dose 240 mg over 30 minutes IV infusion (Cohort D) every 2 weeks until progression or unacceptable toxicity. **In revised protocol 04c**, subjects in Cohorts A, B, and C will switch to IV infusion over 30 minutes of nivolumab 480 mg flat dose every 4 weeks or 240 mg flat dose every 2 weeks until progression or unacceptable toxicity.

Study Phase: 2b

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 the 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.

Primary Objective:

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).

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.

Secondary Objectives:

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.

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.

Exploratory Objectives:

Cohorts A, B, and C

- To assess the progression free survival (PFS) based on IRRC assessment
- To assess the overall survival (OS)
- To assess the overall safety and tolerability of nivolumab, as measured by incidence and severity of adverse events, serious adverse events, and specific laboratory abnormalities
- To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy measures
- To characterize pharmacokinetics of nivolumab and explore exposure-response relationships
- To characterize the immunogenicity of nivolumab monotherapy
- To evaluate both generic health-related quality of life as assessed by the EQ-5D and cancer specific quality of life as assessed by the EORTC QLQ-C30
- To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression (microarray technology, quantitative RT-PCR).
- For Cohort C, to evaluate risk-benefit of discontinuation schedule of the study drug for the subjects who have persistent CR for 1 year.

Cohort D

- To evaluate IRRC-assessed OR rate, and investigator-assessed CR and OR rates at the planned end of therapy
- To evaluate the CR rate and OR rate at the planned end of Nivolumab monotherapy based on IRRC assessment and based on investigators assessment
- To evaluate the CR rate and OR rate at the planned end of two combocycles based on IRRC assessment and based on investigators assessment
- To evaluate the PFS based on IRRC assessment and based on investigators' assessment
- To assess the OS
- To assess the duration of objective response (DOR) and duration of complete response based on IRRC assessment and based on investigators assessment
- To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy measures
- To characterize pharmacokinetics of nivolumab and explore exposure-response relationships
- To characterize the immunogenicity of nivolumab
- To evaluate the change from baseline of pulmonary function after treatment
- To evaluate generic health-related quality of life as assessed by the EQ-5D
- To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry (IHT), soluble factor analysis, and gene expression (microarray technology, quantitative reverse transcription polymerase chain reaction (RT-PCR).

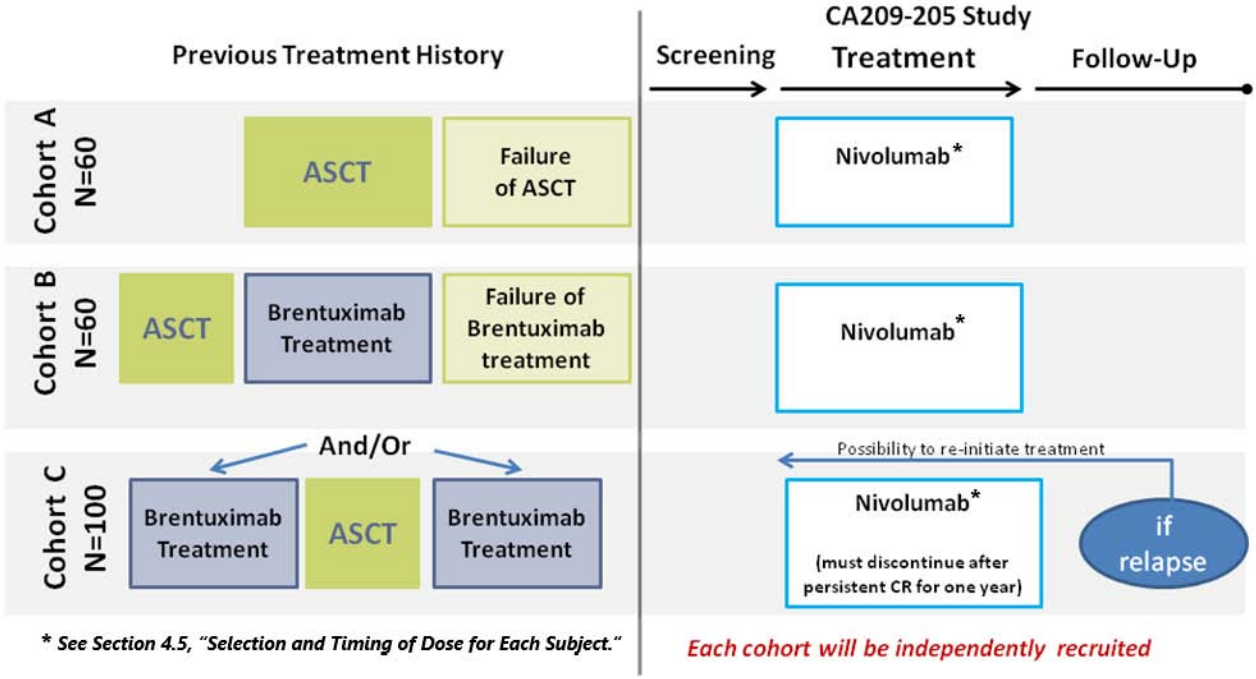
Study Design:

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 autologous stem cell transplant (ASCT). Subjects can be brentuximab vedotin-naïve (Cohort A), or can have 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) is being added to the study with broader eligibility criteria. Subjects with a treatment

history of brentuximab vedotin before first ASCT will not be eligible, except in Cohort C. The original protocol requires nivolumab dosing 3 mg/kg every 2 weeks. Approximately 220 subjects with failure after ASCT will be treated with nivolumab 3 mg/kg IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity, consisting of approximately 60 subjects for Cohorts A and B respectively, and approximately 100 subjects for Cohort C. **In revised protocol 04c**, subjects will switch to IV infusion over 30 minutes of nivolumab 480 mg flat dose every 4 weeks (Q4W) or 240 mg flat dose every 2 weeks (Q2W). For those subjects receiving a 480 mg flat dose Q4W, a cycle will be a 28-dosing period. For those subjects receiving a 240 mg flat dose Q2W, a cycle will be a 14-day dosing period. Subjects will be independently enrolled for each cohort. If one of these cohorts complete enrollment earlier, the other cohorts will remain open until complete accrual is reached. Once a new dosing regimen has been selected for the subject, either flat dose 280 mg Q2W or flat dose 480 mg Q4W, the dosing regimen will remain in effect until the end of treatment and not change. Primary analysis will be performed separately for each cohort (ie, at separate time points) upon completion of a pre-specified amount of follow-up after last patient first treatment (LPFT). All analyses will be performed separately for each cohort upon completion of follow-up for the primary endpoint in each cohort. In addition safety analyses will be performed on combined cohorts.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Subjects may be dosed no less than 12 days from the previous dose during every 2-week cycle. For every 4-week dosing cycle, subjects may be dosed within a ± 3-day window.



Cohort D

Cohort D is a non-comparative single-arm cohort in subjects ≥ 18 years old who have newly diagnosed, previously untreated cHL with advanced stage (Stage IIB, III and IV) disease. Cohort D consists of approximately 50 subjects.

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

Treatment for Cohort D consists of two phases: monotherapy and combination phases. Subjects will be treated with four doses of nivolumab flat dose 240 mg IV every 2 weeks (two months of monotherapy phase), followed by twelve doses of the combination of AVD chemotherapy and nivolumab flat dose 240 mg IV for 6 cycles (six months of combination phase). The primary analysis for Cohort D will be conducted when all treated subjects from 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.

Study Population:

Cohorts A, B, and C

Male and female, ages 18 and above, with cHL after failure of ASCT and who are naïve to brentuximab vedotin (Cohort A), who had prior brentuximab vedotin treatment after failure of ASCT (Cohort B) or who had prior brentuximab vedotin treatment before and/or after failure of ASCT (Cohort C) will be eligible to participate in the study. Other key inclusion criteria include ECOG PS 0-1, biopsy confirmation of cHL prior to initiation of study drug (See protocol Sections 3.3.1 and 3.3.2 for full list of criteria).

Cohort D

Male and female, ages 18 and above, with newly diagnosed, previously untreated cHL lymphoma (Stage IIB, III and IV) will be eligible to participate in the study. Other key inclusion criteria include ECOG PS 0 - 1, biopsy confirmation of cHL prior to initiation of study drug (See protocol Sections 3.3.1 and 3.3.2 for full list of criteria).

Study Drug: includes Investigational [Medicinal] Products (IP/IMP) as listed:

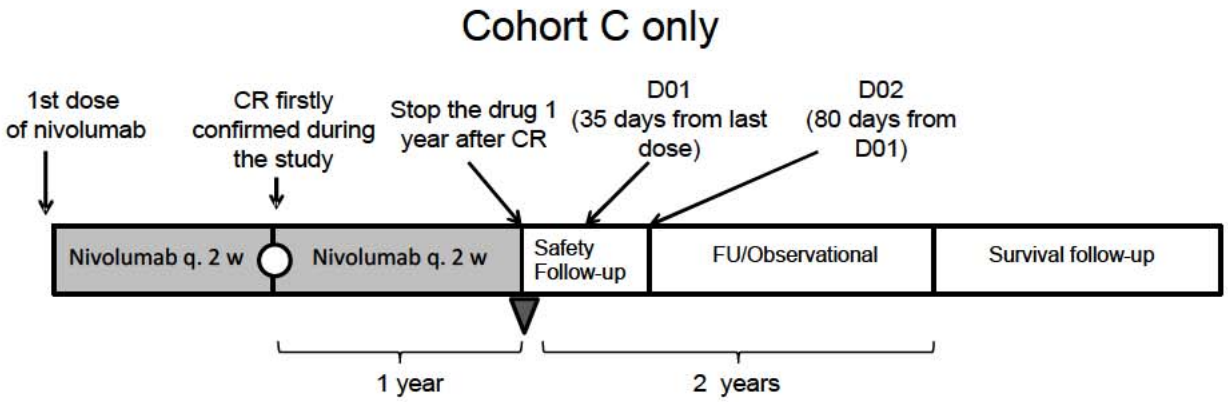
Study Drug for CA209205		
Medication	**Potency**	**IP/Non-IP**
BMS-936558-01 Solution for Injection (Nivolumab)	100 mg (10 mg/mL)	IP
Dacarbazine Powder for IV Solution	200 mg	IP
Doxorubicin Powder for Solution for Injection	50 mg	IP
Vinblastine Solution for Injection	10 mg (1 mg/mL)	IP

Study Assessments:

Cohorts A, B, and C:

The primary endpoint is ORR as determined by an IRRC according to the revised International Working Group Criteria for Malignant Lymphoma. Subjects will be assessed for response by imaging (CT or MRI) beginning at Week 9 (± 7 days) after the start of therapy and then at Weeks 17, 25, 37 and 49 during the first year of treatment, then every 16 weeks (± 14 days) for the second year of treatment up to Week 97, continuing every 26 weeks (± 21 days) beyond Week 97 for the third year or beyond treatment, until disease progression is documented. A FDG-PET scan is required at screening, Weeks 17 and 25 in all subjects, and at Week 49 for subjects who do not have two consecutive negative FDG-PET scans after Week 1 and prior to Week 49, and to confirm CR.

Cohort C subjects who have persistent CR for one year will discontinue study treatment and have a specific follow-up schedule. Should those subjects relapse, they will have the possibility to re-initiate treatment.



- Subjects who have persistent one year CR will discontinue nivolumab.
- Confirmation of CR by CT (preferred) or MRI ▼ will be required before discontinuation
- Subjects enter safety follow-up phase and subsequently observation follow-up.
- After FU/Observational phase is completed (2 years from the last dose), survival follow-up visits continue every 3 months
- In case of relapse during the FU/Observational phase, possibility to re-initiate treatment

Cohort D

The primary endpoint for Cohort D is overall safety and tolerability, measured by the proportion of subject 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, in subjects receiving at least one dose of study treatment.

Statistical Considerations:

Sample Size: 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), and treatment with brentuximab vedotin at any time point (n = 100; Cohort C), and first-line subjects (n = 50; Cohort D).

Endpoints:

Cohorts A, B, and C

The primary objective will be measured by the primary endpoint of IRRC-assessed ORR. 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. DOR is defined as the time from first response (CR or PR) to the date of initial objectively documented progression or death from any cause, whichever occurs first.

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.

Analyses:

Cohorts A, B, and C

Primary analysis will be performed separately for each cohort (ie, at separate time points) upon completion of a pre-specified amount of follow-up after last patient first treatment (LPFT). The ORR based on IRRC assessment will

be summarized by binomial response rates and their corresponding two-sided 95% exact confidence intervals using the Clopper-Pearson method. The null hypothesis will be rejected if the 2-sided 95% CI lower bound is greater than 20%. DOR will be summarized for subjects who achieve PR or CR using the Kaplan-Meier product-limit method. Median values of DOR along with two-sided 95% CIs and range will also be calculated.

Cohort D

Analysis of Cohort D will be performed separately from Cohorts A, B and C.

Safety analyses will be performed in all treated subjects from cohort D. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

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1 INTRODUCTION AND STUDY RATIONALE

Hodgkin lymphoma (HL) is a lymphoid malignancy characterized by the presence of multinucleated Reed-Sternberg cells, which are generally accepted to be of B-cell origin and usually account for only 1% to 10% of the cells in the tumor tissue. The majority of cells in HL tumor tissue are a mixed infiltrate of various lymphoid cells, including regulatory T-cells and macrophages.[1] The updated 2008 WHO classification recognizes two histologic groups: nodular lymphocyte predominant, which accounts for about 5% of all HL cases and "classical" HL (cHL) which accounts for the remainder. In cHL, four subgroups are identified: nodular sclerosis (75% to 80% of cases), mixed cellularity, lymphocyte depletion, and lymphocyte rich.[2] Importantly, Epstein-Barr (EB) virus may play both an etiologic and pathogenetic role in about 40% of cHL (usually in mixed cellularity and lymphocyte depleted HL), where three predominant viral proteins are typically expressed potentially contributing to dysregulated HL growth.[3]

In 2013, the National Cancer Institute estimated that 9,290 men and women would be diagnosed with HL and 1,180 would die of HL.[4] The prevalence of HL in the US in 2013 was estimated to be 181,928. The median age of diagnosis of HL in the US is 38 years; there is a bimodal age-specific incidence pattern, in which the incidence is highest between 15 and 34 years, declines between ages 35 and 54, and increases again after 55 years.

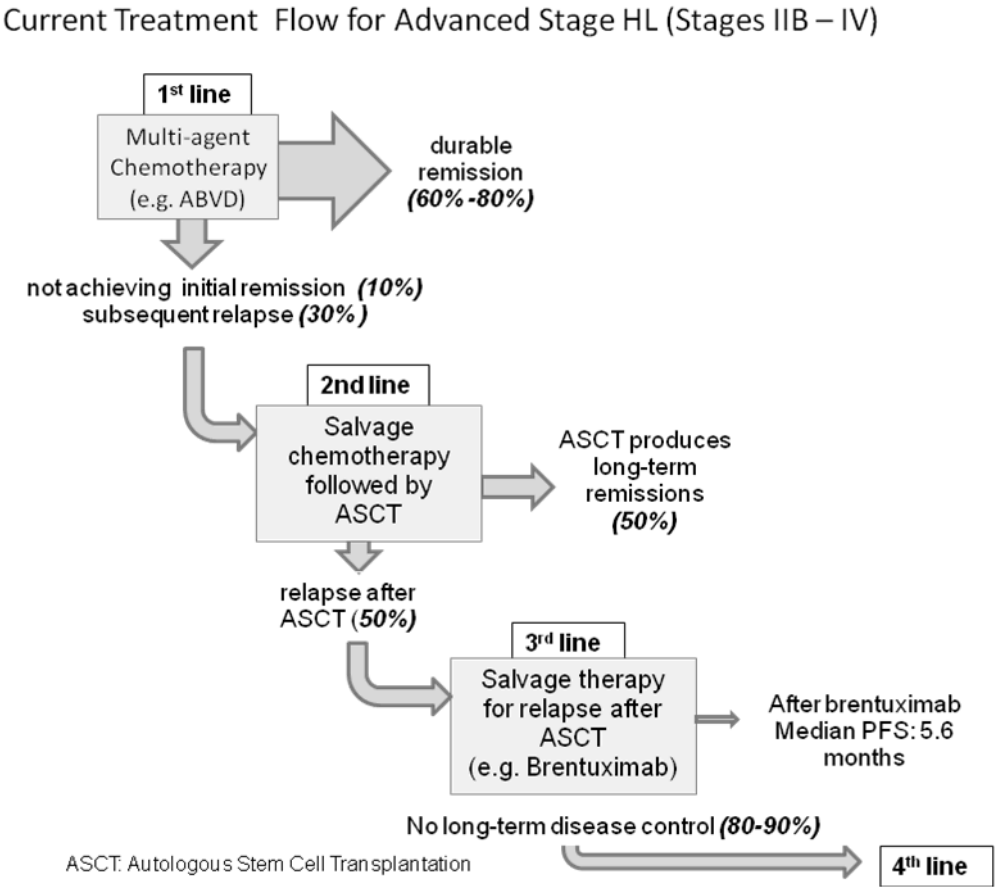
The treatment of limited-stage HL has improved significantly since the adoption of combined modality therapy, with treatment failure occurring in approximately 10% of patients.[5] However, approximately 30% of patients presenting with newly diagnosed HL have advanced stage disease (Stages IIB - IV). Improvements in the use of combined chemotherapy and radiotherapy in advanced stage newly diagnosed HL have resulted in durable remission rates of approximately 60% to 80%.[6]However, there continues to be a significant opportunity for improvement in treatment of HL, including the frontline setting for patients with advanced-stage disease.[6,7,8] Although multiagent chemotherapy regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) have been established as standard initial therapy for advanced-stage cHL,[9,10,11] an Eastern Cooperative Oncology Group (ECOG) study showed ABVD regimen provided 71% and 67% 3-year and 5-year failure-free survival rates, respectively.[12] This is particularly important considering young patient population,[13] and when compared to the excellent long-term disease control for limited-stage cHL (over 90%).[5]

More intensified regimen such as escalated bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone (BEACOPP) demonstrated an improvement in disease control.[14] However this intensive approach was associated with a greater frequency of initial toxicities,[14] treatment-related mortality,[15] and long-term toxicities, including higher incidences of secondary acute myeloid leukemia and myelodysplastic syndrome (MDS),[14] and anticipated infertility.[16] A more recent randomized Phase 3 study directly comparing ABVD with BEACOPP failed to show a significant difference in overall survival (OS) despite statistically higher progression free survival (PFS) for the

BEACOPP arm.[15] The results from these first-line studies indicate the challenges to improve the outcomes for advanced-stage cHL.

A substantial fraction of patients with HL are not cured; up to 10% of patients with advanced stage HL will not achieve an initial remission, and 30% of responding patients subsequently relapse.[7,8] The standard of care for patients with relapsed and refractory HL is intensive salvage chemotherapy followed by autologous stem cell transplant (ASCT), which can produce long-term remissions in approximately 50% of patients. Unfortunately, the remaining 50% of ASCT patients do not experience long-term disease control with median overall survival of approximately 27 months.[17] In particular, the prognosis remains exceedingly poor for patients who experience relapse or progressive HL within one year after ASCT where the median survival time is approximately 1.2 years.[18] Several small clinical studies have examined various agents in the ASCT relapsed HL population with uniformly poor results. Therefore, the therapeutic options for these patients remain very limited.

Figure 1-1: Current Treatment Flow for Advanced Stage HL (Stages IIB - IV)



More recently, other novel approaches have been investigated in an effort to improve the outcome for HL patients failing ASCT. The malignant Reed-Sternberg cells of classical HL are

characterized by the expression of CD30, a member of the tumor necrosis factor superfamily, whose expression is restricted to a subset of activated B-cells, T-cells, and eosinophils.[19] Brentuximab vedotin (Adcentrix, SGN-35) is an antibody drug conjugate (ADC) comprising an anti-CD30 monoclonal antibody conjugated by a protease cleavable linker to the potent antimicrotubule disrupting agent, monoethyl auristatin E (MMAE). Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, followed by lysosomal proteolytic cleavage with the resultant release of MMAE, disruption of the microtubule network, and apoptotic cell death.[20,21]

In a Phase 1 study brentuximab vedotin was studied in 45 patients with relapsed or refractory CD30 lymphomas where the maximum tolerated dose (MTD) was determined to be 1.8 mg/kg every 3 weeks.[22] Treatment was reasonably well tolerated with the most common adverse events (AEs) being fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. Because a substantial proportion of patients achieved objective responses, brentuximab vedotin was subsequently evaluated in a Phase 2 trial in a larger homogeneous population of HL patients who had relapsed or had refractory disease after ASCT.[23] In this open-label Phase 2 study, 102 were patients treated up to a maximum of 16 cycles. Although the overall response rate (ORR) was 75% with complete remissions (CR) in 34% and partial remission (PR) in 41% of patients, median progression free survival (PFS) and overall survival (OS) were 5.6 months and 22.4 months for all patients. The median duration of response for patients who achieved a CR (n = 35) and a PR (n = 41) was 21.7 and 5.1 months, respectively. A recent update with longer follow up of the original patient population (median observation time 32.7 months) has shown that 14 patients remain in remission, with 9 patients who have not started a new anti-cancer therapy and 5 patients who received ASCT after brentuximab vedotin treatment.[24] Despite the encouraging high response rate obtained with brentuximab vedotin, long-term disease control remains challenging since only a small proportion of patients can maintain complete responses. Additionally, in the Phase 2 trial, 21% of patients discontinued treatment due to AEs, most commonly peripheral sensory and peripheral motor neuropathies. Tolerability may also be of increased concern in patients > 60 years, where higher rates of anemia and peripheral neuropathy have been reported.[25]

Clearly for the relatively young and otherwise fit HL population who has relapsed after ASCT, there still remains a compelling unmet need for improved salvage therapy. Despite the high initial rate of OR obtained with brentuximab vedotin after ASCT failure, relapse for most patients occurs after a relatively short disease free interval. Unfortunately, for the population of HL patients who have failed both ASCT and brentuximab vedotin salvage therapy, there currently is no uniform approach to their treatment, underscoring the need for novel approaches to improve treatment outcomes for this group of patients as well.

1.1 Study Rationale

1.1.1 Scientific Rationale

Immunotherapeutic approaches for the treatment of HL are well-established components of current treatment paradigms for these diseases.[22,26,27,28] T cell checkpoint regulators such as programmed death-1 receptor (PD-1, CD279) and CTLA-4 (CD152) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. Several models have been proposed to explain these activities, including the breaking of immune tolerance to tumor cell antigens by evasion of physiological T cell checkpoint controls. Other mutually non-exclusive models propose that PD-1 antagonists like nivolumab reverse the exhausted/arrested T cell phenotype by activating tumor reactive T cells in lymphoid organs and in the periphery, allowing for enhanced trafficking of tumor adjacent T cells into the tumor.[29]

Nivolumab is a fully human, IgG4 (κ) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1(B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab monotherapy has demonstrated activity in several tumor types, including melanoma, renal cell cancer, and non-small cell lung cancer (NSCLC).[30] Additionally, in an ongoing Phase 1 study in subjects with relapsed hematologic malignancies (CA209039), nivolumab has demonstrated preliminary activity in subjects with HL, follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL). In general, nivolumab has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.[31]

Expression of PD-L1 by malignant lymphoma cells and by other cells in the tumor microenvironment including infiltrating T cells, dendritic cells, and monocytes, has the potential to interact with tumor specific T cells that express PD-1. The interaction of PD-1 on tumor specific cytotoxic T cells with its ligands PD-L1 and PD-L2 causes a decrease in the ability of these cells to proliferate and exert cytotoxic effects, increases their apoptotic rate and alters the functional characteristics of the cells to produce a tolerogenic and/or exhausted phenotype.[32,33] This study will evaluate the effects of PD-1 blockade by nivolumab in subjects with cHL.

1.1.2 Study Design Rationale for Cohorts A, B, and C

A single-arm study design was chosen because there is no appropriate, fully-approved active comparator for relapsed third-line or later cHL subjects failing ASCT. Although brentuximab vedotin may be an effective treatment option for this patient population, its regulatory approval is provisional: accelerated approval in the US and the conditional approval in EU. As recently reported, long-term disease control has been observed in a very limited patient population; it is still uncertain whether patients are curable with this approach. Thus, this population still has limited therapeutic options, representing a substantial unmet medical need.

A parallel cohort approach was selected because the target population of cHL failing ASCT requires clear distinction based upon prior brentuximab vedotin treatment. This study design will test nivolumab in parallel treatment groups; brentuximab vedotin- naïve subjects (Cohort A) who have failed ASCT, or those who received brentuximab vedotin treatment as salvage following failure of ASCT (Cohort B). Cohort A or Cohort B represents the subjects who require the third or fourth line of therapy (in Figure 1-1). The two cohorts will enroll independently and will be analyzed separately. A third Cohort (Cohort C) is being added. This new cohort will start to enroll after completion of Cohort B enrollment. Analysis will be also conducted independently for Cohort C.

1.1.2.1 Rationale for Cohort C

Cohort C will provide an extended assessment of the benefit-risk for this study drug in advanced stage cHL patients in a larger patient population. Approximately 100 subjects treated from Cohort C will assist in the identification and characterization of less common safety events as well as further confirmation of the activity initially observed in Cohort B.

Importantly, Cohort C will also provide initial data concerning whether discontinuation of nivolumab monotherapy is safe in subjects who have remained in CR for one year on nivolumab. Most currently ongoing nivolumab Phase 2 and Phase 3 studies for solid tumor and hematologic malignancies permit treatment until disease progression or unacceptable toxicity. Because nivolumab is generally tolerable, some subjects who have achieved CR may remain on study therapy indefinitely unless disease progression occurs. It will be helpful to answer whether these subjects can safely stop treatment at some point in order to avoid unnecessary exposure to study drug, and can experience similar benefit. To address this scientific question, a discontinuation schedule will be examined in Cohort C. Subjects who have persistent CR for one year on study drug will discontinue the study drug. If 15 to 20% of the subjects from Cohort C achieve CR and maintain their CR for one year, the discontinuation schedule will be assessed on approximately 15 to 20 subjects. To ensure that subjects can safely discontinue study therapy, regular follow-up observational visits will be conducted after treatment discontinuation for up to two years. Furthermore, re-initiation of study therapy will be permitted for those subjects relapsing within two years of study drug discontinuation. This discontinuation schedule will provide important information as to whether the subjects who have attained good disease control can safely discontinue study drug without increasing risk of relapse.

In addition, plasma samples will be collected in Cohort C subjects for, but not limited to, the determination of Minimal Residual Disease (MRD) for molecular monitoring of the disease.

1.1.2.2 Justification for Doses in Cohorts A, B, and C

The benefit-risk profiles of nivolumab 240 mg every 2 weeks (Q2W) and 480 mg every 4 weeks (Q4W) are expected to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response (E-R) relationships across indications. Given that nivolumab has linear PK over a dose range of 0.1 to 10 mg/kg across multiple tumor types, the 240 mg Q2W regimen was selected based on the

approximate median body weight of 80 kg for subjects treated in nivolumab clinical trials. The 480 mg Q4W regimen was selected as it translates to a doubling of the 240 mg flat dose given Q2W. With reduced dosing frequency from Q2W to Q4W, the average nivolumab exposure with 480 mg Q4W is expected to be comparable to that from 3 mg/kg Q2W or 240 mg Q2W.

Using a previously developed population pharmacokinetic (PPK) model that incorporated time-varying CL, nivolumab exposures were estimated in advanced melanoma, NSCLC, advanced RCC, SCCHN, cHL, and UC subjects for nivolumab 240 mg Q2W and 480 mg Q4W dosing.

The geometric means of key summary measures of exposure achieved with nivolumab 240 mg Q2W including peak (Cmax), time-averaged (Cavg) and trough (Cmin) concentrations after the first dose or at steady-state were similar (<6% difference) to the corresponding exposures achieved with nivolumab 3 mg/kg Q2W. The magnitude of the difference is not expected to be clinically significant.

In comparing nivolumab 480 mg Q4W to 3 mg/kg Q2W, the geometric mean time-averaged concentration over the first 28 days (Cavgd28) was approximately 27% higher with 480 mg Q4W, whereas the geometric mean steady-state time-averaged concentration (Cavgss) for both dosing regimens was similar. Nivolumab geometric mean trough concentrations at Day 28 (Cmind28) and at steady-state (Cminss) were 22% and 16% lower, respectively, with 480 mg Q4W dosing. Conversely, geometric mean peak nivolumab concentrations after the first dose (Cmax1) and at steady-state (Cmaxss) were 111% and 43.4% higher, respectively, with 480 mg Q4W dosing.

Extensive E-R analyses were conducted for OS, OR, and tumor growth dynamics to bridge efficacy of nivolumab 240 mg Q2W and 480 mg Q4W with the clinically evaluated 3 mg/kg Q2W dosing regimen. The primary exposure measure used in the analyses was Cavgd28 because it represents the relevant drug concentration over the entire duration of earlier dosing intervals from Q2W and Q4W regimens. The hazard ratios with nivolumab 240 mg Q2W or 480 mg Q4W were predicted to be similar to 3 mg/kg Q2W across multiple tumor types (melanoma, RCC, SQ and NSQ NSCLC). There were no differences in predicted response rate with nivolumab 240 mg Q2W or 480 mg Q4W compared to 3 mg/kg Q2W. There was also no apparent relationship between Cavgd28 and individual estimates of tumor growth rate.

To evaluate safety, the exposure margin of nivolumab 240 mg Q2W and 480 mg Q4W relative to the safe and well-tolerated dose of 10 mg/kg Q2W was determined. In addition, extensive E-R analyses for AE-DC/D, AE-Grade 3+, and Grade 2+ immune-mediated adverse events (AE-IM Grade 2+) were conducted with pooled safety data across multiple tumor types (melanoma, RCC, SQ NSCLC, NSQ NSCLC, SCCHN, cHL, and UC). Exposure margins with 240 mg Q2W or 480 mg Q4W were below that achieved with nivolumab 10 mg/kg Q2W indicating that these dosing regimens are expected to be safe and tolerable. In addition, the risk of AE-DC/D, AE-Grade 3+, and AE-IM Grade 2+ was not significantly associated with Cavgd28 or Cmax1 in the E-R analyses.

1.1.3 Study Design Rationale for Cohort D

Cohort D will investigate the overall safety and tolerability of nivolumab monotherapy (240 mg flat dose) followed by nivolumab (240 mg flat dose) in combination with chemotherapy (doxorubicin, vinblastine, and dacarbazine: AVD where A stands for Adriamycin, which is the trade name of doxorubicin) in subjects who are newly diagnosed, previously untreated cHL with advanced stage (Stage IIB, III and IV) disease. The first segment of the tested regimen in this cohort will consist of 4 doses of nivolumab monotherapy on a 2-week schedule. The second segment of the regimen will consist of 6 cycles (12 doses) of nivolumab in combination with three chemotherapy drugs (doxorubicin, vinblastine, and dacarbazine: AVD) which are frequently used as standard-of-care for newly diagnosed cHL.

As explained in more detail below, a nivolumab-based regimen has the potential to improve long-term clinical outcome due to its capacity to reduce tumor burden and induce durable response as a single agent, in addition to its tolerable safety profile.

Rationale for Nivolumab Monotherapy

This study will evaluate nivolumab monotherapy (four doses) as the first component of the tested regimen in first line cHL subjects with advanced stage disease based on the following considerations.

First, nivolumab monotherapy in CA209039 significantly reduced tumor burden in the first 16 weeks (Figure 1.4.3.4-1), where 39.1% of heavily pretreated subjects with cHL were able to achieve an overall response within the first 8 weeks of nivolumab monotherapy, and 65.2% were able to achieve an overall response (CR or PR) within the first 16 weeks (Table 1.1.3-1). This indicates that nivolumab monotherapy can potentially be utilized as induction therapy for newly diagnosed cHL, given that monotherapy generated high response rate (87%) and the remaining subjects (13%) had stable disease. The earliest progression noted in the HL cohort was observed at 15 weeks. It is reasonable to presume that the durability of response will be similar between newly diagnosed cHL patients and heavily pre-treated cHL patients.

Table 1.1.3-1: Cumulative Response Rate in cHL Subjects Treated with Nivolumab Monotherapy (CA209039)

Time from the First Dose	Responders[a] with Overall Response (CR or PR) N	Cumulative Response Rate % (95% CI)
8 weeks	9	39.1 (22.6, 61.7)
16 weeks	15	65.2 (46.3, 83.4)
24 weeks	16	69.6 (50.7, 86.5)
48 weeks	19	82.6 (65.0, 94.6)

cHL = classical Hodgkin lymphoma; CR = complete remission; PR = partial remission

[a] Twenty out of the 23 subjects with cHL achieved overall response

Second, nivolumab monotherapy generates durable responses in heavily pretreated cHL subjects. Out of 20 responders in the Phase 1 study (CA209039), the median duration of response in the 14 subjects who did not proceed to stem cell transplant (SCT) was over 14 months (57.0 weeks; range: 23.3 - 76.3+ weeks).[34] This is in contrast to the relative short durability of response (6.7 months 95% CI: 3.6 - 14.8), which was reported for 76 responders in a similar population who were treated with brentuximab vedotin monotherapy[35]. Again, there is no reason to consider that durability of response will be different in newly diagnosed cHL subjects from that observed in heavily treated cHL subjects.

Third, treatment with immune modulating therapy early in the disease course and prior to immunosuppressive/myelosuppressive effects of chemotherapy may be advantageous for therapies that require a host's ability to mount an initial immune response. Chemotherapies suppress myelopoiesis, and decrease the number of red blood cells, platelets, and lymphocytes (including T-lymphocytes) in the peripheral circulation. By lowering the overall number of T-lymphocytes, a checkpoint inhibitor such as nivolumab will have fewer effector cells for potential lessened downstream anti-tumor activity during the combination therapy period.

Fourth, introduction of nivolumab would provide an opportunity to spare patients from toxicity associated with certain chemotherapy in the future. Due to the significant reduction of tumor burden by nivolumab monotherapy observed in the Phase 1 study, a nivolumab-incorporated regimen might reduce the number of required cycles of multiagent chemotherapy while maintaining long-term disease control in future studies. This would be beneficial for young patients to avoid late adverse effects of traditional chemotherapy (eg, secondary malignancies, cardiovascular disease, or pulmonary dysfunction)[36,37] While nivolumab monotherapy in newly diagnosed advanced stage cHL in the front line setting is investigational, it was already investigated in two randomized phase III trials (CA209066 and CA209067) in the treatment naive setting in a different tumor, melanoma.[38,39] These results indicated favorable safety profile of nivolumab monotherapy as a front line therapy in untreated melanoma patients. For example, treatment-related adverse events of grade 3 or 4 in the nivolumab-treated subjects were reported as 11.7% and 16.3%, respectively.[38,39] Hence, nivolumab safety profile permits study of a relatively short monotherapy course prior to addition of proven chemotherapeutic regimen.

Lastly, the Phase 1 study (CA209039) showed a favorable safety profile for nivolumab monotherapy in heavily treated cHL subjects. Drug-related Grade 3 adverse events were reported in five subjects out of 23 (22%), whereas there were no drug-related Grade 4 or 5 adverse events. Only two subjects (9%) of 23 heavily treated subjects discontinued the drug due to toxicity. Discontinuation was reported at 39.6 weeks and at 40 weeks from first dose of nivolumab due to MDS and thrombocytopenia in one subject, and due to pancreatitis in the other subject, respectively. None of the cHL subjects discontinued nivolumab monotherapy due to toxicity before 39.6 weeks. This safety profile for the cHL cohort did not differ significantly compared to that for other tumor types, where over 8,000 subjects have been treated with nivolumab monotherapy.

Rationale for Nivolumab in Combination with AVD

This study will also evaluate nivolumab used in combination with AVD as the second segment of the proposed regimen. As shown in Table 1.1.3-1, responses continue to accumulate with longer nivolumab exposure. For example, nivolumab monotherapy continued to be effective beyond the first 16 weeks of therapy since the cumulative response rate continued to increase up to 82.6% response rate at 48 weeks from the first dose. Therefore, longer exposure with nivolumab maximizes its clinical benefits. However, multiagent chemotherapy which has been proven to generate long-term disease control is likely to still be needed to maximize treatment effect and ensure the opportunity for long term benefit in advanced stage cHL.

ABVD is one of the most frequently used cHL regimens, where long-term clinical outcomes have been proved in randomized studies.[40,41] However, bleomycin is considered as the least effective drug among the four drugs.[42,43,44] A recent prospective study from the UK randomized 952 subjects who had negative PET scans after two cycles of ABVD.[44] The omission of bleomycin from the last four cycles resulted in no significant difference of PFS or OS. PFS at 3 years was 85.5 % for the patients who continued ABVD vs. 84.5% for the patients who switched to AVD. OS at 3 years was 97.0 % for ABVD who continued ABVD vs. 97.5% for the patients who switched to AVD. The CR and unconfirmed CR rates are also similar 65 % for ABVD who continued ABVD vs. 69 % for the patients who switched to AVD. Importantly, the most serious toxicity associated with ABVD is bleomycin-related pulmonary toxicity, which was observed in 18% (25 of 141) of the patients from a Mayo Clinic series.[43] When patients eliminated bleomycin during the ABVD cycles, there was no impact on CR rates, PFS, or OS.[42,43] This analysis suggests that bleomycin has a limited role in the ABVD regimen, and omitting bleomycin is reasonable in the appropriate context.

Importantly, nivolumab could have the potential for overlapping toxicity with bleomycin. Nivolumab has been associated with immune-mediated pneumonitis. The incidence of pneumonitis, including interstitial lung disease, is relatively low (3.4% in unresectable or metastatic melanoma patients and 6% in metastatic squamous non-small cell lung cancer patients), whereas fatal immune-mediated pneumonitis has occurred in 0.7% (5/691) of patients receiving single agent nivolumab.[45] On the other hand, bleomycin could cause pulmonary toxicity in 15 - 18%[43,46] of all subjects where the majority was treated with ABVD. The mortality rate from bleomycin pulmonary toxicity was reported as 3.0 to 4.2% in all bleomycin-treated patients, and 24% in patients who developed the pulmonary syndrome.[43,47] When brentuximab vedotin was combined with ABVD in a Phase 1 study, unexpected pulmonary toxicity was observed in 44% (11/25) of subjects with two fatal cases due this event.[48] This study was amended by omitting bleomycin, and reported no subsequent pulmonary toxic effect when brentuximab vedotin was combined with AVD. Consequently, if nivolumab is combined with bleomycin-included multiagent chemotherapy, there is the potential of additive toxicity similar to what was observed when brentuximab vedotin was added to ABVD. Hence, in order to minimize potential toxicity with potentially superior efficacy, nivolumab will be included without bleomycin.

While, there are no clinical or nonclinical data of the addition of nivolumab to the AVD regimen or individual components, the addition of nivolumab to other conventional chemotherapy regimens does not seem to increase the toxicity from other drugs.[49,50] Nivolumab was evaluated with concomitant administration of three different combinations (gemcitabine and cisplatin, pemetrexed and cisplatin, and paclitaxel or carboplatin) in subjects with an advanced non-small cell lung cancer.[49,50] No dose-limiting toxicities (DLTs) were observed during the DLT period (the first 6 weeks) of nivolumab treatment in combination with platinum-based doublet chemotherapy. The frequencies of the most common treatment-related AEs were similar to those observed with platinum-based doublet chemotherapy alone, indicating a safety profile similar to that of individual chemotherapeutic agents. Additionally, drug-drug interaction between nivolumab and other chemotherapeutic agents is not expected. It is not likely that other drugs will affect the PK of nivolumab because nivolumab is an IgG4 monoclonal antibody, which is eliminated by non-specific catabolism (often by reticuloendothelial system proteases); this elimination process is not known to be inhibited or induced by specific drugs. Nivolumab is also unlikely to impact the PK of other companion drugs when used in combination regimens. A Phase 1 study in metastatic clear cell renal cell carcinoma (CA209009) demonstrated that nivolumab at all dose levels (0.3, 2, and 10 mg/kg) did not modulate cytokine levels (IL6, IL2, and IL10). Because no change in cytokine level was observed, nivolumab is not considered to mediate CYP induction, and has no or low potential for modulating CYP enzymes, and thereby a low risk of interaction with other drugs. Thus, combined toxicities from nivolumab and AVD are unlikely to be observed, whereas there are appropriate safety guards in place within this protocol to detect and manage any unanticipated toxicity from the combination (Section 7).

In conclusion, it will be clinically important to understand the safety and tolerability of nivolumab monotherapy in newly diagnosed cHL population. Additionally, the safety and tolerability of the nivolumab-AVD combination should be evaluated. Overall, this new regimen, consisting of two temporal components (nivolumab monotherapy followed by nivolumab and AVD), may improve clinical outcomes newly diagnosed advanced stage cHL.

Rationale for Nivolumab Flat Dose and 30 Minutes Infusion in Cohort D

The nivolumab dose of 240 mg every 2 weeks (Q2W) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than the proportional with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg

(35 kg - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate virtual trials, each consisting of two arms, nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of subjects randomly sampled from aforementioned pooled database of cancer patients. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to patients with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg Q2W.

Nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level. Adverse events have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put subjects at increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg Q2W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of nivolumab 240 mg Q2W will be similar to that of nivolumab 3 mg/kg Q2W. Therefore, a flat dose of nivolumab 240 mg every 2 weeks will be used in cohort D.

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided there is no change in safety profile.

Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. Reduced infusion time is currently under investigation in study CA209038, an exploratory study of the biologic effects of Nivolumab and Nivolumab in combination with Ipilimumab treatment in subjects with advanced melanoma.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical studies. A change in safety profile is not anticipated with 30-minute infusion of nivolumab.

1.1.3.1 Summary Information for AVD

Summary information for the individual agents in the chemotherapy combination AVD is provided below. Refer to the local product information for each product for more details.

Doxorubicin (Adriamycin)

Doxorubicin is an antitumor anthracycline antibiotic. Doxorubicin intercalates between adjoining nucleotide pairs in the DNA helix, and inhibits DNA and RNA synthesis. The terminal half-life of doxorubicin is 20 to 48 hours. Doxorubicin is used for Hodgkin's lymphoma. AEs associated with doxorubicin include **myocardial toxicity which is manifested in its most severe form by potentially fatal congestive heart failure. Myocardial toxicity may occur either during therapy or months to years after termination of therapy. Therefore, monitoring for potential cardiotoxicity is important.** Secondary acute myelogenous leukemia (AML) or MDS have been reported in patients treated with doxorubicin. Severe local tissue necrosis will occur if there is extravasation during administration. Other reported adverse effects include, but are not limited to, hematologic (myelosuppression), hepatic (increased aspartate aminotransferase [AST], alanine aminotrasferase [ALT], alkaline phosphatase, and bilirubin), dermatologic (alopecia, red streaks along the injected vein), gastrointestinal (anorexia, nausea, vomiting, diarrhea, mucositis, dysphagia), other cardiovascular (electrocardiogram [ECG] change, arrhythmias), neurologic (peripheral neurotoxicity in the form of local-regional sensory and/or motor disturbances), ocular events (conjunctivitis, keratitis, lacrimation), and hypersensitivity (fever, chills, and urticaria, and anaphylaxis).[51]

Vinblastine (Vinblastine Sulphate)

Vinblastine is a vinca alkaloid, which binds to tubulin, a protein that forms microtubules. The mechanism of action is disruption of mitotic spindle assembly through the interaction with tubulin. The terminal half-live of vinblastine is 24.8 hours. AEs associated with vinblastine include **severe hypomotility with constipation or ileus. Therefore, assessment for constipation and auscultate abdomen for bowel sounds will be important**. Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. Other reported adverse effects include, but are not limited to, hematologic (myelosuppression), dermatologic (alopecia, skin vesiculation,), gastrointestinal (nausea, vomiting abdominal pain, cramps, diarrhea, mucositis, gastrointestinal hemorrhage), cardiovascular (hypertension, myocardial infarction, angina pectoris and transient abnormalities of ECG, Raynaud's phenomenon), and neurologic events (peripheral neuropathy, loss of deep tendon reflexes, paresthesias, paralysis, autonomic neuropathy such as paralytic ileus, urinary retention, orthostasis, vocal cord paralysis, myalgias, headache, convulsions, depression, dizziness, malaise), jaw pain, and the syndrome of inappropriate secretion of antidiuretic hormone.[52]

Dacarbazine (DTIC)

Although the exact mode of action is unknown, dacarbazine hypothetically works by alkylation, inhibition of DNA synthesis as a purine analogue and interaction with sulfhydryl (SH) groups in

proteins. The terminal half-life of dacarbazine is 5 hours. Dacarbazine is used to treat Hodgkin's lymphoma. AEs associated with dacarbazine include hematologic (myelosuppression), dermatologic (alopecia, facial flushing, extravasation with pain), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased AST, ALT, hepatic vein thrombosis, hepatocellular necrosis), renal (increased serum creatinine, blood urea nitrogen [BUN]), neurologic (facial flushing paresthesia) events, influenza-like syndrome (with fever, malaise, myalgia) and anaphylaxis.[53]

1.2 Research Hypothesis

1.2.1 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 the heavily treated cHL subjects.

1.2.2 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.

1.3 Objectives(s)

1.3.1 Primary Objective

1.3.1.1 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 PR or CR according to the revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria), see Appendix 2.

1.3.1.2 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.

1.3.2 Secondary Objectives

1.3.2.1 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.

1.3.2.2 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.

1.3.3 Exploratory Objectives

1.3.3.1 Cohorts A, B, and C

- To assess the PFS based on IRRC assessment
- To assess the OS
- To assess the overall safety and tolerability of nivolumab, as measured by incidence and severity of AEs, serious adverse events, and specific laboratory abnormalities
- To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy measures
- To characterize pharmacokinetics of nivolumab and explore E-R relationships
- To characterize the immunogenicity of nivolumab monotherapy
- To evaluate both generic health-related quality of life as assessed by the EQ-5D and cancer specific quality of life as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30
- To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry (IHT), soluble factor analysis, and gene expression (microarray technology, quantitative reverse transcription polymerase chain reaction (RT-PCR).
- For Cohort C, to evaluate risk-benefit of discontinuation schedule of the study drug for the subjects who have persistent CR for 1 year.

1.3.3.2 Cohort D

- To evaluate IRRC-assessed OR rate, and investigator-assessed CR and OR rates at the planned end of therapy
- To evaluate the CR rate and OR rate at the planned end of Nivolumab monotherapy based on IRRC assessment and based on investigators assessment
- To evaluate the CR rate and OR rate at the planned end of two combocycles based on IRRC assessment and based on investigators assessment
- To evaluate the PFS based on IRRC assessment and based on investigators' assessment
- To assess the duration of objective response (DOR) and duration of complete response based on IRRC assessment and based on investigators assessment
- To assess the OS
- To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy measures
- To characterize pharmacokinetics of nivolumab and explore E-R relationships
- To characterize the immunogenicity of nivolumab
- To evaluate the change from baseline of pulmonary function after treatment
- To evaluate generic health-related quality of life as assessed by the EQ-5D
- To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry (IHT), soluble factor analysis, and gene expression (microarray technology, quantitative reverse transcription polymerase chain reaction (RT-PCR).

1.4 Product Development Background

Nivolumab is in clinical development for the treatment of subjects with solid tumors and hematological malignancies. In addition to study CA209205, studies to be conducted in the hematologic malignancies program will assess the efficacy and safety of nivolumab in subjects with DLBCL who have relapsed following high dose chemotherapy ASCT or after failure of at least two prior multi-agent chemotherapy regimens in ASCT ineligible subjects (CA209139) and in subjects with relapsed or refractory FL (CA209140).

1.4.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. This functions by aborting the emergence of tumors as they arise and/or causing tumor shrinkage where it is present. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response.[54] This evasion may occur by exploiting any of the checkpoints that control the regulatory immune

response, including display of antigens and control of co-stimulatory pathways that affect the proliferation of cells involved in immunity. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system, either directly by stimulation of immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, costimulatory signals in addition to antigen recognition by the T-cell receptor.[55] Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.[54]

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[55] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[56,57] PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[58,59] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[60]

Further evidence for a negative regulatory role for PD-1 comes from studies of PD-1 deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[61,62,63] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.[64,65] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1.[66,67,68,69,70,71] This suggests that host mechanisms (ie, expression of PD-L1 on antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies.[72,73,74,75,76,77,78] PD-L1 expressed by tumor cells, including FL and

DLBCL, has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[59,79,80] Moreover, the expression of PD L1 may protect the tumor cells from the induction of apoptosis by effector T cells.[81] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by IHC) of PD-L1 may permit immune evasion by tumors.

Blockade of the PD 1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and interferon-gamma (IFN-γ) release in the MLR.[82] The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T-cells in a dose-dependent manner. PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic option.

1.4.2 PD-1 Expression in Classical Hodgkin Lymphoma

PD-L1 is expressed on the malignant cells in patients with a variety of hematologic malignancies including patients with HL, primary mediastinal B cell lymphoma, T cell lymphomas, multiple myeloma, and acute leukemias. Membranous staining of cHL tumors indicated that 82% of the cases showed ≥ 5% positive malignant cells.[80]

Although cHLs have an extensive polymorphous inflammatory infiltrate, there is little evidence of an effective host anti-tumor immune response. In fact, recent studies indicate that Hodgkin RS cells produce certain molecules that limit the efficacy of T-cell mediated anti-tumor immune responses.[83,84] By integrating high-resolution copy number data with transcriptional profiles, the immunoregulatory genes, PD-L1 and PD-L2, were found to be key targets of the 9p24.1 amplification in cHL cell lines and primary tumors.[85] PD-1 ligand gene amplification was associated with increased protein expression in primary cHLs using quantitative immunohistochemical methods.[85] In additional recent studies, EBV infection was found to be another mechanism of upregulating PD-L1.[86,87] These findings suggest that targeting the PD-1-PD-L1/PD-L2 axis could have therapeutic implications in cHL patients.

1.4.3 Summary of Results for Nivolumab Program

1.4.3.1 Summary of Nivolumab Monotherapy Safety in Solid Tumors

Nivolumab is well tolerated based upon experience in approximately 1,500 subjects (as of 21-Jul-2013) treated with nivolumab as a monotherapy or in combination with other therapeutic agents. Special attention is given to unique AEs which are referred to as “Select AEs” in the BMS-936558 (nivolumab) Investigator Brochure (IB) and as described below.

An ongoing Phase 1 study (CA209003) has enrolled 306 subjects with advanced solid tumors including melanoma, renal cell carcinoma (RCC), and NSCLC has provided the most mature safety data from nivolumab monotherapy. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks. No MTD was identified. Drug-related AEs of any

grade occurred in 72.4% of subjects. The most frequent drug-related AEs included fatigue (25.7%), rash (13.5%), diarrhea (11.8%), and pruritis (10.2%). Grade 3 or 4 drug-related AEs were observed in 14.8% of subjects. The most common Grade 3 or 4 drug-related AEs occurring in 1% of subjects were: fatigue (1.6%), lymphopenia (1.3%), abdominal pain (1%), diarrhea (1%), hypophosphatemia (1%) and pneumonitis (1%).

As an immuno-oncology (I-O) agent, nivolumab is associated with unique AEs, whose mechanism of action is consistent with a potential inflammatory mediated process. These unique immune-related AEs, referred to as "select AEs" in the nivolumab IB, have not typically been observed with cytotoxic agents. Select AEs have been categorized into seven areas: pulmonary toxicity, gastrointestinal toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and renal toxicity. Select AEs have occurred with low frequency (< 5%) are manageable, and are reversible with drug interruption, discontinuation, or with the use of corticosteroid and/or other immunosuppressants. Select AEs, in particular pneumonitis, are considered clinically meaningful as they require greater vigilance and for early recognition and prompt intervention. Therefore, management algorithms have been developed and implemented for each immunologically-associated select AE category [refer to IB and in Appendix 1 of the protocol.].

1.4.3.2 Nivolumab Monotherapy Safety in Phase 1 Study for Hematologic Malignancies Including cHL

Preliminary safety data from an ongoing Phase 1 study for subjects with a variety of hematologic malignancies (CA209039) suggested that the safety for these malignancies seems similar to that for solid tumors. As of 27-Feb-2014, data were available for 103 subjects, including 23 subjects with cHL. Treatment with nivolumab in subjects with hematological malignancies has been well tolerated and toxicities have been generally manageable. There was 1 DLT (Dose Limiting Toxicity) at the 1 mg/kg dose level in a subject with multiple myeloma who experienced Grade 3 pneumonia and Grade 3 pneumonitis. There was 1 DLT at the 3 mg/kg dose level in a subject with small lymphocytic lymphoma who experienced Grade 3 hypereosinophilia and Grade 3 diplopia. The MTD was not reached. All of the subjects with HL were treated at a dose of 3 mg/kg of nivolumab.

Adverse events were reported in 91 of 103 (88.3%) subjects and Grade 3 - 4 events in 40 (38.8%) subjects. Related AEs were reported in 63 (61.2%) subjects. Those that occurred in more than 5% of subjects included: fatigue (12.6%), rash (10.7%), diarrhea (8.7%), pneumonitis (8.7%), pyrexia (7.8%), and pruritus (7.8%). Related Grade 3 - 4 events were reported in 16 (15.5%) subjects; the most common of which was leukopenia that occurred in 3 (2.9%) subjects. Sixteen (15.5%) subjects discontinued therapy due to AEs, 7 of which were related to study therapy. A total of 18 (17.5%) subjects died: 14 due to disease, 3 due to other causes, and 1 due to drug toxicity. Drug-related pneumonitis was observed in 9 subjects (8.7%): B-cell lymphoma (n = 5), T-cell lymphoma (n = 2), multiple myeloma (n = 1), and HL (n = 1). Six subjects had Grade 1 or 2 pneumonitis; 2 had Grade 4; one patient with small lymphocytic lymphoma suffered from Grade 5. In the CA209039 study, pneumonitis is slightly higher than that seen in the nivolumab studies in total and that now includes approximately 1,500 subjects.

The safety experience focusing on the 23 subjects in the HL cohort did not differ significantly compared to that for all 103 subjects with other hematologic malignancies on the CA209039 study. AEs were reported in 21 (91.3%) subjects and Grade 3 - 4 events in 10 (43.5%) subjects. Related serious adverse events (SAEs) were reported in 2 (8.7%) subjects. With the exception of myelodysplastic syndrome (MDS), the other related high grade events did not require treatment and resolved spontaneously at the next visit. Related AEs were reported in 16 (69.6%) subjects. Those that occurred in more than 2 (> 5%) subjects included: rash (17.4%), fatigue (13.0%), pyrexia (13.0%), diarrhea (13.0%), nausea (13.0%), decreased platelet count (13.0%), cough (8.7%), hypothyroidism (8.7%), ALT increased (8.7%), and AST increased (8.7%). Related Grade 3 events were reported in 4 (17.4%) subjects and included and low platelets (described in detail below), lipase increase, decreased lymphocytes and decreased leukocytes.

Drug-related pneumonitis was reported in one patient from 23 subjects with cHL. This patient had decreased leukocytes which resulted in discontinuation of the therapy. One month later, the patient underwent BCNU (carmustine), etoposide, cytarabine and melphalan (BEAM) conditioning and ASCT. The patient subsequently developed Grade 3 caecitis, mucositis, and pneumonitis, all considered possibly related to prior therapy with nivolumab.

One patient discontinued therapy due to Grade 3 MDS. This patient had received BEAM conditioning, ASCT in 2008, and received 7 systemic treatment regimens including doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine (ABVD), ifosfamide, carboplatin, etoposide (ICE), brentuximab from 2007 to 2012. Although it was unclear if MDS was due to prior chemotherapy or prior ASCT, the possibility that it could have been due to nivolumab could not be excluded.

Six subjects elected to stop therapy with a best response of CR or PR to pursue transplant options, including 1 patient who died of graft-versus-host-disease (GVHD) that was not related to nivolumab therapy.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials, including CA209039 and the HL cohort.

Adverse Event Management Algorithms

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, gastrointestinal, hepatic toxicity, endocrinopathy, skin toxicity, neurological toxicity and renal toxicity.

The algorithms recommended for utilization in CA209205 are contained in the nivolumab (BMS-936558) IB and in Appendix 1 of the protocol.

1.4.3.3 Nivolumab Monotherapy Clinical Activity in Solid Tumors

The clinical activity of nivolumab monotherapy has been observed in subjects with melanoma, RCC, and NSCLC in a Phase 1 study (CA209003), and in two subjects with colorectal cancer in other Phase 1 studies (MDX1106-01, ONO-4538-01).

In a Phase 1 study (CA209003, N = 306), nivolumab monotherapy demonstrated clinical activity in a variety of solid tumor types across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg). A response of either CR or PR, as determined by investigator assessed tumor evaluations based on modified RECIST 1.0, has been reported at all dose levels. Among 107 subjects with advanced melanoma, the ORR was 33 (31%) whereas progression-free survival rate (PFSR) at 24 week was 44% (95% confidence interval (CI): 34 - 54 weeks). Among 129 subjects with advanced NSCLC, the ORR was 22 (17%) where as PFSR at 24 week was 34% (95% CI: 25 - 42 weeks). Among 34 subjects with advanced RCC, the ORR was 10 (29%) where as PFSR at 24 weeks was 59% (95% CI: 42 - 75 weeks). The nivolumab IB includes details of clinical efficacy data from this study as well as additional solid tumor studies.

1.4.3.4 Nivolumab Monotherapy Clinical Activity in Hematologic Malignancies Including cHL

Nivolumab monotherapy clinical activity (at either the 1 mg/kg or 3 mg/kg dose levels) has been observed in heavily pretreated NHL and cHL subjects in an ongoing Phase 1 study for subjects with a variety of hematologic malignancies (CA209039). Three of nine subjects (33%) with relapsed or refractory DLBCL treated have experienced an OR (2 PR and 1 CR), with the current response duration ranging between 12 to 24 weeks. Two of eight subjects (25%) with relapsed or refractory FL have experienced an OR (1 PR and 1 CR), with the current response duration ranging between 12 to 54 weeks.

Preliminary data has shown clinical activity in 23 subjects with cHL (average age: 35 year old; range 20 - 54). The Phase 1 study defined ORR as the proportion of subjects whose best overall response is either investigators-assessed CR or PR. The ORR in the cHL cohort is 87% (20 out of 23 subjects) with a CR rate of 26% (6 out of 23 subjects). Fifteen out of 23 subjects (65%) received brentuximab as salvage therapy after failure of ASCT. In this subset of subjects, the ORR is 87% (13 out 15 subjects); CR in 2 and PR in 13. Five subjects are brentuximab-naive consisting of three without previous ASCT and two with previous ASCT. Two of the three without prior ASCT achieved CR, whereas both subjects with ASCT attained CR. Six subjects elected to stop therapy with a best response of CR or PR to pursue allogeneic SCT options. One heavily treated patient stopped nivolumab therapy due to development of MDS; this patient had a best overall response (BOR) of PR. Two subjects came off study due to progressive disease (SD of 8 and 16 weeks then PD). All other subjects continue on study. Table 1.4.3.4-1 summarizes the preliminary investigator assessed efficacy data as of 27-Feb-2014.

Table 1.4.3.4-1: Investigator Assessed Clinical Response in Study CA209039

	Total (N = 23)	**Auto Failure Bren Failure (n = 15)**	**Auto Naive Bren Failure (n = 3)**	**Bren Naive (n = 5)**
Best Overall Response (%)				
CR[a]	6 (26.1)	2 (13.3)	0	4 (80.0)
PR	14 (60.9)	11 (73.3)	3 (100)	0

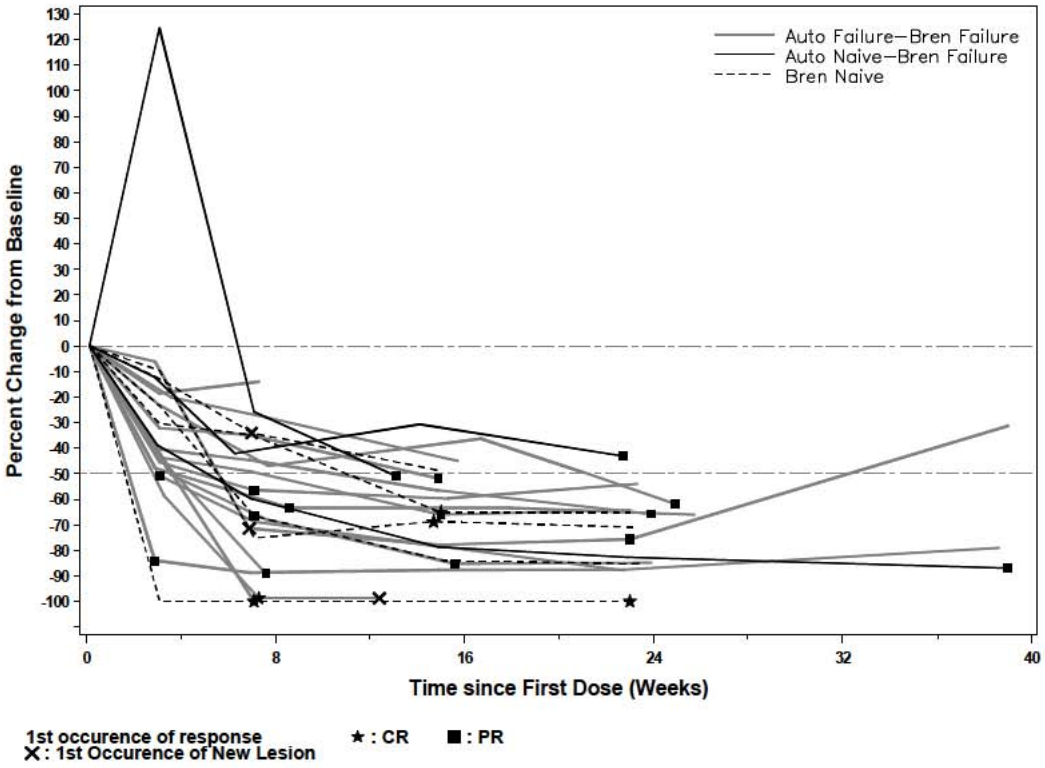
Table 1.4.3.4-1: Investigator Assessed Clinical Response in Study CA209039

	Total (N = 23)	Auto Failure Bren Failure (n = 15)	Auto Naive Bren Failure (n = 3)	Bren Naive (n = 5)
SD	3 (13.0)	2 (13.3)	0	1 (20.0)
Overall ORR (%)	20 (87.0)	13 (86.7)	3 (100.0)	4 (80.0)
95% Confidence Limit	(66.4, 97.2)	(59.5, 98.3)	(29.2, 100.0)	(28.4, 99.5)

[a] This protocol (CA209039) requires confirmation of CR with a negative PET scan if the baseline PET was positive as well as a durable response for at least 4 weeks off study therapy. The analysis of confirmatory PET scan data is ongoing and final CR results may differ based on these analyses.

An individual plot of target tumor burden percent change from baseline over time is depicted in Figure 1.4.3.4-1. Results were consistent across cHL subgroups who received prior brentuximab and those who were brentuximab naive. The median estimate of the DOR has not been reached due to a high percentage (90%, 18/20) of on-going responders. Additionally, the median estimate of the duration of follow-up has not been reached due to a high percentage (96%, 22/23) of on-going subjects in follow-up.

Figure 1.4.3.4-1: Individual Plot of Target Tumor Burden Percent Change from Baseline Over Time for All Treated Subjects



In horizontal lines denote 50% decrease (threshold for PR) and no change. Subjects with baseline and at least one post-baseline assessment are presented.

In summary, nivolumab monotherapy reduced tumor burden in subjects with advanced stage cHL including in both brentuximab vedotin-naïve subjects who had failed prior ASCT, as well as in subjects who had failed both previous ASCT and brentuximab vedotin treatment. Prolonged DOR (CR and PR) has also been observed.

1.4.3.5 Nivolumab Monotherapy Clinical Pharmacology Summary

Single-dose pharmacokinetics (PK) of nivolumab were evaluated in 39 subjects with multiple tumor types in study MDX1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab was linear in the range of 0.3 to 10 mg/kg with dose proportional increases in Cmax and AUC(INF) and low to moderate inter-subject variability observed at each dose level (ie, coefficient of variation ranging from 7 to 45%). Geometric mean clearance after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied from 83 to 113 mL/kg across doses. The mean terminal half-life of nivolumab is 17 to 25 days, which is consistent with the half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied.

A preliminary PPK model was developed using data from 350 subjects from MDX1106-01, MDX1106-02 and CA209003. Clearance of nivolumab was found to be similar in all tumor types studied and is independent of dose range studied (0.1 to 10 mg/kg). Body weight normalized dosing produces approximately uniform trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

The dose and schedule selected for evaluation in this study, 3 mg/kg every 2 weeks (Q2W), has been evaluated in solid tumors in the ongoing CA209003 study. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no MTD was identified. Anti-tumor activity was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, NSCLC, and RCC, as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma. The antitumor activity of nivolumab tended to increase with dose, as did the incidence of SAEs. The anti-tumor activity of BMS-936558 nivolumab in RCC was investigated at dose levels 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg. The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. The ongoing CA209039 study in hematologic malignancies includes 2 dose levels: 1 mg/kg and 3 mg/kg Q2W. The 3 mg/kg dose level has been shown to be adequately tolerable and has been expanded in select tumor types for further evaluation. Objective responses have been observed at both dose levels in study CA209039. Based upon the totality of available data across the program, a dose of 3 mg/kg Q2W is selected as the dose anticipated to maximize the benefit-risk ratio.

For revised protocol 04c, subjects in Cohorts A, B, and C will switch to being administered nivolumab as a 480 mg IV flat dose Q4W or a 240 mg IV flat dose Q2W (see also Section 3.1).

Refer to the current BMS-936558 (nivolumab) IB for full details on the clinical pharmacology aspects of nivolumab.

1.4.4 Rationale for Exploratory Studies of Tumor PD-L1 Expression as a Potential Predictive Biomarker in HL

Aberrant expression of PD-L1 protein by tumor cells (retrospectively detected by IHC) has been reported in a number of human malignancies, including cHL.[80] Elevated PD-L1 expression has been proposed to enhance immune evasion; this notion is supported by separate studies demonstrating that PD-L1 expressed by tumor cells enhances apoptosis of activated tumor-specific T cells in vitro and that the expression of PD-L1 protects tumor cells from the induction of apoptosis by effector T cells.[30] In vitro, anti-PD-L1 blocking antibody boosts proliferation and IFN-γ secretion by allogeneic T cells responding to DLBCL cells and in autologous cultures of primary DLBCL, PD-L1 blockade enhanced secretion of inflammatory cytokines IFN-γ, granulocyte macrophage colony-stimulating factor, IL-1, IL-6, IL-8, IL-13, TNF-α, and macrophage inflammatory protein-1α.

Preliminary data indicate PD-L1 protein expression in solid tumors may correlate with nivolumab clinical activity. Of 38 evaluable melanoma pre-treatment biopsies, 17 were PD-L1+ (45% positivity rate) and 7/17 of these PD-L1+ subjects had an OR (41%). Clinical activity of nivolumab was also seen in the PD-L1 negative population, however, at a much lower rate (3/21; 14%). This data suggests that, in melanoma, PD-L1 expression on tumor cells may correlate with clinical activity. Additional analysis is underway to further evaluate this hypothesis in solid tumors.

In order to more thoroughly assess the role of PD-L1 protein expression as a predictive biomarker in hematological malignancies, available archival or recent tumor tissue will be collected from all consenting subjects in this study, and PD-L1 expression will be tested retrospectively. Analyses to assess the association of PD-L1 and efficacy measures will be conducted.

1.4.5 Rationale and Aims for Biomarker Assessments

The biological basis of nivolumab in the treatment of oncological disease is to modulate the immune system to both generate and restore a durable anti-tumor response leading to clearance of tumor. The nivolumab clinical data supports the hypothesis that inhibition of the PD-1 pathway results in rejection of tumor by the host immune system.

The precise mechanisms by which nivolumab exerts its anti-tumor activity is unclear, however, particular cell types, such as effector T cells and regulatory T cells are critical for the anti-tumor response.

Therefore, the major hypotheses that will be addressed are:

- Does expression of PD-L1 on tumor cells prior to therapy correlate with clinical efficacy to monotherapy or study therapy?

- Does the mutational status of tumor cells or tumor infectivity (ie EBV status) correlate with clinical efficacy to monotherapy?
- Can we define distinct pharmacodynamic markers of monotherapy in the peripheral compartment?
- How does nivolumab alter the activating and negative costimulatory molecules on immune cells in the periphery and at the tumor site? Are their distinct mechanisms of resistance to nivolumab or study therapy?
- Is the intratumoral or peripheral T cell repertoire predictive of response to nivolumab?
- Does the composition and phenotype of the tumor microenvironment, at baseline, or on-treatment, correlate with clinical efficacy?

1.4.6 Rationale for Quality of Life Evaluation

Outcomes research data including health-related quality of life and patient reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the patients' perspective. These data offer insights into the patient experience that may not be captured through physician reporting. Generic health-related quality of life scales provide data necessary in calculating utility values for health economic models. The EQ-5D will be collected in order to assess the impact of nivolumab on generic health-related quality of life and the data will be used for populating health economic models most notably, cost effectiveness analysis. The EORTC QLQ-C30 will be collected in cohort A, B and C subjects in order to assess cancer specific health-related quality of life. The combination of the generic scale for general health status and economic evaluation and the cancer specific scale will provide a robust outcomes research package.

1.5 Overall Risk/Benefit Assessment

Patients with cHL who failed ASCT represent an area of substantial unmet medical need. The clinical activity of nivolumab (ORR: 87%, 20 out of 23 subjects) observed to date in heavily pretreated subjects with cHL suggests the potential for improved clinical outcomes for this patient population. Meanwhile, nivolumab also has the potential for clinically relevant unique AEs potentially caused by an inflammatory mechanism. These include pulmonary toxicity, hepatotoxicity, diarrhea/colitis, endocrinopathies, and nephrotoxicity. To date, these unique AEs have been manageable with frequent monitoring, prompt diagnosis, and initiation of corticosteroids, dose interruption, and adequate supportive care. Together the data suggest a positive benefit-risk potential, supporting a Phase 2 study to further assess the safety and efficacy of nivolumab in subjects with cHL in advanced stage.

Approximately 70% of patients with cHL with advanced-stage disease can expect long-term disease control. Nevertheless, the remaining 30% of patients will either relapse or have primary refractory disease. Salvage multi-agent chemotherapy, followed by ASCT, can only provide long-term disease control in approximately half of the patients with relapsed or refractory disease. Compared to the high probability (> 90%) of long-term disease control for limited-stage

cHL, there remains substantial room for improvement in disease outcome for advanced-stage patients. Furthermore, where possible, these relatively young patients should avoid intensified chemotherapy (such as a preparative regimen for ASCT) because of concerns regarding long-term chemotherapy-related toxicities. Therefore, it is critical to improve long-term disease control by an improved first line therapy. A nivolumab-based first line regimen may have the potential to substantially improve long-term clinical outcomes due to its capacity to effectively and safely reduce tumor burden and induce durable response, as well as its favorable safety profile. Thus, it is reasonable to evaluate a new nivolumab-based regimen together with standard of care chemotherapy in newly diagnosed, previously untreated cHL with advanced stage as a pilot study.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject

must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

3.1.1 Study Design and Duration for Cohorts A, B, and C

This is a non-comparative, multi-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) is being added to the study with broader eligibility criteria. Subjects with a treatment history of brentuximab vedotin before first ASCT will not be eligible, except in Cohort C.

The original protocol requires nivolumab dosing 3 mg/kg Q2W. Approximately 220 subjects with failure after ASCT will be treated with nivolumab 3 mg/kg IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity; Cohorts A and B consist of approximately 60 subjects each and Cohort C will treat approximately 100 subjects.

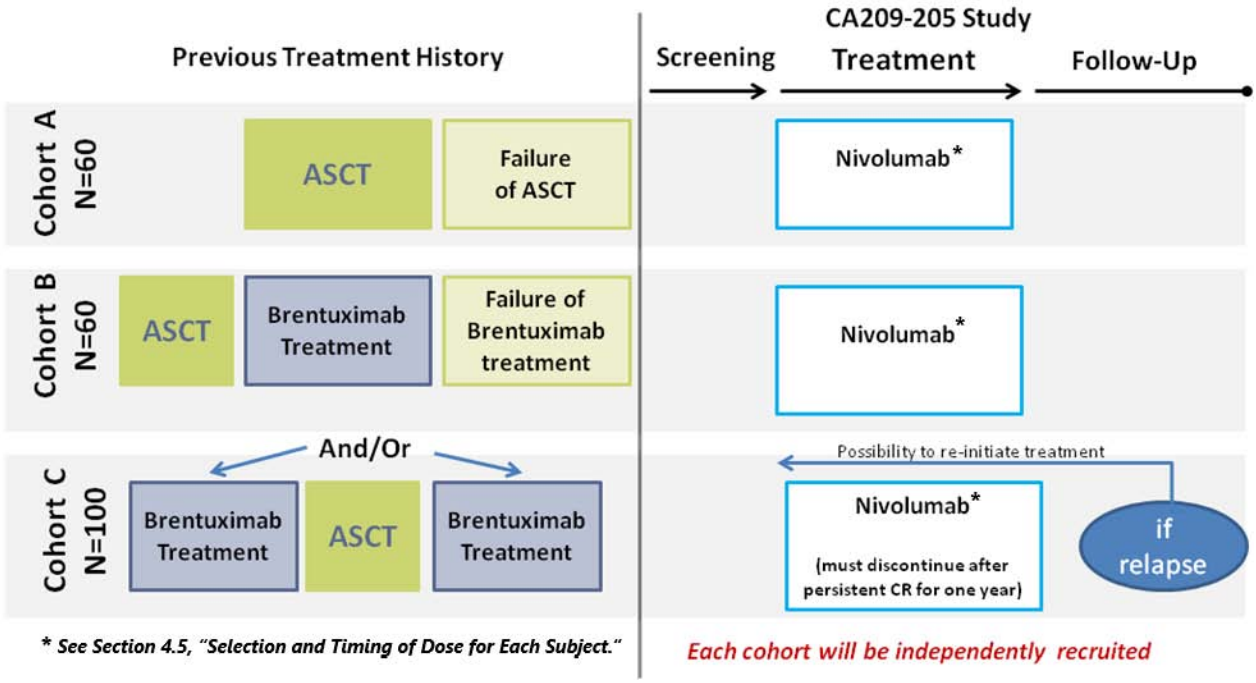
In revised protocol 04c, subjects will switch to IV infusion over 30 minutes of nivolumab 480 mg flat dose Q4W or 240 mg flat dose Q2W. For those subjects receiving a 480 mg flat dose Q4W, a cycle will be a 28-dosing period. For those subjects receiving a 240 mg flat dose Q2W, a cycle will be a 14-day dosing period.

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. Primary analysis will be performed separately for each cohort (ie, at separate time points) upon completion of a pre-specified amount of follow-up (Table 8.3.1.1-1) after last patient first treatment (LPFT). All analyses will be performed separately for each cohort upon completion of follow-up for the primary endpoint in each cohort. In addition, safety analyses will be performed on combined cohorts.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Subjects may be dosed no less than 12 days from the previous dose during every 2-week cycle. For every 4-week dosing cycle, subjects may be dosed within a ± 3-day window.

The study design schematic is presented in Figure 3.1.1-1.

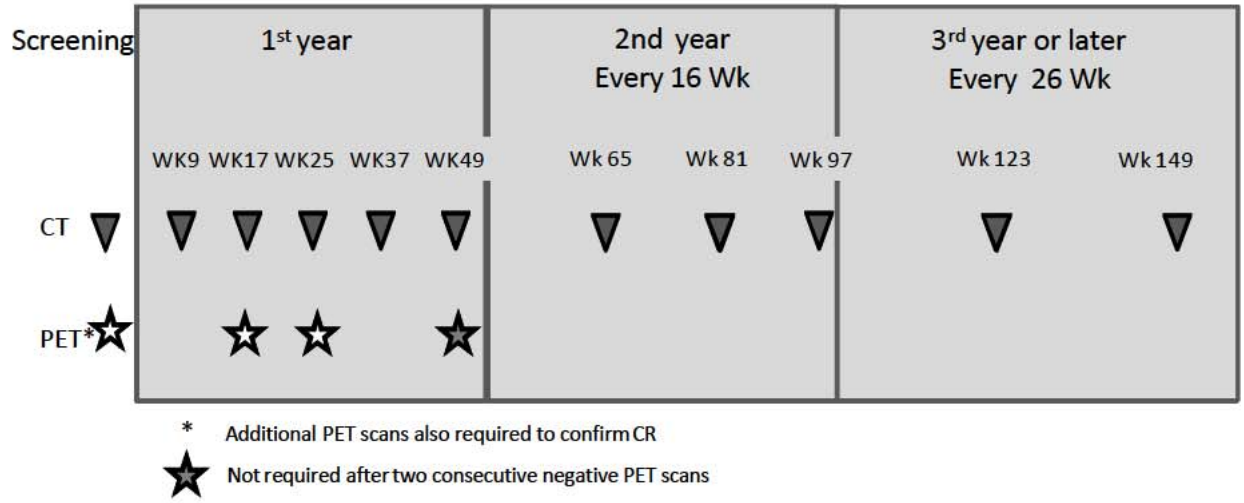
Figure 3.1.1-1: Study Design Schematic for Cohorts A, B, and C



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 time points 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 SCT or ASCT, whichever occurs earlier. If the subject discontinues treatment prior to disease progression, tumor assessment will continue in the follow-up phase. In rare cases, disease progression is clinically determined by investigators although disease progression does not meet 2007 IWG criteria. In these cases, tumor assessment will not be required if clinical disease progression is documented and if investigators discontinue the study drug. If the subject discontinues study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo IRRC radiographic assessments described here, but will be followed with a specific schedule (see Section 5.4).

Figure 3.1.1-2: CT or MRI and FDG-PET Scans Schedule for Cohorts A, B, and C



Nivolumab will be administered until one of the discontinuation criteria is met (see Section 3.5). An IRRC will also be utilized. The primary endpoint of this study is objective response rate (ORR) based on IRRC assessments, using the 2007 IWG criteria. Secondary endpoints include DOR, as well as complete and partial remission rates and durations based on IRRC assessments.

In Cohort C, subjects who have persistent CR for one year will discontinue the study drug and continue in the follow-up (FU)/Observational phase of the study. These subjects will be closely observed for up to two years from the date of last dose of study drug. Re-initiation of study therapy is allowed should these subjects relapse according to the 2007 IWG criteria during these two years.

Treatment beyond investigator-assessed progression is permitted in the circumstances specified in Section 4.5.7.

Study Duration for Cohorts A, B, and C

Primary analysis will be performed separately for each cohort (ie, at separate time points) upon completion of a pre-specified amount of follow-up (Table 8.3.1.1-1) after last patient first treatment (LPFT).

Additional survival analysis will be conducted for up to 5 years beyond analysis of the primary endpoint.

For most subjects, this study will consist of 3 phases: screening, treatment, and follow-up. Cohort C subjects who have persistent CR for one year will have a different schedule, with a FU/Observational phase (max. 2 years) following the treatment phase and also the possibility to re-initiate treatment in case of relapse during the FU/Observational phase. After 2 years in the FU/Observational phase, if no relapse is observed, those Cohort C subjects will enter the survival follow-up phase.

Revised Protocol 04c Update:

Subjects receiving nivolumab every 2 weeks at 3 mg/kg will switch to receive either a flat dose of 480 mg Q4W or a flat dose of 240 mg Q2W. Subjects may be dosed no less than 12 days from the previous dose during every 2-week cycle. For every 4-week dosing cycle, subjects may be dosed within a ± 3-day window.

Subjects must sign an informed consent document prior to switching dosing schedule.

Once a new dosing regimen has been selected for the subject, either flat dose 240 mg Q2W or flat dose 480 mg Q4W, the dosing regimen will remain in effect until end of treatment and not change.

Screening for Cohorts A, B, and C:

- Begins by signing the informed consent form (ICF)
- Subject is enrolled using the Interactive Voice Response System (IVRS) to obtain a subject ID
- Confirm that documentation of cHL after failure of ASCT or after failure of ASCT and brentuximab vedotin is present in the subject's medical record;
- Submission of tumor tissue (formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or 10 unstained slides) from a biopsy performed during screening is mandatory. If this is not possible, the following exceptions are allowed:
  - Subjects who do not have any accessible lesions which can be safely biopsied, or
  - Subjects who have archival tissue from a previous tumor biopsy that can be used for PD-L1 expression analysis. These subjects must submit archival tissue from the most recent tumor biopsy if archival tissues are available from tumor biopsies at multiple time points. While submission of archival tissue from the most recent tumor biopsy is mandatory, archival tissue from other tumor biopsy is strongly encouraged. For example, subjects who must submit archival tissue from a tumor biopsy at relapse may optionally also submit archival tissue for tumor biopsy at initial diagnosis as well.

    Note: For these exceptions, the reason must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted. Subjects may initiate the study drug before the outcome of PD-L1 expression status become available.
  - Biopsy samples should be excisional, incisional or core needle.
- For Cohorts A and B, confirm that a bone marrow biopsy/aspirate was performed within 90 days prior to enrolment and is documented in the subject's medical record;
  - If a bone marrow biopsy/aspirate was not performed within 90 days prior enrolment, a bone marrow biopsy/aspirate must be performed during the screening period.
  - If a bone marrow biopsy/aspirate needs to be performed during the screening period, submission of an aspirate sample for biomarker analyses is mandatory as per Table 5.1.1-1
  - Subjects may start the study drug before bone marrow biopsy results become available; results of a bone marrow biopsy must be documented in the subject's medical record when becoming available.

- Bone marrow biopsy/aspirate is optional for Cohort C. If the procedure is done during screening, an aspirate sample can be optionally submitted for biomarker analyses.
- The Hasenclever-Index for Hodgkin's disease also known as International Prognostic Score (IPS) at initial diagnosis must be reported in the eCRF. (See Appendix 3.)

Baseline assessments should be performed within 28 days of first dose of study drug, according to Table 5.1.1-1

- Subject is assessed for study eligibility within the required timeframe found in Table 5.1.1-1.
- The screening phase either ends with confirmation of full eligibility and treatment of the subject or with the confirmation that the subject is a screen failure.

Treatment for Cohorts A, B, and C:

- Treatment begins with the call to the IVRS to obtain vial assignments. A negative pregnancy test should be documented within 24 hours prior to first dose of investigational product. Subsequently, women of childbearing potential (WOCBP) must have a pregnancy test every 4 weeks (± 7 days) regardless of dosing schedule.
- The subject should receive the dose of study medication within 1 day of vial assignment.
- Subjects may be dosed no less than 12 days from the previous dose during every 2-week cycle. For every 4-week dosing cycle, subjects may be dosed within a ± 3-day window. Doses given after the 3-day window are considered dose delays. A maximum delay of 42 days between doses is allowed.
- All vital signs starting after Cycle 1 will be collected within 72 hours prior to dosing.
- Extended on-study local laboratory assessments should be done within 72 hours prior to dosing from Cycle 1 through Cycle 5 and every alternate dose thereafter (Cycles 7, 9, 11, 13, etc.). Limited on-study local laboratory assessment should be done within 72 hours prior to dosing beginning at Cycle 6 and every alternate dose thereafter (Cycles 8, 10, 12, 14, etc.).
- AE assessments should be documented at each clinic visit.
- Biomarker, PK and immunogenicity samples will be done according to the schedules in Sections 5.5 and 5.6.
- Subjects should receive nivolumab at a flat dose of either 240 mg Q2W or flat dose of 480 mg Q4W as an IV infusion over 30 minutes on Day 1 of each treatment cycle until disease progression or discontinuation due to toxicity, withdrawal of study consent, or the study ends. Study drug dosing may be delayed for toxicity (see Section 4.5.2).
- On-treatment CT (preferred) or MRI will begin at Week 9 (± 7 days) after the start of therapy and then will occur at Weeks 17, 25, 37 and 49 during the first year of treatment, then every 16 weeks (± 14 days) for the second year of treatment up to Week 97, continuing every 26 weeks (± 21 days) beyond Week 97 for the third year or beyond treatment, until disease progression is documented. On-treatment FDG-PET scan will be required in all subjects at Weeks 17 and 25 (± 7 days). The FDG-PET scan performed on Week 49 will be required only for those subjects who do not have two consecutive negative FDG-PET scans after Week 1 and prior to Week 49.

- Screening/Baseline and all subsequent scans will be submitted to an IRRC, once the subject has been enrolled and throughout the study period.
- Quality of Life (QoL) tools must be completed at Treatment Day 1 prior to the first dose of study drug. Following that, QoL tools will be completed according to the schedule in Table 5.1.1-2 and Table 5.1.1-3.
- The presence or absence of B symptoms will be assessed during treatment.
  - On Cycle 1 Day 1, presence of B symptoms is defined as:
    a) Unexplained weight loss of more than 10% during the last 6 months, or
    b) Unexplained, persistent, recurrent fever with temperatures above 38 degree Celsius during the previous month, or
    c) Recurrent drenching night sweats during the previous month.
  - For subsequent assessments after Cycle 1 Day 1 (see Table 5.1.1-2), the presence of B symptoms is defined as:
    a) Unexplained weight loss of more than 10% during the last 6 months from the current assessment, or
    b) Unexplained, persistent, recurrent fever with temperatures above 38 degree Celsius since the last assessment, or
    c) Recurrent drenching night sweats since the last assessment.
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, refer to Sections 3.5 and 4.5.5.

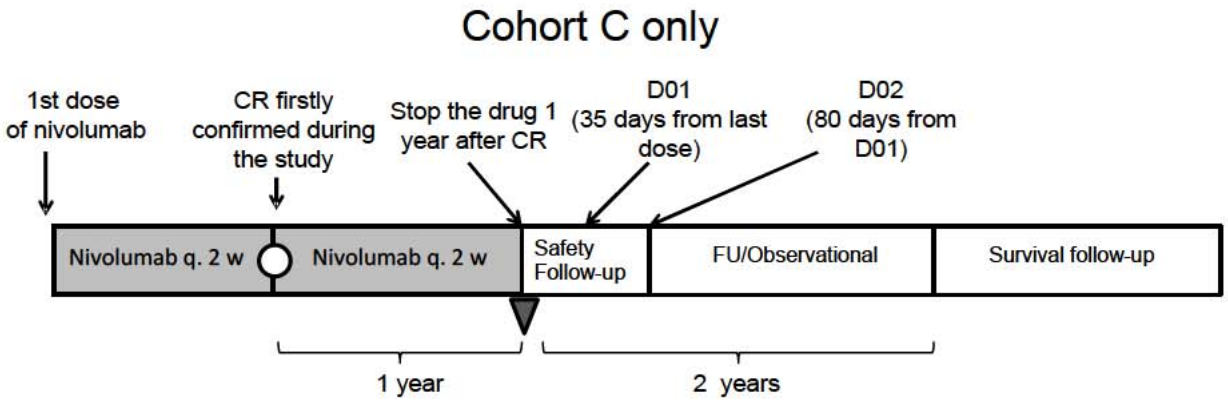
Follow-up for Cohorts A, B, and C:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study drug).
- All treated subjects will have two follow-up visits for safety. Follow-up visit 1 (X01), 35 days (± 7 days) from the last dose of study therapy and Follow-up visit 2 (X02), 80 days (± 7 days) from X01. After X02, subjects will be followed every 3 months for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.
- PK and immunogenicity samples will be collected at the first two follow-up visits.
- Subjects who discontinue study therapy for reasons other than disease progression or allogeneic SCT or ASCT will continue to have radiographic assessments at the intervals described in the Treatment Phase until disease progression, lost to follow-up, or withdrawal of study consent. In rare cases, disease progression is clinically determined by investigators although disease progression does not meet 2007 IWG criteria. In these cases, tumor assessment will not be required thereafter if clinical disease progression is documented and if investigators discontinue the study drug.

- For subjects who discontinue study therapy by proceeding to allogeneic SCT or ASCT, tumor assessment by the investigator will be required after allogeneic SCT or ASCT (see Section 5.4). For the subjects who discontinue study therapy by proceeding to allogeneic SCT, acute and chronic GVHD documentation will also be simultaneously collected (see Section 5.3).
- After completion of the two follow-up visits for safety, subjects will be followed every 3 months for survival, until death, lost to follow-up or withdrawal of study consent.
- QoL tools will be completed according to the schedule in Table 5.1.1-2 and Table 5.1.1-3.

Discontinuation and Follow-up of Cohort C Subjects Who Have Reached One Year of CR

Figure 3.1.1-3: Cohort C Subjects Schedule when Reaching One Year CR



- Subjects who have persistent one year CR will discontinue nivolumab.
- Confirmation of CR by CT (preferred) or MRI ▼ will be required before discontinuation
- Subjects enter safety follow-up phase and subsequently observation follow-up.
- After FU/Observational phase is completed (2 years from the last dose), survival follow-up visits continue every 3 months
- In case of relapse during the FU/Observational phase, possibility to re-initiate treatment

When persistent CR is observed and confirmed for one year, subjects will discontinue study therapy (see Figure 3.1.1-3). The one-year CR duration will be confirmed as described below:

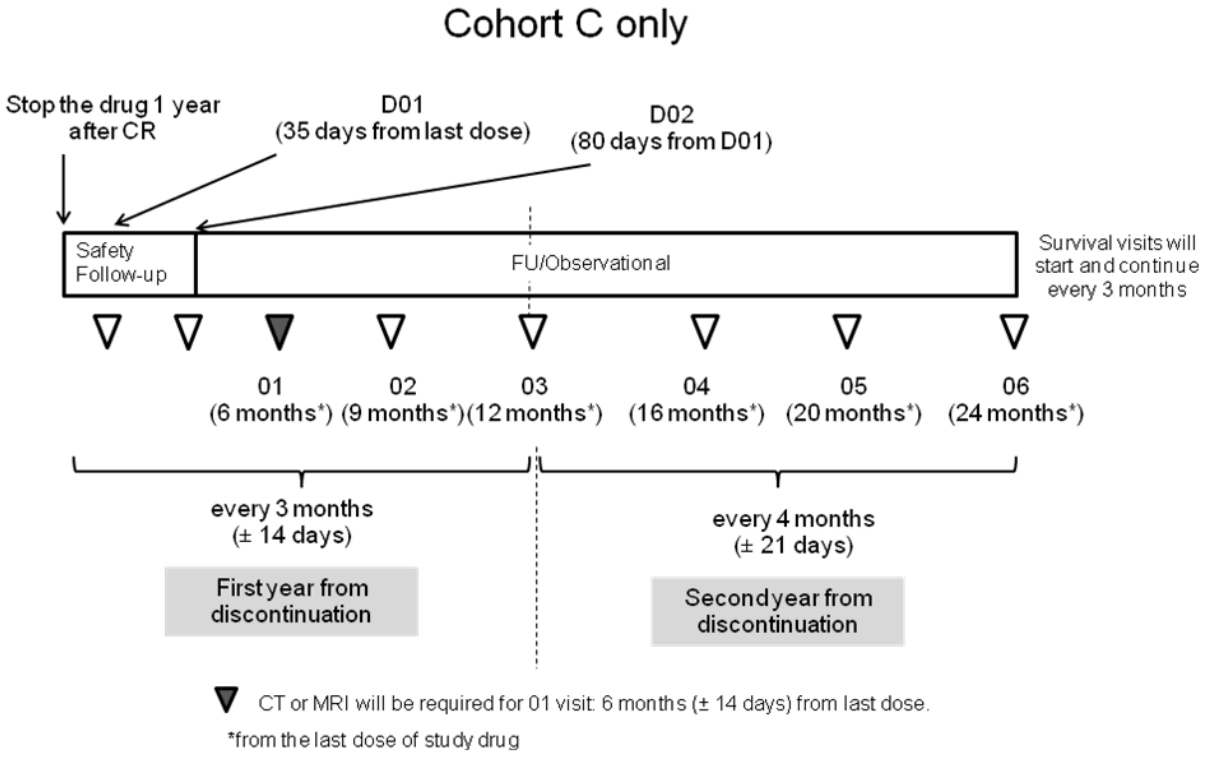
- CT (preferred) or MRI should be performed ± 14 days of the date of one year after firstly confirmed CR during study.

CT (preferred) or MRI will not have to be repeated for discontinuation purpose if scheduled CT (preferred) or MRI assessment (Figure 3.1.1-2) was performed within 8 weeks from the date first on-study CR was observed plus one year, and it confirmed CR.

- Confirmation of CR by CT (preferred) or MRI is based on investigators' assessment
- Investigators must confirm that there are no clinical findings indicating disease progression before discontinuation.
- The last dose of study therapy must be administered within 21 days of the date first on-study CR was observed plus one year.

After discontinuation, subjects will enter the FU/Observational phase as described in Figure 3.1.1-4.

Figure 3.1.1-4: FU/Observational Phase of Cohort C Subjects Who Have Reached One Year CR



- CT (preferred) or MRI will be required at the time of the first observation follow-up visit: 6 months (± 14 days) from last dose.
- CT (preferred) or MRI will be conducted when clinically indicated.
- FU/Observational visits occur every 3 months (± 14 days) in the first year from the last dose of study drug: 01 (6 months), 02 (9 months), and 03 (12 months).
- Thereafter, FU/Observational visits occur every 4 months (± 21 days) in the second year from the last dose of study drug: 04 (16 months), 05 (20 months), and 06 (24 months).
- Targeted physical examination and laboratory tests will be conducted during those FU/Observational visits (01 - 06), see Table 5.1.1-4.

- Subjects will also be followed every 3 months for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.
- PK and immunogenicity samples will **not** be collected after X02
- QoL tools (EQ-5D and EORTC QLQ-C30) will be completed at X01, X02 and during FU/Observational visits, then EQ-5D only during survival follow-up.
- For subjects who proceed to allogeneic SCT or ASCT during FU/Observational phase, tumor assessment by the investigator will be required after allogeneic SCT or ASCT as described in Section 5.4.
- For the subjects who proceed to allogeneic SCT, acute and chronic GVHD documentation will also be simultaneously collected as described in Section 5.3.
- FU/Observational phase will end after two years from the last dose of study therapy.
- If, despite absence of relapse, subjects do not continue in the FU/Observational phase before reaching 2 years from the last dose, the reason for the discontinuation from this phase must be documented in the subject's medical records and entered on the appropriate CRF page. If the subject did not withdraw consent, subject will continue to be followed for survival.
- After completion of FU/Observational visits, subjects will be followed every 3 months for survival, until death, lost to follow-up or withdrawal of study consent.

Re-initiation of Treatment (Cohort C Only):

- Re- initiation of study treatment is allowed when subjects who discontinued study therapy due to persistent one year CR have relapsed within two years from last dose. Re-initiation of treatment will not be permitted after completion of the FU/observational visits.
- Treatment must be re-initiated within 28 days after documented relapse which meets 2007 IWG criteria
- The same procedures described in the on-treatment phase will performed for the subjects who re- initiate study treatment except for the following:
  - QoL tools (EQ-5D and EORTC QLQ-C30) will **not** be competed after Re-initiation of Treatment.
- Subjects who achieved second on-study CR after re-initiation of treatment do not have to discontinue the study drug when second on-study CR persists for 1 year.

3.1.2 Study Design and Duration 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 240 mg IV every 2 weeks (monotherapy phase), followed by twelve doses of the combination of AVD chemotherapy and nivolumab flat dose 240 mg IV for 6 cycles (combination phase). The primary analysis for Cohort D will be

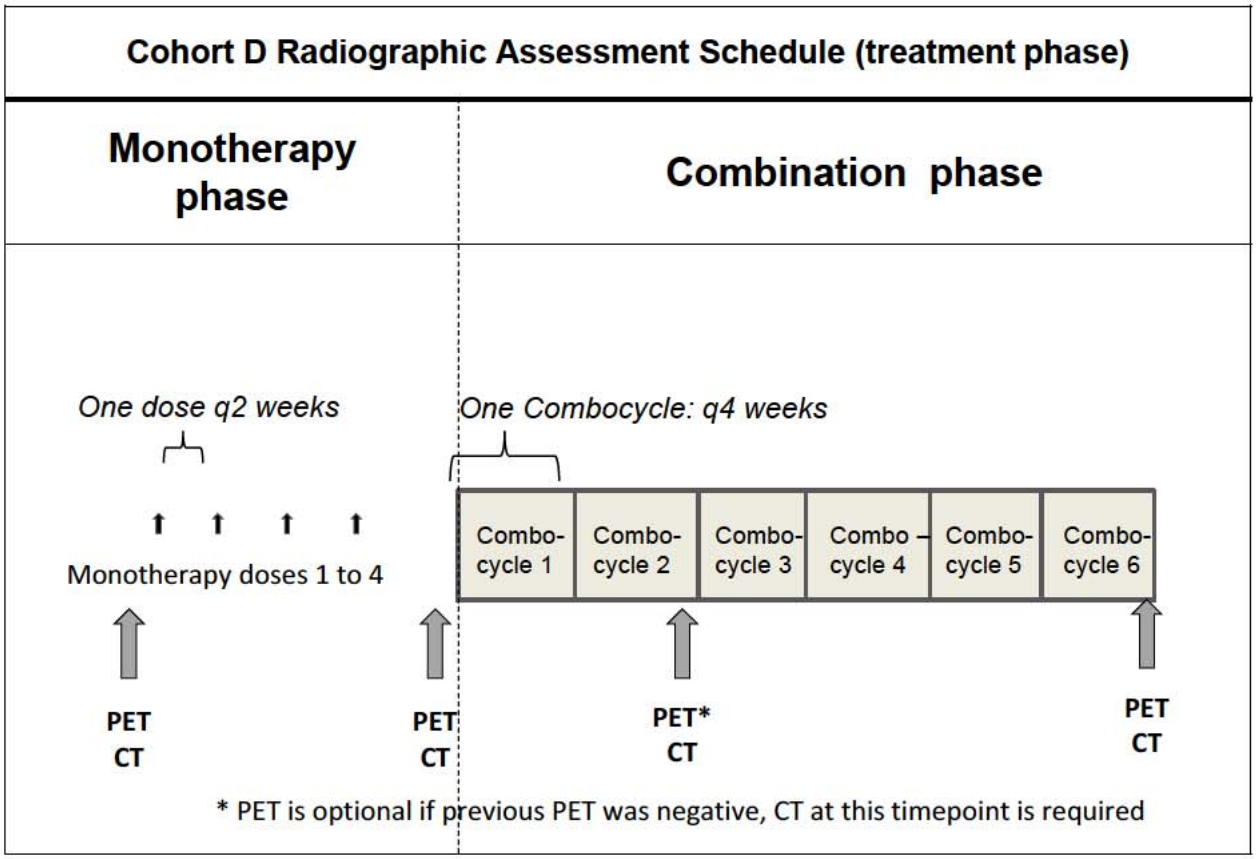
conducted when all treated patients for Cohort D have completed Follow-up visit 1 and end-of-therapy response assessment. All analyses for Cohort D will be performed separately from other cohorts.

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

Subjects must have newly diagnosed, previously untreated cHL with advanced stage (Stage IIB, III and IV) disease. Cohort D consists of approximately 50 subjects.

The study design schematic is presented in Figure 3.1.2-1.

Figure 3.1.2-1: Treatment Schedule for Cohort D



Note: Each Combocycle = two doses (Day 1 and Day 15) of the combination therapy per 28-day cycle

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 240 mg) 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), or subjects who meet dose delay criteria (Section 4.5.2) 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.

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 240 mg) and AVD (Adriamycin/ doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/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. **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 3.1.2-1: 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) are met	AVD
Subjects who have discontinued monotherapy before completing four doses of nivolumab because Nivolumab Delay Criteria (Section 4.5.2.1) 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), 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 Section 4.5.7

Study Duration for Cohort D

Analysis of the primary endpoints will take place after the last patient for Cohort D completes Follow-up visit 1 and the end-of-therapy response assessment. Additional survival analysis will be conducted for up to five years from the last dose of study treatment.

For most subjects, this study will consist of four phases: screening, monotherapy phase, combination phase, and FU/Observational phase (max. 2 years). After two years in the FU/Observational phase, if no relapse is observed, those Cohort D subjects will enter the survival follow-up phase for up to five years from the last dose of study treatment.

Screening for Cohort D

- Begins by signing the ICF
- Subject is enrolled using the IVRS to obtain a subject ID

- Confirm that documentation of cHL newly diagnosed, previously untreated, advanced stage (Stage IIB, III and IV) by Cotswold modified Ann Arbor staging[88] is present in the subject's medical record; documentation of cHL histology by a local pathological laboratory is sufficient for subject to start the first dose. Histology of cHL will be confirmed later by a central pathological laboratory.
- Submission of tumor tissue (FFPE tumor tissue block or at minimum 15 unstained slides, preferably 20) from a biopsy performed during screening is mandatory. Alternatively, submission of tumor tissue from a biopsy performed within 90 days prior to enrollment is allowed. A central laboratory will confirm the pathology, but subjects can proceed to the study drug with documentation of cHL by a local pathology laboratory.
- Bone marrow biopsy/aspirate is not required for Cohort D. An aspirate sample does not need to be submitted if conducted as a standard of care.
- The Hasenclever-Index for Hodgkin's disease also known as International Prognostic Score (IPS) must be reported in the source documents and collected in the eCRF. (See Appendix 3)
- Evaluation for pulmonary and cardiac functions will be required.

Baseline assessments should be performed within 28 days of first dose of study drug, according to Table 5.1.2-1.

- Subject is assessed for study eligibility within the required timeframe found in Table 5.1.2-1
- The screening phase either ends with confirmation of full eligibility and treatment of the subject or with the confirmation that the subject is a screen failure.

Treatment During the Monotherapy Phase for Cohort D

- Treatment begins with the call to the IVRS to obtain vial assignments. A negative pregnancy test should be documented within 24 hours prior to first dose of investigational product. Subsequently, women of childbearing potential (WOCBP) must have a pregnancy test every 4 weeks (± 7 days) regardless of dosing schedule.
- The subject should receive the dose of study medication within 1 day of vial assignment.
- Subjects may be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date. Dose given after the 3-day window is considered a dose delay. A maximum delay of 6 weeks between doses is allowed, except as specified in Section 4.5.5. When the dose delay is > 4 weeks from a previous nivolumab dose for subjects in the monotherapy phase, discontinuing the monotherapy phase and entering the combination phase is allowed after consultation with the medical monitor.
- All vital signs starting after Monotherapy dose 1 will be collected within 72 hours prior to dosing.
- Extended on-study local laboratory assessments should be done within 72 hours prior to monotherapy dose 1 through monotherapy dose 4. Extended on-study local laboratory assessment is also required on day 8 of after monotherapy dose 1.
- AE assessments should be documented at each clinic visit.

- Biomarker, PK and immunogenicity samples will be done according to the schedules in Sections 5.5 and 5.6.
- Nivolumab monotherapy (flat dose 240 mg) is administered as an IV infusion over 30 minutes on Treatment Day 1 of each Monotherapy dose. The planned total dose is four doses of nivolumab flat dose 240 mg every two weeks. The monotherapy will continue until completing four doses, or until disease progression, discontinuation due to toxicity, with withdrawal of study consent, or the study ends. Nivolumab dosing may be delayed for toxicity (Section 4.5.2). When the dose delay is > 4 weeks from a previous nivolumab dose, discontinuing the monotherapy phase and entering the combination phase is allowed after consultation with the medical monitor.
- When subjects meet nivolumab Treatment Discontinuation Criteria (Section 4.5.5), subjects must terminate the monotherapy phase, and may enter the combination phase.
- When subjects meet nivolumab Dose Delay Criteria (Section 4.5.2) for more than 4 weeks from a previous dose, subjects may opt to terminate the monotherapy phase, and enter the combination phase.
- Post-Monotherapy Dose 4: FDG-PET scan and CT (preferred) or MRI scans will also be required after Monotherapy Dose 4 and before entering Combination phase.
- Screening/Baseline and all subsequent scans will be submitted to an IRRC, once the subject has been enrolled and while on study.
- QoL tools must be completed at Treatment Day 1 prior to the first dose of nivolumab. Following that, QoL tools will be completed according to the schedule in Table 5.1.2-2 and Table 5.1.2-3
- The presence or absence of B symptoms will be assessed during treatment.
  - On the day of Monotherapy dose 1, presence of B symptoms is defined as:
    a) Unexplained weight loss of more than 10% during the last 6 months, or
    b) Unexplained, persistent, recurrent fever with temperatures above 38 degree Celsius during the previous month, or
    c) Recurrent drenching night sweats during the previous month.
- For subsequent assessments after Monotherapy dose 1 (Table 5.1.2-2 and Table 5.1.2-3), the presence of B symptoms is defined as:
    a) Unexplained weight loss of more than 10% during the last 6 months from the current assessment, or
    b) Unexplained, persistent, recurrent fever with temperatures above 38 degree Celsius since the last assessment, or
    c) Recurrent drenching night sweats since the last assessment.
- The monotherapy phase ends when the subject starts combination therapy.
- Subjects who were treated with at least one dose of nivolumab, and who discontinue nivolumab monotherapy by meeting discontinuation criteria (Section 4.5.5) and choose not to enter the combination phase will require two follow-up visits for safety: Follow-up visit 1, 35 days (± 7 days) from the last dose of nivolumab and Follow-up visit 2, 80 days (± 7 days) from Follow-up visit1. These subjects will enter survival follow-up (every 6 months) after Follow-up visit 2. FU/Observational visits starting at visit 03 (26 weeks) will not be required

for these subjects. The end-of-therapy radiographic tumor assessments will not be required for these subjects.

Selection of Combination Therapy during Combination phase (See Table 3.1.2-1):

- Subjects who have completed all four doses of nivolumab monotherapy must use Nivolumab-AVD as a combination regimen.
  - After entering Combination phase, the combination regimen can be changed to AVD if subjects meet Nivolumab Delay Criteria (Section 4.5.2.1) or Nivolumab Discontinuation Criteria (Section 4.5.5).
- Subjects who have discontinued monotherapy before completing four doses of nivolumab due to Nivolumab Discontinuation criteria (Section 4.5.5) must use AVD as a combination regimen for all six Combocycles.
- Subjects who have discontinued monotherapy before completing four doses of nivolumab due to Nivolumab Delay Criteria (Section 4.5.5), and due to the dose delay > 4 weeks from a previous dose must use AVD as a combination regimen until subjects meet Criteria to Resume Nivolumab Dosing (Section 4.5.4).
  - If subjects meet Criteria to Resume Nivolumab Dosing (Section 4.5.4) before or at the first dose of the combination therapy, Nivolumab-AVD should be used. AVD may be optionally used based on investigator's judgment.
  - Nivolumab-AVD can be used later once subjects meet Criteria to Resume Nivolumab Dosing (Section 4.5.4). Based on investigator s' judgment, continuing AVD through the end of Combocycle 6 is also acceptable.

Treatment During Combination Phase for Cohort D:

- The subject should receive the dose of study medication within 1 day of vial assignment.
- All vital signs starting after Combocycle 1 will be collected within 72 hours prior to dosing.
- Combination phase (approximately 22 weeks) begins from the first dose of the combination therapy (Dose 1 of Combocycle).
- Dose 1 of Combocycle 1 will be administered with AVD (Adriamycin/doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2) with or without nivolumab (flat dose 240 mg) on Day 1 of Combocycle 1. AVD only (without nivolumab) is permitted as an alternative regimen only when the conditions are met as described above and in Table 3.1.2-1.

Table 3.1.2-2: Combocycle 1 - 6

Drug	Dose	Each Combocycle	
		Dose 1 (Day 1)	Dose 2 (Day 15)
Nivolumab	Flat dose 240 mg	X	X
Doxorubicin (Adriamycin)	25 mg/m^2	X	X
Vinblastine	6 mg/m^2	X	X
Dacarbazine	375 mg/m^2	X	X

Note 1: Nivolumab should be administered first before AVD administrations when Nivolumab-AVD is the combination therapy

Note 2: AVD without nivolumab is permitted as an alternative regimen only when the conditions are met as described above and in Table 3.1.2-1.

- The combination therapy (nivolumab-AVD or AVD only) should be administered as Dose 1 on Day1 and as Dose 2 on Day 15 of each Combocycle. 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. Combination phase will end at Dose 2 (Day 15) of Combocycle 6. Thereafter, subjects will enter the FU/Observational phase. Subjects who discontinue combination treatment before completing Combocycle 6 Dose 2 (Day 15) will also enter the FU/Observational phase. For subjects who started subsequent anti-lymphoma therapy (systemic chemotherapy and/or radiotherapy), FU/Observational visits and the end-of-therapy radiographic tumor assessments will no longer be necessary. These subjects will enter survival follow-up (every 6 months) once subsequent anti-lymphoma therapy begin.
- The combination therapy should be administered every 2 weeks for 12 doses (two doses per Combocycle). If this is not feasible, subjects may be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date. A dose given after the 3 day window is considered a dose delay. Dosing delay or dose reduction (except for nivolumab) is allowed for toxicity. See Sections 4.5.2 and 4.5.3.
- Nivolumab should be administered first before AVD administration when Nivolumab-AVD is the combination therapy.
- Administration method and sequence of each component of AVD (doxorubicin, vinblastine, and dacarbazine) will be according to local and institutional standards. Dosing calculations should be based on the body surface area (BSA) and calculated using the body weight of first dose of the combination phase. However, if the subject's weight later changes by > 10% from the previous weight used to calculate BSA, then BSA should be recalculated and AVD dose corrected accordingly. All doses should be rounded to the nearest milligram.
- Extended on-study local laboratory assessments should be done within 72 hours prior to dosing at each Dose 1 (Day1) of Combocycle 1-6, and Dose 2 (Day 15) of Combocycle 1
- Limited on-study local laboratory assessment should be done within 72 hours prior to dosing at each Dose 2 (Day15) of Combocycle 2 through Combocycle 6.
- AE assessments should be documented at each clinic visit.

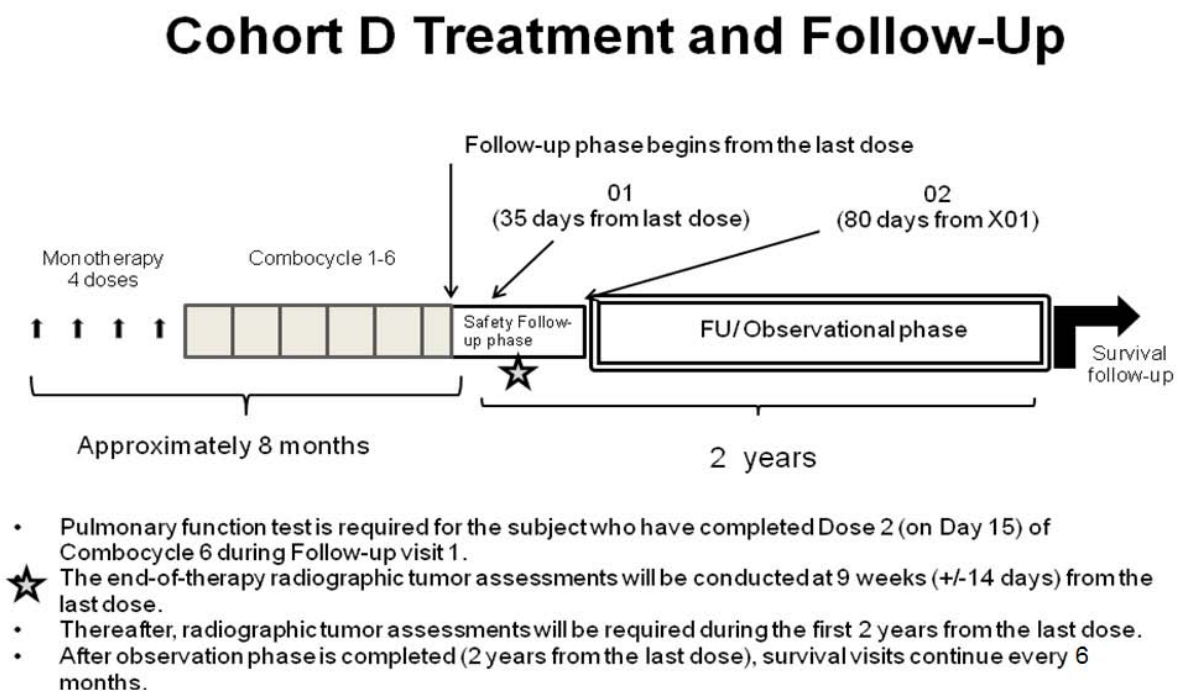
- Biomarker, PK and immunogenicity samples will be done according to the schedules in Sections 5.5 and 5.6.
- Post-Combocycle 2 FDG-PET and CT (preferred) or MRI scans should be performed after Combocycle 2 and before Combocycle 3. This interim FDG-PET scan is optional if a previous scheduled or unscheduled FDG-PET scan after the first dose of nivolumab monotherapy was negative based on investigator's assessment.
- The end-of-therapy radiographic 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 for all subjects. When end-of-therapy FDG-PET scan are positive based on investigator's assessment, tumor biopsy for FDG-avid lesion is strongly encouraged whenever possible.
- QoL tools will be completed according to the schedule in Table 5.1.2-2 and Table 5.1.2-3.
- The presence or absence of B symptoms will be assessed during treatment in the same way as described for monotherapy phase.
- The combination phase ends when the subject completes Dose 2 (Day 15) of Combocycle 6, or when the subject is discontinued from study therapy. Thereafter, subjects will enter the FU/Observational phase.
- Subjects with documented evidence of disease progression meeting 2007 IWG criteria during the Combination phase are not eligible for any further treatment on the study.
- Subjects who discontinued combination therapy (Nivolumab-AVD or AVD) before completing a total of 12 doses with combination therapy will require two follow-up visits for safety: Follow-up visit 1, 35 days (± 7 days) from the last dose of study therapy and Follow-up visit 2, 80 days (± 7 days) from Follow-up visit1. The end-of-therapy radiographic tumor assessments and FU/Observational visits starting at visit 3 (26 weeks) will be required for these subjects. However, once subjects start subsequent anti-lymphoma therapy (systemic chemotherapy and/or radiotherapy), FU/Observational visits and the end-of-therapy radiographic tumor assessments will be no longer necessary. These subjects will enter survival follow-up (every 6 months) once subsequent anti-lymphoma therapy begins. Safety Follow-up visit1 and Safety Follow-up visit 2 are required for all subjects.
- For a complete list of reasons for treatment discontinuation, refer to Sections 3.5 and 4.5.5.

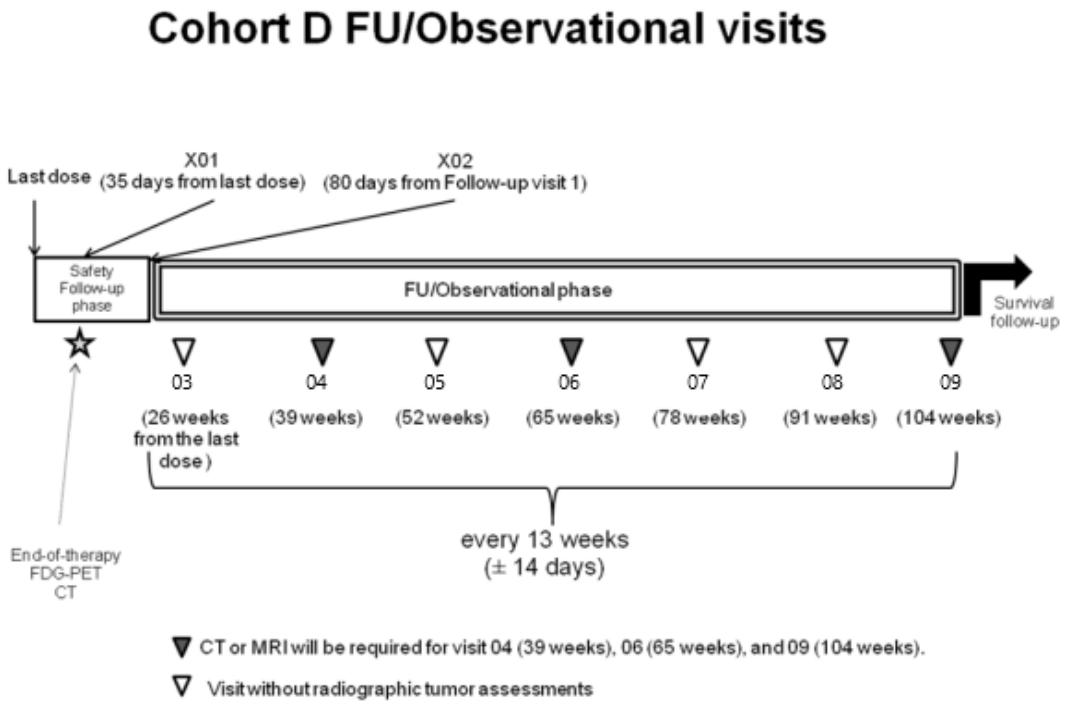
Follow-up (FU)/Observational Phase

- Begins when the subject completes Dose 2 (Day 15) of Combocycle 6, or when the decision to discontinue a subject from study therapy is made (no further treatment with study drug).
- After discontinuation, subjects will enter the FU/Observational phase as described in Figure 3.1.2-2.
- All treated subjects will have two follow-up visits for safety. Safety Follow-up visit 1, 35 days (± 7 days) from the last dose of study therapy, and Safety Follow-up visit 2, 80 days (± 7 days) from Safety Follow-up visit1.
- A pulmonary function test is required for the subjects who have completed Dose 2 (Day 15) of Combocycle 6 during Follow-up visit 1. The test can be conducted 35 days (± 14 days) from the last dose of study therapy.
- PK and immunogenicity samples will be collected at the first two safety follow-up visits.

- **The end-of-therapy radiographic tumor assessments will be conducted at 9 weeks (± 14 days) from the last dose, which is between Safety Follow-up visit 1 and Safety Follow-up visit 2.** FDG-PET and CT (preferred) or MRI scans are mandatory for all subjects unless previous evidence of disease progression meeting 2007 IWG criteria is documented. When end-of-therapy FDG-PET scan are positive based on investigator's assessment, tumor biopsy for FDG-avid lesion is strongly encouraged whenever possible. Submission of tumor biopsy specimen for biomarker analysis is encouraged.
- After Safety Follow-up visit 2, subjects will be followed every 3 months for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.
- QoL tools (EQ-5D) will be completed at Safety Follow-up visit 1 and Safety Follow-up visit 2, during FU/Observational visits, and during survival follow-up according to the schedule in Table 5.1.2-4
- PK and immunogenicity samples will **not** be collected after Follow-up visit 2
- FU/Observational visits occur every 3 months (± 21 days) in the first two years from the last dose of study treatment: 03 (26 weeks), 04 (39 weeks), 05 (52 weeks), 06 (65 weeks), 07 (78 weeks), 08 (91weeks), and 09 (104 weeks).
- The radiographic tumor assessments, are required at visit 04 (39 weeks), 06 (65 weeks), and 09 (104 weeks). Only CT (preferred) or MRI is required. Thereafter, no radiographic tumor assessment is required. FDG-PET and CT (preferred) or MRI can be conducted when clinically indicated. All scans for radiographic tumor assessments will be collected and be evaluated by IRRC.
- Targeted physical examination will be conducted during the safety follow-up visits 1 &2 and during FU/Observational visits (03 - 11), see Table 5.1.2-4. Laboratory tests will be performed during safety follow-up visits 1 &2.
- Subjects who have disease progression or relapse during the FU/Observational phase may end the FU/Observational phase, and enter survival follow-up (every 6 months) once subjects start subsequent anti-lymphoma therapy (systemic chemotherapy and/or radiotherapy). Safety Follow-up visit 1 and Safety Follow-up visit 2 will still be required if these were not completed yet.
- For subjects who have disease progression and undergo other anti-lymphoma treatment, information on these anti-lymphoma therapies will be collected as much as possible along with survival status. Investigators will make telephone contacts with the subject's current physician to obtain disease status and document the status if subject is being followed by another physician.
- If, despite absence of relapse, subjects do not continue in the FU/Observational phase before reaching three years from the last dose, the reason for the discontinuation from this phase must be documented in the subject's medical records and entered on the appropriate CRF page. If the subject did not withdraw consent, subject will continue to be followed for survival.
- After completion of FU/Observational visits, subjects will be followed every 6 months for survival for up to 5 years from the last study treatment, until death, lost to follow-up, or withdrawal of study consent.

Figure 3.1.2-2: Treatment and Follow-up Phase for Cohort D





3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug for the subjects in Cohorts A, B, and C. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

2. Target Population

a) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1, see Appendix 4.

b) For Cohorts A, B, and C, subjects must have received prior high-dose conditioning chemotherapy followed by ASCT as a part of salvage therapy for cHL:

i) Cohort A: Subjects who are naïve to brentuximab vedotin- treatment and who meet one of the following criteria according to the 2007 IWG criteria:

(1) Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT; or,

(2) Documented relapsed disease (after CR) or disease progression (after PR or SD)

ii) Cohort B: Subjects who failed treatment with brentuximab vedotin which was administered following failure of ASCT, and who meet one of the following criteria according to the 2007 IWG criteria:

(1) Documented failure to achieve at least PR after the most recent treatment; or,

(2) Documented relapse disease (after CR) or disease progression (after PR or SD)

iii) Cohort C: Subjects who failed ASCT and who have received prior treatment* with brentuximab vedotin at any time point, and who meet one of the following criteria according to the 2007 IWG criteria:

(1) Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT; or,

(2) Documented failure to achieve at least PR after the most recent chemotherapy or radiation therapy; or,

(3) Documented relapse disease (after CR) or disease progression (after PR or SD)

*This includes brentuximab vedotin treatment as an initial therapy or salvage therapy before ASCT, and/or brentuximab vedotin treatment after ASCT (eg, salvage and maintenance therapy after ASCT)

c) Must have at least one lesion that is > 15 mm (1.5 cm) in the longest diameter on cross-sectional imaging and measureable in two perpendicular dimensions on CT (or MRI) and FDG avid by PET.

d) Biopsy confirmation of cHL prior to the initiation of study drug. cHL should be pathologically confirmed by standard immunohistochemical or flow cytometric techniques.

e) Subject re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.

f) For Cohort D, subjects must have newly diagnosed, previously untreated cHL lymphoma (except for corticosteroid use)

g) For Cohort D, subjects must be Stage IIB, III and IV by Cotswold modified Ann Arbor staging[88]

i) If Stage IIB, subjects must have B symptoms *and* either bulky disease *or* extranodal disease*:*

(1) bulky disease, defined as one or more of the following:

(a) a node or nodal mass >10 cm)

(b) a mediastinal mass with the maximum width is ≥ 1/3 of the internal transverse diameter of the thorax at the level of T5/6

(2) extranodal disease

3. Age and Reproductive Status

a) Males and Females, ≥ 18 years of age.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with nivolumab plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a

total of 5 months post treatment completion. Only for Cohort D, after a total of 23 weeks elapses from the last dose of nivolumab, WOCBP subjects must agree to follow instructions for method(s) of contraception for the duration of treatment with AVD plus 5 half-lives of AVD plus 30 days (duration of ovulatory cycle) for a total of 6 weeks from the last dose of AVD when AVD only is used as combination therapy. Doxorubicin, vinblastine, and dacarbazine are teratogenic.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. Only for Cohort D, after a total of 31 weeks elapses from the last dose of nivolumab, men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with AVD plus 5 half-lives of AVD plus 90 days (duration of ovulatory cycle) for a total of 15 weeks from the last dose of AVD when AVD only is used as combination therapy. Doxorubicin, vinblastine, and dacarbazine are teratogenic. In addition, male subjects must be willing to refrain from sperm donation during this time.

f) Azospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment. Local laws and regulations may require use of alternative and/or additional contraception methods.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Failure rate of < 1% per year when used consistently and correctly.[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - injectable
- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants, transdermal, and intrauterine hormone-releasing system (IUS)[c]

- Intrauterine devices (IUDs)[c]
- Bilateral tubal ligation
- Vasectomized partner
  - *NOTE: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
- Sexual abstinence
  - *NOTE: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
  - It is not necessary to use any other method of contraception when complete abstinence is elected.
  - WOCBP subjects who choose complete abstinence must continue to have pregnancy tests as specified per protocol.
  - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

UNACCEPTABLE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only

- Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

4. Physical and Laboratory Test Finding

a) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:

i) Absolute neutrophil Count ≥ 750/μL (no WBC growth factors for prior 14 days).

ii) Platelets ≥ 50 x10^3/μL (no platelet transfusions for prior 14 days).

iii) Hemoglobin ≥ 8.5 g/dL (no RBC transfusions for prior 7 days).

iv) Serum creatinine ≤ 1.5 x Upper limit of normal (ULN) or creatinine clearance (CrCl) ≥ 40 mL/min (measured using the Cockcroft-Gault formula below):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

v) AST/ALT ≤ 3 x ULN.

vi) Total bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).

b) For Cohorts A, B, and C, subjects with a prior history of chemotherapy-induced or radiation-induced pulmonary toxicity require confirmation of diffusing capacity of the lung for carbon monoxide (DLCO) over 60% (adjusted for hemoglobin) by a pulmonary function test prior to study enrollment.

c) For Cohort D, subjects require confirmation of diffusing capacity of the lung for carbon monoxide (DLCO) over 60% (adjusted for hemoglobin) by a pulmonary function test during screening.

d) For Cohort D, subjects require left ventricular ejection fraction over 50% at rest by echocardiography or over 55% by isotopic measurement during screening.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Known central nervous system lymphoma.

b) Subjects with nodular lymphocyte-predominant HL.

2. Medical History and Concurrent Diseases

a) Subjects with active interstitial pneumonitis.

b) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

c) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

d) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

e) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Only for Cohort D, prior treatment with corticosteroids for cHL are acceptable.

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

4. Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody with the following exception: subjects who experienced Grade 3 or 4 infusion-related reaction

with the first dose of rituximab, but who were able to receive subsequent rituximab without recurrence of Grade 3 or 4 infusion-related reaction are eligible.

5. Prohibited Treatments and/or Therapies

a) Prior treatment history with brentuximab vedotin administered before first ASCT, for Cohorts A and B.

b) ASCT ≤ 90 days prior to first dose of study drug.

c) Prior chemotherapy within 4 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin immunoconjugates (excluding brentuximab vedotin) within 10 weeks and brentuximab vedotin within 4 weeks or major surgery within 2 weeks prior to first dose of study drug.

d) Carmustine （BCNU) ≥ 600 mg/m² received as part of the pre-transplant conditioning regimen.

e) Prior radiation therapy within 3 weeks, or chest radiation ≤ 24 weeks prior to first dose of the study drug.

f) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

g) Prior allogeneic SCT.

h) For Cohort D, prior treatment for cHL (prior use of corticosteroid is acceptable).

i) For Cohort D, planned post-treatment consolidative radiotherapy.

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required)

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

*Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 3.3.2 or to treat a drug-related AE), except for Cohort D.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer), except for Cohort D. Protocol defined chemotherapy (doxorubicin, vinblastine, and dacarbazine) is permitted in Cohort D.

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

3.4.2 Other Restrictions and Precautions

3.4.2.1 Permitted Therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the case report form (CRF). All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and

different from the study drug must be documented in the concomitant therapy section of the CRF.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Disease progression as determined by investigator assessment following the guidelines given in Section 5.4.6 with the exception described in Section 4.5.7.
- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol-specific reasons for discontinuation (See Section 4.5.5).

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female subject becomes pregnant during a clinical trial, the study drug must be discontinued immediately. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Follow up

For Cohorts A, B, and C, ORR and DOR are key endpoints of the study. For all cohorts, post study drug follow-up is of critical importance and is essential to preserve subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death, withdrawal of consent, lost to follow-up, or the conclusion of the study.

In addition, for Cohorts A, B, and C, subjects who discontinue study therapy by proceeding to allogeneic SCT or ASCT will require tumor assessment (CR or non-CR) by the investigators according to the 2007 IWG criteria 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 (see Section 5.4). For the subjects who discontinue study therapy by proceeding to allogeneic SCT, documentation of acute and chronic GVHD will be simultaneously collected (see Section 5.3).

For Cohort D, if subjects have disease progression during study treatment, or have relapse disease after the end of study treatment, limited information of anti-lymphoma salvage treatment will be collected along with survival status Table 5.1.2-4.

BMS may request that survival data be collected on all treated subjects outside of the protocol window (section 5.1). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow up.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject

remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes Investigational [Medicinal] Product (IP/IMP):

Table 4-1: Study Drugs for CA209205 - Treatment Period

Product Description / Class and Dosage Form	Potency/Route of Administration	IP/Non-IMP	Blinded or Open-Label	Packaging/Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open-label	Vial or various packaging configurations	Refer to the label on container and/or pharmacy manual.
Dacarbazine Powder for IV Solution[b]	200 mg	200 mg per vial Open-label	10 vials per carton/ Open-label	White to pale yellow powder	Do not store above 25° C. Protect from light.
Doxorubicin Powder for Solution for Injection[b]	50 mg (2 mg/mL)	25 mL per vial/ Open-label	1 vial per carton/ Open-label	Red, compact unit or fragment with a porous appearance	Store at 15° to 25 °C.
Vinblastine (Sulphate) Solution for Injection[b]	10 mg (1 mg/mL)	10 mL per vial/ Open-label	2 vials per carton/ Open-label	A clear, colorless pale to yellow solution	2° to 8°C. Protect from light.

[a] Product may be labeled as either "BMS-936558" or "Nivolumab".

[b] May be obtained by the investigational sites in certain countries as local commercial product (which may be available as a different potency/package size than listed above) if local regulations allow this. Locally sourced marketed product utilized for this study should be stored in accordance with the package insert, summary of product characteristics (SmPC), or equivalent document.

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are:

- BMS-936558 (nivolumab) for Cohorts A, B, C, and D
- Dacarbazine for Cohort D
- Doxorubicin for Cohort D
- Vinblastine for Cohort D.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Not applicable for this study.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the IB and/or pharmacy reference sheets/pharmacy manual for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab).

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) IB section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets/pharmacy manual.

At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose.

For Cohort D, for the drugs used during the combination phase (AVD), refer to SmPC or USPI.

4.4 Method of Assigning Subject Identification

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 IVRS to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator (or designee) will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date of informed consent
- Date of birth
- Gender at birth
- Prior Brentuximab vedotin exposure (Cohorts A, B, and C, only).
- Prior anti-lymphoma treatment history (Cohort D).

4.5 Selection and Timing of Dose for Each Subject

Cohorts A, B and C eligible subjects will receive nivolumab at either a 480 mg IV flat dose Q4W or a 240 mg IV flat dose Q2W. Subjects should receive nivolumab as a 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. There will be no dose escalations or reductions of nivolumab allowed. Once a new dosing regimen has been selected for the subject, either flat dose 240 mg Q2W or flat dose 480 mg Q4W, the dosing regimen will remain in effect until the end of treatment and not change. For subjects being treated with nivolumab at 3 mg/kg every 2 weeks who switch dosing to every 4 weeks at 480 mg flat dose, the first dose of nivolumab at 480 mg should be administered 2 weeks after the last 3 mg/kg Q2W dose. Cohorts A, B, and C subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

Cohort D subjects will receive nivolumab at a flat dose of 240 mg as a 30-minute IV infusion every 2 weeks. Subjects must be treated within one day after study drug vial assignment. There will be no dose escalations or reductions of nivolumab allowed. Subjects should be carefully

monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

There are no premedications recommended for nivolumab on the first cycle.

Cohorts A, B, and C subjects may be dosed no less than 12 days from the previous dose during every 2-week cycle. Doses given after the 3-day window are considered dose delays.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

For every 4-week dosing cycle, Cohorts A, B, and C subjects may be dosed within a ± 3-day window. Cohorts A, B, and C subjects receiving nivolumab every 4 weeks may be allowed to interrupt longer delay after discussion and written approval by the BMS Medical Monitor, in subjects with expected clinical benefit as per investigator assessment and after resolution of any AE leading to dosing interruption with stable performance status.

For Cohorts A, B, and C, tumor assessments by CT or MRI should continue as per protocol even if dosing is delayed. For Cohort D, tumor assessment by CT, MRI, FDG-PET should be conducted based on cycles, not weeks.

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay or discontinuation) will be based on specific laboratory and AE criteria.

4.5.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of nivolumab monotherapy. For Cohort D, antiemetic premedications during combination therapy is according to local or institutional standards. Corticosteroid use for antiemesis is permitted for the entire study for Cohort D.

4.5.2 Dose Delay Criteria

4.5.2.1 Nivolumab Dose Delay Criteria

Dose delay criteria apply for all drug-related AEs. Nivolumab must be delayed until treatment can resume (see Section 4.5.4). For Cohort D, these criteria apply both for the Monotherapy and Combination phases. During the Combination phase, only nivolumab must be delayed if the AE is considered to be nivolumab-related, whereas AVD can be dosed at the planned schedule per the protocol.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE

- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia or leukopenia does not require dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

4.5.2.2 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in the Nivolumab IB and in Appendix 1 of this protocol. Discussions with the BMS Medical Monitor on how to apply these algorithms are strongly encouraged. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

4.5.2.3 AVD Dose Delay Criteria (Only for Cohort D)

This rule applies to subjects in Cohort D during the combination phase. When an investigator judges that dose is delayed > 21 days from a previous dose due to an AVD-related AE, the BMS medical monitor should be contacted.

- If neutrophils < 1,500/mm^3 (≥ Grade 1) on the day of drug administration, treatment (Nivolumab-AVD or AVD) can be delayed until normalization of the values. G-CSF is

permitted for leucopenia or neutropenia. Prophylactic use of G-CSF is also permitted for subsequent treatment.

- If platelets are < 75,000/mm^3 (≥ Grade 1) on the day of drug administration, treatment can be delayed until normalization of the values.

When the causality of AE resulting in a dose delay > 21 days from a previous dose is not determined due to either nivolumab or AVD from the Nivolumab-AVD regimen, the BMS medical monitor should be contacted.

4.5.3 Doses Reductions and Escalations

In all cohorts, dose reductions and escalations of nivolumab are not permitted.

Only for Cohort D: omitting only nivolumab from Nivolumab-AVD is permitted during the combination phase. When an investigator judges that a dose is delayed > 21 days from a previous dose due to a nivolumab-related AE, the BMS medical monitor must be contacted. Subjects who meet Nivolumab Delay Criteria (Section 4.5.2.1) may eliminate nivolumab and use only AVD for the subsequent combination treatment after the BMS medical monitor is consulted. If the subject subsequently meets Criteria to Resume Nivolumab Dosing (Section 4.5.4), the regimen may be changed back to Nivolumab-AVD, after the BMS medical monitor is consulted again. Dose interruption of nivolumab > 6 weeks during combination phase is permitted. Skipped nivolumab doses will not be compensated.

Only for Cohort D: each component of AVD should reduce its dose when subjects are treated with AVD or Nivolumab-AVD during combination phase, as follows:

- If ≥ Grade 3 febrile neutropenia is observed, the dose of doxorubicin and vinblastine can be reduced by up to 50% reduction for subsequent treatment.
- If plasma bilirubin concentration is between 1.2 - 3.0 mg/dL, the dose of doxorubicin and vinblastine can be reduced by 50%.
- If plasma bilirubin concentration is > 3.0 - 5.0 mg/dL, the dose of doxorubicin and vinblastine can be reduced by 75%.
- If ≥ Grade 2 peripheral motor neuropathy, or/and if ≥ Grade 3 peripheral sensory neuropathy is observed, the dose of vinblastine can be reduced by up to 50% reduction for subsequent treatment.

When AVD is delayed, nivolumab should also be delayed.

The BMS medical monitor should be contacted when dose is reduced regardless of the causality.

4.5.4 Criteria to Resume Nivolumab Dosing

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue

- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criterion to resume treatment is met, the subject should restart treatment at the next scheduled time point per protocol.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.

For Cohort D, these criteria apply both for the monotherapy and combination phases. During the combination phase, when only nivolumab is delayed due to nivolumab-related AE, nivolumab can be resumed in combination with AVD if these resuming criteria are met. Withholding dose of nivolumab for > 6 weeks during the combination phase is permitted.

4.5.5 Nivolumab Discontinuation Criteria

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with clinically significant bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 5-10 x ULN for > 2 weeks

  - AST or ALT > 10 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities
  - Grade 4 drug-related endocrinopathy AEs such as adrenal insufficiency, ACTH (Adrenocorticotropic Hormone) deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Any dosing delay lasting > 6 weeks from the previous dose with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
  - Dosing delays > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
  - Withholding dosing for > 6 weeks during combination phase (only for Cohort D).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
- Disease progression as determined by investigator assessment following the guidelines given in Section 5.4.6 with the exception described in Section 4.5.7. For Cohort D, subjects who discontinued nivolumab monotherapy due to 2007 IWG criteria-met disease progression based on investigators' assessment during the Monotherapy phase are allowed to enter the Combination phase when AVD is used as a combination therapy. For Cohort D, subjects who had 2007 IWG criteria-met disease progression based on investigators' assessment and who had treatment beyond progression during the Monotherapy phase are allowed to use Nivolumab-AVD combination therapy during the Combination phase.
- Subject who initiated the preparative regimen for allogeneic SCT or ASCT after the first dose of nivolumab treatment.

- Initiation of antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer).
- Cohort C subjects who have persistent CR for 1 year will discontinue the study drug when CR is confirmed by CT (preferred) or MRI. Please refer to section 3.1.

For Cohort D, these criteria apply both for monotherapy and combination phases.

During monotherapy phase, subjects who meet Nivolumab Delay Criteria (Section 4.5.2) may enter the combination phase when nivolumab monotherapy requires dose delay > 4 weeks from a previous dose after the BMS medical monitor is consulted.

During combination phase, if nivolumab meet one of these discontinuation criteria due to nivolumab-related AE, nivolumab must be permanently discontinued, whereas AVD can be dosed as planned.

4.5.5.1 Discontinuation of Nivolumab Monotherapy During Monotherapy Phase of Cohort D

Subjects who meet Nivolumab Discontinuation Criteria (Section 4.5.5) may enter the combination phase if AVD only (without nivolumab) is used as the combination therapy. The BMS medical monitor should be contacted before starting AVD. These subjects are not allowed to use the combination of nivolumab and AVD (See Table 3.1.2-1).

When nivolumab monotherapy dose delays are > 4 weeks from a previous dose, the BMS medical monitor should be contacted. Withholding dosing of nivolumab monotherapy is permitted up to 6 weeks. However, based on the investigator's judgment, subjects who meet Nivolumab Delay Criteria (Section 4.5.2.1) may also enter the combination phase if nivolumab monotherapy dose delay > 4 weeks from a previous dose after the BMS medical monitor is consulted.

- If subjects meet Criteria to Resume Nivolumab Dosing (Section 4.5.4) before or when they enter combination phase, the combination of nivolumab and AVD should be used. However, based on investigators' judgment, AVD only (without nivolumab) may be used (See Table 3.1.2-1).
- If subjects do not meet Criteria to Resume Nivolumab Dosing (Section 4.5.4) when they enter combination phase, AVD only (without nivolumab) must be used. If subjects subsequently meet Criteria to Resume Nivolumab Dosing (Section 4.5.4), the regimen may switch from AVD only to the combination of nivolumab and AVD, after the BMS medical monitor is consulted. For example, a subject who has started Combocycle 1 with AVD only may start using the combination of nivolumab and AVD from Combocycle 4 after discussion with the BMS medical monitor. Based on investigator s' judgment, continuing AVD only through the end of Combocycle 6 is also acceptable (See Table 3.1.2-1).

4.5.5.2 Discontinuation of Nivolumab from the Combination Therapy During Combination Phase for Cohort D

Subjects who meet Nivolumab Discontinuation Criteria (Section 4.5.5) due to a nivolumab-related AE must eliminate nivolumab, and must use AVD only for the subsequent combination treatment after the BMS medical monitor is consulted. The use of nivolumab as a part of the combination is no longer allowed (See Table 3.1.2-1).

4.5.6 Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional

nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.5.7 Treatment Beyond Disease Progression

4.5.7.1 Circumstances in which Post-progression Treatment is Permitted

Subjects meeting progression defined by relapsed disease (after CR) or progressive disease (after PR, SD) per 2007 IWG criteria may continue receiving study medication beyond investigator-assessed progression as long as they meet the following criteria:

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Subjects will be re-consented with an informed consent document describing any reasonably foreseeable risks or discomfort and other alternative treatment options
- Tolerance of study drug.

The decision to continue treatment beyond investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records. Subjects for Cohorts A, B, and C should continue to meet all other study protocol eligibility criteria. Treatment beyond disease progression is permitted for subjects in Cohort D only during the monotherapy phase. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

4.5.7.2 Assessment Schedule for the Subjects with Post-progression Treatment

The subject should continue to receive monitoring according to the On-Treatment Assessments on Table 5.1.1-2 except for FDG-PET scans. Radiographic assessment by CT (preferred) or MRI described in Section 5.4.1 and Table 5.4.1.1-1 are required when subjects continue post-progression treatment. FDG-PET scans are not mandated after investigator-assessed progression.

4.5.7.3 Discontinuation due to "Further Progression"

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

- Further progression is evaluated by a subsequent CT or MRI which is performed at least 8 weeks from previous CT or MRI.
- The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.
- New lesions are considered measurable at the time of initial progression if the long axis is more than 15 mm regardless of the short axis. If a lymph node has a long axis of 11 to 15 mm, it should only be considered measurable if its short axis is more than 10 mm.
- Any new lesion considered non-measurable at the time of or after initial progression may become measurable and therefore included in the tumor burden determination.

4.5.7.4 Radiographic Assessment for the Subjects who Discontinue Study Drug during Post-progression Treatment

When subjects stop post-progression treatment, no additional radiographic assessment will be required and they will continue in the follow-up phase of the study (see Section 5.1). The subjects who proceed to allogeneic SCT or ASCT will be followed with specific schedule (see Section 5.4).

4.5.8 Re-Initiation of Study Therapy for Cohort C subjects

As described in Section 4.5.5, subjects in Cohort C will discontinue study therapy after maintaining CR for one year. If subjects relapse within 2 years from last dose, subjects may reinitiate study therapy. Relapse must meet 2007 IWG criteria based on investigators' assessment, and must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted. Re-initiation of treatment after relapse is not mandatory, should a subject chose not to re-initiate treatment, this subject will continue to be followed every three months for survival.

Subjects re-initiating study therapy should continue to meet eligibility criteria at the time study drug resumes. FDG-PET is not mandated if FDG-avid disease was previously proved. Pulmonary function test is not required if DLCO was previously over 60% (adjusted for

hemoglobin) at initial enrollment and if no drug-related pulmonary toxicity was reported during the study therapy. Re-initiation of study therapy is not allowed for subjects who proceeded to ASCT or allogeneic SCT, and for subjects who initiated other anti-neoplastic therapy after study drug discontinuation. Re-initiation of treatment procedures are described in Table 5.1.1-5.

When subjects achieve second on-study CR by re-initiation of study drug, subjects do not have to discontinue the study drug when second on-study CR persists for 1 year.

Additional safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

4.5.9 Guidelines for Assessment and Initial Management of Tumor Lysis Syndrome

The possibility of tumor lysis syndrome cannot be ruled out for the subjects with lymphoma. Therefore, adequate management such as hydration and/or the use of allopurinol is recommended in the subjects who have risk factor of potential tumor lysis syndrome, for example the subjects with high tumor burden, reflected by high serum LDH levels, or bulky disease, or those with preexisting renal failure.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and CRF.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

5.1.1 Time and Events Schedule for Cohorts A, B, and C

Table 5.1.1-1: Screening Procedural Outline for Cohorts A, B, and C (CA209205)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Include Height, Weight, and ECOG performance Status
Hasenclever-Index for Hodgkin's Disease also known as IPS at Initial Diagnosis	X	Composite score, see Appendix 3.
Vital Signs and Oxygen saturation	X	Temperature, BP, HR, and O_2 saturation by pulse oximetry (at rest and after exertion).
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose

Table 5.1.1-1: Screening Procedural Outline for Cohorts A, B, and C (CA209205)

Procedure	Screening Visit[a]	Notes
Laboratory Tests	X	Complete blood count (CBC) with differential, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, P, glucose, albumin, amylase, lipase, thyroid stimulating hormone (TSH) (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA) within 14 days prior to first dose.
Urinalysis	X	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH, within 14 days prior to first dose.
Pregnancy Test	X	For WOCBP only (serum or urine - local/site)
Efficacy/Biomarker Assessments		
Radiographic Tumor Assessment	X	Must be performed within 28 days prior to first dose.
CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease (eg neck)		Additional sites of known or suspected disease (eg neck) should be imaged at the screening visit and at subsequent on-study assessments.
FDG-PET scan		FDG-PET scan required at screening.
Bone Marrow Biopsy/Aspirate (Submission of aspirate sample is mandatory for biomarker analyses for subjects who have a bone marrow aspirate performed during screening.) for Cohorts A and B, optional for Cohort C.	X	See Table 5.6-1 of Biomarker Sampling Schedule.
Collection of tumor tissue	X	Submission of tumor tissue (FFPE tumor tissue block or 10 unstained slides) from a biopsy performed during screening is mandatory. If this is not possible, the following exceptions are allowed: Subjects who do not have any accessible lesions, or Subjects who have archival tissue from a previous tumor biopsy that can be used for PD-L1 expression analysis. These subjects must submit archival tissue from the most recent tumor biopsy if archival tissues are available from tumor biopsies at multiple time points. While submission of archival tissue from the most recent tumor biopsy is mandatory, archival tissue from other tumor biopsy is strongly encouraged. For example, subjects who mandatorily submit archival tissue from a tumor biopsy at relapse may optionally submit archival tissue for

Table 5.1.1-1: Screening Procedural Outline for Cohorts A, B, and C (CA209205)

Procedure	Screening Visit[a]	Notes
		tumor biopsy at initial diagnosis. Note: For these exceptions, the reason must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted. Subjects may initiate the study drug before the outcomes of PD-L1 expression status become available. Biopsy samples should be excisional, incisional, or core needle. Tumor biopsies (FFPE) for IHC of tumor and TIL and RNALater for gene expression.
IVRS/Clinical Drug Supplies		
Phone calls to IVRS		Phone calls must be made to IVRS as follows: For subject cohort and number assignment at the time informed consent is obtained. Prior to dosing for study drug vial assignment (call should be made within 1 day prior to dosing).

[a] Within 28 days prior to first dose

Table 5.1.1-2: On-Treatment Assessments for Cohorts A, B, and C (CA209205)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (240 mg Q2W or 480 mg Q4W [a]) on Day 1	Notes Dosing cycle = 240 mg Q2W or 480 mg Q4W
Safety Assessments				
Targeted Physical Examination	X		X	Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver)
Vital Signs and Oxygen Saturation	X	X	X	Temperature, BP, HR, O2 saturation by pulse oximetry at rest and after exertion (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X	X	X	Includes Weight and ECOG performance status
Adverse Events Assessment	---------- Continuously ----------			Assessed using NCI CTCAE v. 4.0.
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Extended on-study local laboratory assessments should be done within 72 hours prior to dosing from Cycle 1 through Cycle 5 and every alternate dose thereafter (Cycles 7, 9, 11, 13, etc.) and include: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. Limited on-study local laboratory assessment should be done within 72 hours prior to dosing beginning at Cycle 6 and every alternate dose thereafter (Cycles 8, 10, 12, 14, etc.) and include: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Thyroid Function Testing			See note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 7 days) from first dose regardless of dosing schedule.
Pregnancy Test for WOCBP	X		See note	Serum or urine within 24 hours prior to first dose and then at least

Table 5.1.1-2: On-Treatment Assessments for Cohorts A, B, and C (CA209205)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (240 mg Q2W or 480 mg Q4W [a]) on Day 1	Notes Dosing cycle = 240 mg Q2W or 480 mg Q4W
				once every 4 weeks (± 7 days) regardless of dosing schedule.
Efficacy Assessments				
Radiographic Tumor Assessment CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease FDG-PET Scan			See note	See Table 5.4.1.1-1 and Table 5.4.1.1-2 of CT or MRI and FDG-PET scan schedule and also Section 4.5.7.2 in case of treatment beyond progression.
Bone Marrow Aspirate and Biopsy	See note		See note	For Cohorts A and B: Bone Marrow Aspirate and Biopsy is required to confirm any CR in subjects with lymphoma involvement in bone marrow at study entry. For Cohort C, Bone Marrow Aspirate and Biopsy is optional. If it is done, Bone Marrow Aspirate sample can be optionally submitted for biomarker analysis. See Table 5.6-1 of Biomarker Sampling Schedule.
Additional Exploratory Biomarker Testing				
Serum Whole Blood Tumor Biopsy	See note		See note	See Table 5.6-1 of Biomarker Sampling Schedule
PK and Immunogenicity Assessments				
PK samples	See note			See Table 5.5-1 of PK and Immunogenicity Sampling
Immunogenicity samples	See note			See Table 5.5-1 of PK and Immunogenicity Sampling

Table 5.1.1-2: On-Treatment Assessments for Cohorts A, B, and C (CA209205)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (240 mg Q2W or 480 mg Q4W [a]) on Day 1	Notes Dosing cycle = 240 mg Q2W or 480 mg Q4W
Outcomes Research Assessments				
EORTC QLQ-C30 & EQ-5D	X		See note	Assessments to be collected every 4 cycles for the first 17 cycles; Day 1 (prior to dosing) of Cycles 5, 9, 13, 17 every 6 cycles thereafter; Day 1 (prior to dosing) of Cycles 23, 29, 35+.
B Symptoms	X		See note	Assessments to be collected every 4 cycles for the first 17 cycles; Day 1 (prior to dosing) of Cycles 5, 9, 13, 17. Every 6 cycles thereafter; Day 1 (prior to dosing) of Cycles 23, 29, 35+, and when subjects achieve first PR or first CR after initiation of the study drug. If subjects with previous PR attain CR, B symptoms should be collected again at CR.
Clinical Drug Supplies				
Administer Study Drug	X		X	IVRS should be called within 1 day prior to study drug administration to receive vial assignment.

[a] **Per revised protocol 04c**, subjects will switch to 480 mg flat dose Q4W or 240 mg flat dose Q2W as an IV infusion over 30 minutes. Subjects must sign an informed consent document prior to switching the dosing schedule.

Table 5.1.1-3: Follow-Up Assessments for Cohorts A, B, and C (CA209205)

Procedure	X, Follow-Up,[a] Visits 1 and 2	S, Survival Follow-Up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver). To assess for potential late emergent study drug-related issues
Adverse Events Assessment	X	X	NSAEs and SAEs must be collected up to 100 days after study drug discontinuation. SAEs related to any later protocol-specified procedure must be collected.
Laboratory Tests	X		CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
Thyroid Function Testing	X		TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test	X		Serum or urine (WOCBP only)
GVHD Assessments	See note	See note	Only for subjects who discontinued study therapy by proceeding to allogeneic SCT. To be assessed on Day 100, at 6 months, at 1 year and every one year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented. See Section 5.3.
Efficacy Assessments			
Radiographic Tumor Assessment CT or MRI FDG-PET Scan	See note	See note	See Table 5.4.1.1-1 and Table 5.4.1.1-2 for CT or MRI and FDG-PET scan schedule and also Section 4.5.7.4 for those subjects who discontinue study drug after treatment beyond progression.
Tumor Assessment by the Investigator (CR or non-CR)	See note	See note	Only for subjects who discontinued study therapy by proceeding to allogeneic SCT or ASCT. To be assessed on Day 100, at 6 months, at 1 year and every one year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented.

Table 5.1.1-3: Follow-Up Assessments for Cohorts A, B, and C (CA209205)

Procedure	X, Follow-Up,[a] Visits 1 and 2	S, Survival Follow-Up Visits[b]	Notes
			See Section 5.4
Outcomes Research Assessments			
EORTC QLQ-C30	X		
EQ-5D	X	X	EQ-5D during the survival follow-up will be assessed during a clinic visit or via a phone contact
Exploratory Biomarker Testing			
Serum	See note		Collection of these biomarker samples at time of progression is optional. See Table 5.6-1of Biomarker Sampling Schedule.
Whole Blood			
Tumor Biopsy			
Bone Marrow Aspirate			
Subject Status			
Survival Status	X	X	Survival follow-up, every 3 months after X02 may be accomplished by visit or phone contact to update survival information and assess subsequent anti-cancer therapy.

[a] X visits occur as follows: X01 = 35 days ± 7 days from last dose, X02 = 80 days ± 7 days from X01

[b] S, Survival visits continue every 3 months after X visit

Table 5.1.1-4: Follow-Up Assessments for Cohort C Subjects who Discontinued due to CR (CA209205) or After Re-Initiation of Nivolumab

Procedure	X, Follow-Up, Visits 1 and 2[a]	FU/Observational visits[b]	S, Survival Follow-Up Visits[c]	Notes
Safety Assessments				
Targeted Physical Examination	X	X		Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver)
Adverse Events Assessment	See notes			NSAEs and SAEs must be collected during X01, X02 and FU/Observational visits for a maximum of 2 years and a minimum of 100 days after last dose. After, only SAEs related to study procedures must be collected.
Laboratory Tests	X	X		During X01 and X02 visits: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. During observation follow-up visits, after X02: CBC with differential, BUN or serum urea level, serum creatinine, AST, ALT, total bilirubin
Thyroid Function Testing	X			TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test for WOCBP	X			Serum or urine (WOCBP only).
GVHD Assessments	See note	See note	See note	Only for subjects who proceed to allogeneic SCT. To be assessed on Day 100, at 6 months, at 1 year and every 1 year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented. See Section 5.3

Table 5.1.1-4: Follow-Up Assessments for Cohort C Subjects who Discontinued due to CR (CA209205) or After Re-Initiation of Nivolumab

Procedure	X, Follow-Up, Visits 1 and 2[a]	FU/Observational visits[b]	S, Survival Follow-Up Visits[c]	Notes
Efficacy Assessments				
Radiographic Tumor Assessment CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease		See note		CT (preferred) or MRI to be performed at time of first FU/Observational visit, 6 months (± 14 days) after study drug discontinuation, and if clinically indicated.
Tumor Assessment by the Investigator (CR or non-CR)	See note	See note	See note	Only for subjects who proceed to allogeneic SCT or ASCT. To be assessed on Day 100, at 6 months, at 1 year and every 1 year thereafter from the date of stem cell infusion until the first non-CR after SCT is
Outcomes Research Assessments				
EORTC QLQ-C30	X	X		
EQ-5D	X	X	X	EQ-5D during the survival follow-up will be assessed during a clinic visit or via a phone contact
Pharmacokinetic/Immunogenicity Assessments				
PK samples	X			
Immunogenicity samples	X			

Table 5.1.1-4: Follow-Up Assessments for Cohort C Subjects who Discontinued due to CR (CA209205) or After Re-Initiation of Nivolumab

Procedure	X, Follow-Up, Visits 1 and 2[a]	FU/Observational visits[b]	S, Survival Follow-Up Visits[c]	Notes
Exploratory Biomarker Testing				
Serum	See note	See note	See note	Collection of Biomarker samples at time of progression is optional. See Table 5.6-1 of Biomarker Sampling Schedule.
Whole Blood				
Tumor Biopsy				
Bone Marrow Aspirate				
Subject Status				
Survival Status	X	X	X	Survival follow-up, every 3 months after observation follow-up may be accomplished by visit or phone contact to update survival information and assess subsequent anti-cancer therapy.

[a] X visits occur as follows: X01 = 35 days ± 7 days from last dose, X02 = 80 days ± 7 days from X01

[b] First FU/Observational visit must occur 6 months (± 14 days) after study drug discontinuation, then at Month 9 (± 14 days), 12 (± 14 days), 16 (± 21 days), 20 (± 21 days), and 24 (± 21 days)

[c] S, Survival visits continue every 3 months after last FU/Observational visits

Table 5.1.1-5: Re-Initiation of Treatment Assessments for Cohort C subjects (CA209205)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (240 mg Q2W or 480 mg Q4W[a]) on Day 1	Notes Dosing cycle = 240 mg Q2W or 480 mg Q4W
Safety Assessments				
Targeted Physical Examination	X		X	Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver)
Vital Signs and Oxygen Saturation	X	X	X	Temperature, BP, HR, O2 saturation by pulse oximetry at rest and after exertion (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X	X	X	Includes Weight and ECOG performance status
Adverse Events Assessment	---------- Continuously ----------			Assessed using NCI CTCAE v. 4.0.
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Extended on-study local laboratory assessments should be done within 72 hours prior to dosing from Cycle 1 through Cycle 5 and every alternate dose thereafter (Cycles 7, 9, 11, 13, etc.) and include: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. Limited on-study local laboratory assessment should be done within 72 hours prior to dosing beginning at Cycle 6 and every alternate dose thereafter (Cycles 8, 10, 12, 14, etc.) and include: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Thyroid Function Testing			See note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 7 days) from first dose regardless of dosing schedule.
Pregnancy Test for WOCBP	X		See note	Serum or urine within 24 hours prior to first dose and then at least

Table 5.1.1-5: Re-Initiation of Treatment Assessments for Cohort C subjects (CA209205)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (240 mg Q2W or 480 mg Q4W[a]) on Day 1	Notes Dosing cycle = 240 mg Q2W or 480 mg Q4W
				once every 4 weeks (± 7 days) regardless of dosing schedule.
Efficacy Assessments				
Radiographic Tumor Assessment CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease FDG-PET Scan			See note	See Table 5.4.1.1-1 and Table 5.4.1.1-2 of CT or MRI and FDG-PET scan schedule and also Section 4.5.7.2 in case of treatment beyond progression.
Bone Marrow Aspirate and Biopsy	See note		See note	Bone Marrow Aspirate and Biopsy is optional. If it is done, Bone Marrow Aspirate sample can be optionally submitted for biomarker analysis. See Table 5.6-1 of Biomarker Sampling Schedule.
B Symptoms	X		See note	Assessments to be collected every 4 cycles for the first 17 cycles; Day 1 (prior to dosing) of Cycles 5, 9, 13, 17. Every 6 cycles thereafter; Day 1 (prior to dosing) of Cycles 23, 29, 35+, and when subjects achieve first PR or first CR after re-initiation of the study drug. If subjects with previous PR attain CR, B symptoms should be collected again at CR.
Additional Exploratory Biomarker Testing				
Serum Whole Blood Tumor Biopsy	See note		See note	See Table 5.6-1 of Biomarker Sampling Schedule
PK and Immunogenicity Assessments				
PK samples	See note			See Table 5.5-1 of PK and Immunogenicity Sampling

Table 5.1.1-5: Re-Initiation of Treatment Assessments for Cohort C subjects (CA209205)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (240 mg Q2W or 480 mg Q4W[a]) on Day 1	Notes Dosing cycle = 240 mg Q2W or 480 mg Q4W
Immunogenicity samples	See note			See Table 5.5-1 of PK and Immunogenicity Sampling
Clinical Drug Supplies				
Administer Study Drug	X		X	IVRS should be called within 1 day prior to study drug administration to receive vial assignment.

[a] **Per revised protocol 04c**, subjects will switch to 480 mg flat dose Q4W or 240 mg flat dose Q2W as an IV infusion over 30 minutes. Subjects must sign an informed consent document prior to switching the dosing schedule.

5.1.2 Time and Events Schedule for Cohort D

Table 5.1.2-1: Screening Procedural Outline Cohort D (CA209205)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Include Height, Weight, and ECOG performance Status
Hasenclever-Index for Hodgkin's Disease also known as IPS at Initial Diagnosis	X	Composite score, see Appendix 3.
Vital Signs and Oxygen saturation	X	Temperature, BP, HR, and O_2 saturation by pulse oximetry (at rest and after exertion).
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	Complete blood count (CBC) with differential, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, P, glucose, albumin, amylase, lipase, thyroid stimulating hormone (TSH) (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA) within 14 days prior to first dose.
Urinalysis	X	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH, within 14 days prior to first dose.

Table 5.1.2-1: Screening Procedural Outline Cohort D (CA209205)

Procedure	Screening Visit[a]	Notes
Pregnancy Test	X	For WOCBP only (serum or urine)
Pulmonary function test	X	To confirm that the diffusing capacity of the lung for carbon monoxide (DLCO) is over 60% (adjusted for hemoglobin)
ECG	X	
Cardiac function test	X	To confirm left ventricular ejection fraction is over 50% at rest by echocardiography or over 55% by isotopic measurement
Efficacy/Biomarker Assessments		
Radiographic Tumor Assessment	X	Must be performed within 28 days prior to first dose.
CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease (eg neck)		Additional sites of known or suspected disease (eg neck) should be imaged at the screening visit and at subsequent on-study assessments.
FDG-PET scan		FDG-PET scan required at screening.
Collection of tumor tissue	X	Submission of tumor tissue (FFPE tumor tissue block or a minimum of 15 unstained slides, preferably 20) from a biopsy performed during screening is mandatory. Alternatively, submission of tumor tissue from a biopsy performed within 90 days prior to enrollment is allowed. Biopsy samples should be excisional, incisional, or core needle. Tumor biopsies (FFPE) for IHC of tumor and TIL and RNALater for gene expression.
IVRS/Clinical Drug Supplies		
Phone calls to IVRS		Phone calls must be made to IVRS as follows: For subject cohort and number assignment at the time informed consent is obtained. Prior to dosing for study drug vial assignment (call should be made within 1 day prior to dosing).

[a] Within 28 days prior to first dose

Table 5.1.2-2: On-Treatment Assessments During Monotherapy Phase for Cohort D (CA209205)

Procedure	Monotherapy Dose 1 (Day 1)	Day 8 (after monotherapy dose 1)	Each Monotherapy Dosing (Every 2 Weeks)	Notes
Safety Assessments				
Targeted Physical Examination	X		X	Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver)
Vital Signs and Oxygen Saturation	X	X	X	Temperature, BP, HR, O2 saturation by pulse oximetry at rest and after exertion (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X	X	X	Includes Weight and ECOG performance status
Adverse Events Assessment	---------- Continuously ----------			Assessed using NCI CTCAE v. 4.0.
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Extended on-study local laboratory assessments include CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. Extended on-treatment local laboratory assessments should be done within 72 hours prior to dosing for: − Monotherapy dose 1 through Monotherapy dose 4 Extended on-treatment local laboratory assessments should also be done on Day 8 after Monotherapy dose 1
Thyroid Function Testing			See note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 7 days) from first dose regardless of dosing schedule.
Pregnancy Test for WOCBP	X		See note	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (± 7 days) regardless of dosing schedule.

Table 5.1.2-2: On-Treatment Assessments During Monotherapy Phase for Cohort D (CA209205)

Procedure	Monotherapy Dose 1 (Day 1)	Day 8 (after monotherapy dose 1)	Each Monotherapy Dosing (Every 2 Weeks)	Notes
Efficacy Assessments				
Radiographic Tumor Assessment CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease FDG-PET Scan			See note	See Table 5.4.1.2-1 and Table 5.4.1.2-2 of CT or MRI and FDG-PET scan schedule and also Section 4.5.7.2 in case of treatment beyond progression.
Additional Exploratory Biomarker Testing				
Serum Whole Blood Tumor Biopsy	See note		See note	See Table 5.6-2 of Biomarker Sampling Schedule
PK and Immunogenicity Assessments				
PK samples	See note			See Table 5.5-2 of PK and Immunogenicity Sampling
Immunogenicity samples	See note			See Table 5.5-2 of PK and Immunogenicity Sampling
Outcomes Research Assessments				
EQ-5D	X			Assessment to be collected on Day 1 (prior to dosing)
B Symptoms	X			Assessment to be collected on Day 1
Clinical Drug Supplies				
Administer Study Drug	X		X	IVRS should be called within 1 day prior to study drug administration to receive vial assignment.

Table 5.1.2-3: On-Treatment Assessments During Combination Phase for Cohort D (CA209205)

Procedure	Dose 1 of each Combo cycle (Day 1)	Dose 2 (Day 15) of Combo cycle 1	Dose 2 (Day 15) Beginning Combocycle 2 through Combocycle 6	Notes
Safety Assessments				
Targeted Physical Examination	X		X	Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver)
Vital Signs and Oxygen Saturation	X	X	X	Temperature, BP, HR, O2 saturation by pulse oximetry at rest and after exertion (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X	X	X	Includes Weight and ECOG performance status
Adverse Events Assessment	---------- Continuously ----------			Assessed using NCI CTCAE v. 4.0.
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Extended on-study local laboratory assessments include CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. Extended on-treatment local laboratory assessments should be done within 72 hours prior to dosing for: − Dose 1 (Day 1) of Combocycle 1 through Combocycle 6 − Dose 2 (Day 15) of Combocycle 1 Limited on-study local laboratory assessments includes CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine − Limited on-treatment local laboratory assessments should be done within 72 hours prior to dosing for Dose 2 (Day 15) of Combocycle 2 through Combocycle 6.

Table 5.1.2-3: On-Treatment Assessments During Combination Phase for Cohort D (CA209205)

Procedure	Dose 1 of each Combo cycle (Day 1)	Dose 2 (Day 15) of Combo cycle 1	Dose 2 (Day 15) Beginning Combocycle 2 through Combocycle 6	Notes
Thyroid Function Testing			See note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 7 days) from first dose regardless of dosing schedule.
Pregnancy Test for WOCBP	X		See note	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (± 7 days) regardless of dosing schedule.
Efficacy Assessments				
Radiographic Tumor Assessment CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease FDG-PET Scan			See note	See Table 5.4.1.2-1 and Table 5.4.1.2-2 of CT or MRI and FDG-PET scan schedule and also Section 4.5.7.2 in case of treatment beyond progression.
Additional Exploratory Biomarker Testing				
Serum Whole Blood Tumor Biopsy	See note		See note	See Table 5.6-2 of Biomarker Sampling Schedule
PK and Immunogenicity Assessments				
PK samples	See note			See Table 5.5-2 of PK and Immunogenicity Sampling
Immunogenicity samples	See note			See Table 5.5-2 of PK and Immunogenicity Sampling
Outcomes Research Assessments				
EQ-5D	X		See note	Assessment to be collected on Day 1 Combocycle 1 (prior to dosing), on Day 1 of Combocycle 3, and on Day 1 of Combocyle 5 during the Combination phase.
B Symptoms	X		See note	Assessments to be collected Day 1 (prior to dosing) of

Table 5.1.2-3: On-Treatment Assessments During Combination Phase for Cohort D (CA209205)

Procedure	Dose 1 of each Combo cycle (Day 1)	Dose 2 (Day 15) of Combo cycle 1	Dose 2 (Day 15) Beginning Combocycle 2 through Combocycle 6	Notes
				Combocycle 1, 3, and 5.
Clinical Drug Supplies				
Administer Study Drug	X	X	X	IVRS should be called within 1 day prior to study drug administration to receive vial assignment.

Table 5.1.2-4: Follow-Up Assessments for Cohort D (CA209205)

Procedure	X, Follow-Up,[a] Visits 1 and 2	FU/ Observational visits[b]	S, Survival Follow-Up Visits[c]	Notes
Safety Assessments				
Targeted Physical Examination	X	X		Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver).
Adverse Events Assessment	See Notes			NSAEs and SAEs must be collected during Follow-up visit 1 and Follow-up visit 2. Thereafter, SAEs related to any later protocol-specified procedure must be collected.
Laboratory Tests	X			During Follow-up visit 1 and Follow-up visit 2: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
Pulmonary Function Test	X			Test to be conducted 35 days (± 14 days) from the last dose of study therapy.
Thyroid Function Testing	X			TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test	X			Serum or urine (WOCBP only)
Efficacy Assessments				
End-of-therapy radiographic tumor assessments: FDG-PET CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease		See note		FDG-PET and CT (preferred) or MRI will be conducted at 9 weeks (± 14 days) from the last dose, which is between Follow-up visit 1 and Follow-up visit 2.
Radiographic Tumor Assessment End-of-therapy radiographic tumor assessments CT or MRI of Chest, Abdomen, Pelvis, and any other known sites of disease		See note		CT (preferred) or MRI is required at visit 04 (39 weeks from the last dose), 06 (65 weeks from the last dose), and 09 (104 weeks from the last dose).

Table 5.1.2-4: Follow-Up Assessments for Cohort D (CA209205)

Procedure	X, Follow-Up,[a] Visits 1 and 2	FU/ Observational visits[b]	S, Survival Follow-Up Visits[c]	Notes
Subsequent therapy information	See note	See note	See note	Only for subjects who have disease progression and undergo other anti-lymphoma treatment
Outcomes Research Assessments				
EQ-5D	X	X	X	EQ-5D during the survival follow-up will be assessed during a clinic visit or via a phone contact
B Symptoms	X			To be collected only at Follow-up visit 1
Pharmacokinetic/Immunogenicity Assessments				
PK Samples	X			See Table 5.5-2 of PK and Immunogenicity Sampling
Immunogenicity samples	X			See Table 5.5-2 of PK and Immunogenicity Sampling
Exploratory Biomarker Testing				
Serum	See note	See note	See note	Collection of Biomarker samples at time of progression is optional. See Table 5.6-2 of Biomarker Sampling Schedule.
Whole Blood				
Tumor Biopsy				
Subject Status				
Survival Status & subsequent anti-lymphoma therapies	X	X	X	Survival follow-up, every 6 months after observation follow-up may be accomplished by visit or phone contact to update survival information and assess subsequent anti-cancer therapy

[a] Follow-up visit 1 occurs 35 days ± 7 days from last dose and Follow-up visit 2 occurs 80 days ± 7 days from Follow-up visit.

[b] First FU/Observational visits (visit 03) will occur 26 weeks (± 21 days) after the last dose of study treatment, then approximately every 3 months (± 21 days): visit 04 (39 weeks), visit 05 (52 weeks), visit 06 (65 weeks), visit 07 (78 weeks), visit 08 (91weeks), and visit 09 (104 weeks).

[c] S, Survival visits continue every 6 months after last FU/Observational visits. Please note that this frequency is different from Cohorts A, B, and C.

5.1.3 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within any single Screening will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1.1-1 and Table 5.1.2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- Nivolumab IB
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of IVRS, including enrollment worksheet
- Manual for entry of local laboratory data
- Serious Adverse Events (or eSAE) case report forms
- EORTC QLQ-C30 and EQ-5D questionnaires
- Pregnancy Surveillance Forms
- CA209205 Imaging Manual.

5.3 Safety Assessments

5.3.1 Safety Assessments for Cohorts A, B, and C

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, BP, HR, temperature and oxygen saturation by pulse oximetry at rest and after exertion and should be performed within 28 days prior to first dose as described in Table 5.1.1-1 notes. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to first dose through the study treatment period. Additionally, medications which are used to treat AEs that are late emergent will be captured beyond the last dose for study treatment.

Baseline local laboratory assessments should be done within 14 days prior to first dose to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), uric acid,

BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, P, LDH, glucose, albumin, amylase, lipase, urinalysis, TSH, and Hep B and C testing (HBV sAg, HCV Ab or HCV RNA) (see Table 5.1.1-1). Pregnancy testing for WOCBP (done locally) must be performed at baseline (within 28 days prior to first dose) and repeated within 24 hours prior to the initial administration of study drug, then every 4 weeks (± 7 days) regardless of dosing schedule.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Follow-up visits X01 and X02, Table 5.1.1-3) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase either in person or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

Performance status and body weight should be assessed at each on study visit prior to nivolumab dosing and at Cycle 1 Day 8. Vital signs should also be taken as per institutional standard of care prior to, during, and after dosing. Oxygen saturation by pulse oximetry at rest and after exertion should be assessed at each on-study visit prior to nivolumab dosing. The start and stop time of the nivolumab infusion should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On treatment local laboratory assessments should be done within 72 hours prior to dosing;

- **Extended on-treatment local laboratory assessments**: Cycle 1 through Cycle 5 and every alternate dose thereafter (Cycle 7, 9, 11, 13, etc) and include: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
- **Limited on-study treatment laboratory assessment**: beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14, etc) and include: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.

In addition, TSH (with reflexive Free T4 and Free T3) should be performed every 6 weeks (± 7 days) from first dose regardless of dosing schedule.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug-related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dose of nivolumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related

signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the BMS-936558 (nivolumab) IB.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

For subjects who discontinue study therapy by proceeding to allogeneic SCT, documentation of acute and chronic GVHD will be captured 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 [Appendix 5]. Investigators will make telephone contact with the subject's hematologist /oncologist /transplant physician to obtain this information if the subject is being followed by another physician.

When Cohort C subjects discontinue study therapy due to persistent one year CR, they will enter the Follow-up Phase. Targeted physical examination and laboratory tests will be conducted during FU/Observational visits (Table 5.1.1-4). NSAEs and SAEs must be collected during the safety follow-up visits (X01 and X02) and FU/Observational visits for a maximum of 2 years and minimum of 100 days after last dose, after, only SAEs related to study procedures must be collected. These assessments should be done in person. Once subjects complete the FU/Observational phase and reach the survival follow-up phase, either in person or documented telephone calls to assess the subject's status are acceptable. In the event of study drug re-initiation after relapse, subjects will have safety assessments as described in Table 5.1.1-5.

5.3.2 Safety Assessments for Cohort D

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, BP, HR, temperature and oxygen saturation by pulse oximetry at rest and after exertion and should be performed within 28 days prior to first dose as described in Table 5.1.2-1 notes. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to first dose through the study treatment period. Additionally, medications which are used to treat AEs that are late emergent will be captured beyond the last dose for study treatment.

Only for Cohort D, evaluation for pulmonary functions test will be required during screening and at the end of therapy. Evaluation of cardiac function by echocardiography or nuclear medicine scan, and ECG will be required during screening.

Baseline local laboratory assessments should be done within 14 days prior to first dose to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), uric acid, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, P, LDH, glucose, albumin, amylase,

lipase, urinalysis, TSH, and Hep B and C testing (HBV sAg, HCV Ab or HCV RNA) (see Table 5.1.2-1). Pregnancy testing for WOCBP (done locally) must be performed at baseline (within 28 days prior to first dose) and repeated within 24 hours prior to the initial administration of study drug, then every 4 weeks (± 7 days) regardless of dosing schedule.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Follow-up visits 01 and 02, Table 5.1.2-4) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase either in person or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

Performance status and body weight should be assessed at each on study visit prior to nivolumab dosing and also on Day 8 after monotherapy dose 1. Vital signs should also be taken as per institutional standard of care prior to, during, and after dosing. Oxygen saturation by pulse oximetry at rest and after exertion should be assessed at each on-study visit prior to nivolumab dosing. The start and stop time of the nivolumab infusion should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On treatment local laboratory assessments should be done within 72 hours prior to dosing.

- **Extended on-treatment local laboratory assessments**: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.

  Extended on-treatment local laboratory assessments are required at the following time points:

  – Monotherapy dose 1 through monotherapy dose 4
  – Day 8 after monotherapy dose 1
  – Dose 1 (Day 1) of Combocycle 1 through Combocycle 6
  – Dose 2 (Day 15) of Combocycle 1
- **Limited on-study treatment laboratory assessment**: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.

  Limited on-treatment local laboratory assessments are required at the following time points:

  – Dose 2 (Day 15) of Combocycle 2 through Combocycle 6

In addition, TSH (with reflexive Free T4 and Free T3) should be performed every 6 weeks (± 7 days) from first dose regardless of dosing schedule.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug-related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dose of nivolumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the BMS-936558 (nivolumab) IB.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Cohort D, subject who completes Dose 2 (Day 15) of Combocycle 6, or subject who is discontinued from study therapy during the combination phase, enter FU/observational phase. Targeted physical examination will be conducted during Safety follow-up visits 1 &2 and FU/Observational visits (Table 5.1.2-4), laboratory tests will be performed during Safety follow-up visits 1 &2.

Laboratory Assessment after Completion of Treatment:

- **During Safety Follow up 01 and 02 visits:**
  CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.

NSAEs and SAEs must be collected during the Safety Follow-up visits 1 and 2. All SAEs that occur during the screening period and within 100 days of discontinuation of dosing must be collected. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

5.3.3 Imaging Assessment for the Study

Images will be submitted to an imaging corelab for central review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209205 Imaging Manual to be provided by the corelab.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.4 Efficacy Assessments

For Cohorts A, B, and C, the primary efficacy assessment is ORR, defined as a subject achieving either a PR or CR according to the revised International Working Group Criteria for Malignant Lymphoma (Appendix 2).

For Cohort D, efficacy assessment is conducted according to 2007 IWG criteria (Appendix 2). Additional assessments, for example, Deauville scoring, may also be performed.

The primary efficacy assessment, along with the secondary endpoints of DOR, complete and partial remission rates and durations will be based on IRRC assessments. Assessment of ORR, based on investigator assessments, will be examined as a secondary endpoint. Sites are required to send all on-study disease assessments to the IRRC for review.

For Cohorts A, B, and C, once subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo IRRC- radiographic assessments as described in Table 5.4.1.1-1 and Table 5.4.1.1-2. 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.

For Cohort C subjects, relapse after discontinuation of study therapy due to persistent one year CR will be determined by 2007 IWG criteria.

5.4.1 Radiographic Assessments

5.4.1.1 Radiographic Assessments for Cohorts A, B, and C

Radiographic study evaluations will take place in accordance with the flow charts in Section 5.1 and Table 5.4.1.1-1 and Table 5.4.1.1-2. Baseline assessments should be performed within 28 days prior to the first dose, utilizing CT (preferred) or MRI. In addition to chest, abdomen, and pelvis, all known sites of disease should be assessed at baseline. A baseline FDG-PET scan is required at screening.

On-study assessments should include chest, abdomen, and pelvis, and all known sites of disease (eg neck) and should use the same imaging method as used at baseline.

Subjects will be evaluated for tumor responses by CT (preferred) or MRI at Week 9 (± 7 days) after the start of therapy and then at Weeks 17, 25, 37 and 49 during the first year of treatment, then every 16 weeks (± 14 days) up to Week 97, continuing every 26 weeks (± 21 days) beyond Week 97, until disease progression is documented, or until the subject initiates a preparative regimen for allogeneic SCT or ASCT, whichever occurs earlier. On-treatment FDG-PET scan will be required for all subjects 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 time points where FDG-PET is not otherwise scheduled; this FDG-PET scan should be performed within 4 weeks of a CT scan.

Tumor assessments for ongoing study treatment decisions will be completed by the investigator using 2007 IWG criteria (Appendix 2).

Table 5.4.1.1-1: Schedule of CT or MRI Tumor Assessments for Cohorts A, B, and C

Time On Study	Assessment Frequency	Assessment Week (Day 1 of Week Shown)	Assessment Window
Baseline	Once	Screening	Within 28 days prior to first dose[a]
Until Week 49	-	9, 17, 25, 37, 49	± 7 days
Between Week 50 and Week 97	Every 16 weeks	65, 81, 97	± 14 days
Beyond Week 97	Every 26 weeks	123, 149, 175+	± 21 days
Cohort C subjects, 1 year after first CR confirmation	Once	-	± 14 days[b]

[a] For Cohort C subjects who re-initiate treatment, the CT scan used to confirm relapse will serve as new baseline scan, study drug should then be re-initiated within 28 days

[b] Not required if a scheduled CT or MRI was performed within 8 weeks of the date of first confirmed CR plus 1 year

Note: Once subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo IRRC radiographic assessments described here, but will be followed with specific schedule (see Section 5.4).

Table 5.4.1.1-2: Schedule of FDG-PET Tumor Assessments for Cohorts A, B, and C

	Assessment Week (Day 1 of Week Shown)	Assessment Window
All subjects	Screening	Within 28 days prior to first dose
All subjects	17	± 7 days
All subjects	25	± 7 days
Subjects who do not have two consecutive negative FDG-PET scans after Week 1 and prior to Week 49	49	± 7 days
Confirmation of the first CR after initiation of the study drug	Other time points	Within 4 weeks of CT

Note: Once subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo IRRC radiographic assessments described here but will be followed with specific schedule (see Section 5.4).

When Cohort C subjects discontinue study therapy due to persistent one year CR, CT (preferred) or MRI will be required for CR confirmation as described in Table 5.4.1.1-1. These subjects will then require CT (preferred) or MRI at the time of the first FU/Observational visit: 6 months (± 14 days) from last dose of study drug, or if clinically indicated (ie clinical evidence of relapse).

Relapse will be determined using 2007 IWG criteria, the CT (preferred) or MRI used for relapse assessment will serve as new baseline in case of re-initiation of study drug. A new set of target and non-target lesions will be defined and subsequent response assessment during re-initiation of treatment will be based on this new set.

5.4.1.2 Radiographic Assessments for Cohort D

Radiographic study evaluations will take place in accordance with the flow charts in Section 5.1, Table 5.4.1.2-1 and Table 5.4.1.2-2 and as shown in Figure 5.4.1.2-1. Baseline assessments should be performed prior to the first dose, utilizing CT (preferred) or MRI. In addition to chest, abdomen, and pelvis, all known sites of disease should be assessed at baseline. A baseline FDG-PET scan is also required at screening.

On-study assessments should include chest, abdomen, and pelvis, and all known sites of disease (eg, neck) and should use the same imaging method as used at baseline. Tumor assessments for ongoing study treatment decisions will be completed by the investigator using 2007 IWG criteria (Appendix 2).

The first scheduled on-treatment radiographic assessments are FDG-PET scans and CT (preferred) or MRI after Monotherapy dose 4. FDG-PET scans should be scheduled at least 4 days before the start of Combocycle 1 (4 days excluding the day of subsequent cycle). CT (preferred) or MRI can be performed anytime between the monotherapy Dose 4 and first Combocycle dose.

The subjects who have early discontinuation of nivolumab during monotherapy phase and who enter combination phase will require the following end-of-monotherapy radiographic assessments before starting the combination treatment.

- CT (preferred) or MRI will be required if previous assessment was conducted > 4 weeks ago.
- FDG-PET scan will be required if previous assessment was conducted > 4 weeks ago.

The second scheduled on-treatment radiographic assessments are **post-Combocycle 2** FDG-PET scan, and CT (preferred) or MRI after Combocycle 2 and before Combocycle 3. This interim FDG-PET scan is optional if a previous scheduled or unscheduled FDG-PET scan after the first dose was negative based on investigator's assessment. This interim PET study should be scheduled at least 4 days before the start of Combocycle 3 (4 days excluding the day of subsequent cycle). CT (preferred) or MRI can be performed anytime after Combocycle 2 and before Combocycle 3.

The end-of-therapy radiographic assessments should be conducted at **9 weeks (± 14 days) from the last dose,** which is between Follow-up visit 1 and Follow-up visit 2. End-of-therapy FDG-PET, and CT (preferred) or MRI scans are mandatory for all subjects. When end-of-therapy FDG-PET scans are positive based on investigator's assessment, tumor biopsy for an FDG-avid lesion is strongly encouraged whenever possible. Tumor biopsy for an FDG-avid lesion in other situation is also permitted if clinically indicated

After the end-of-therapy radiographic assessments, CT (preferred) or MRI are required at visit 04 (39 weeks from the last dose), visit 06 (65 weeks from the last dose), and visit 09 (104 weeks from the last dose), during the first two years from the last dose (Table 5.4.1.2-1). Thereafter, no radiographic tumor assessment will be required.

Additional FDG-PET and CT (preferred) or MRI can be conducted when clinically indicated. All scans for radiographic tumor assessments while on study will be collected and be evaluated by IRRC.

Figure 5.4.1.2-1: Cohort D - Radiographic Assessment Schedule (Treatment Phase)

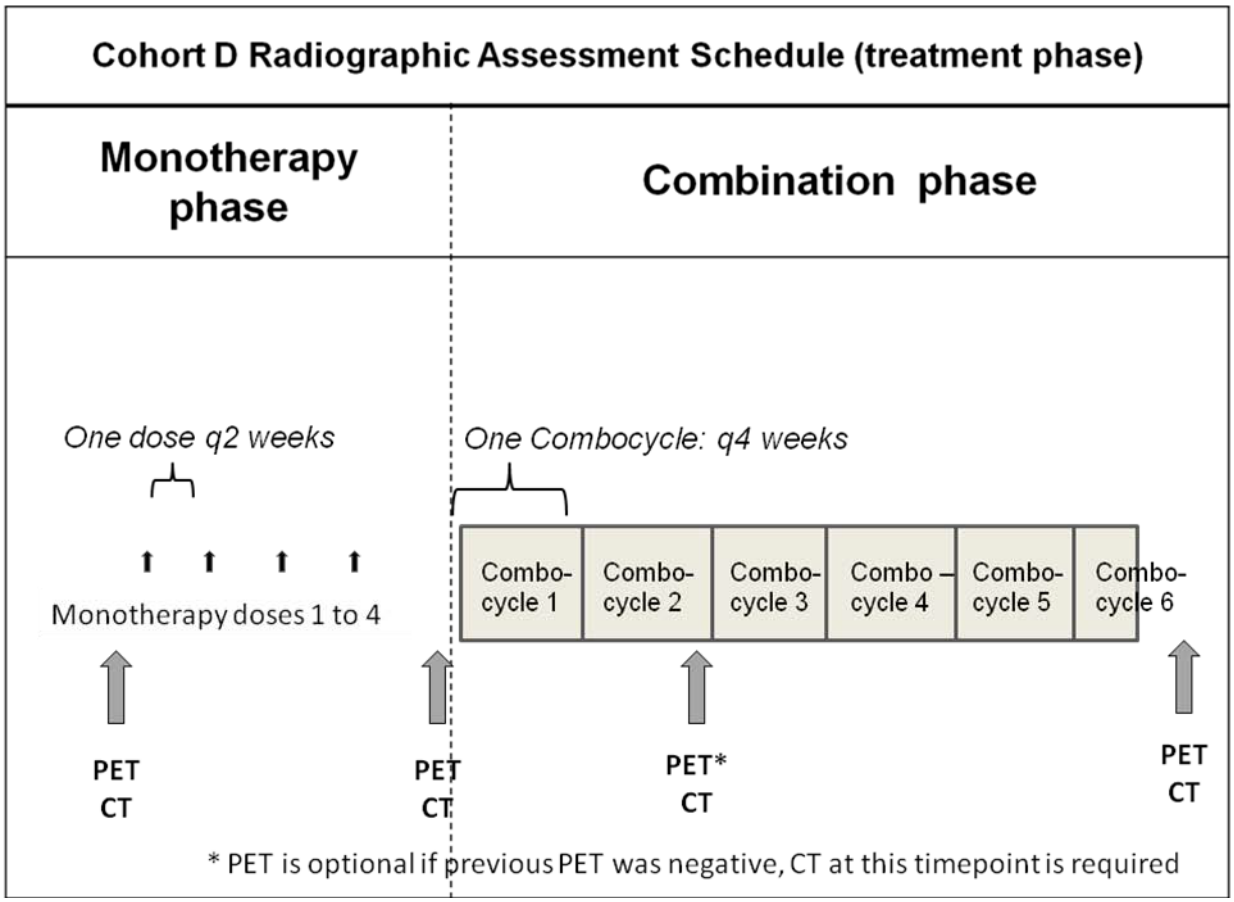


Table 5.4.1.2-1: Schedule of CT (or MRI) Tumor Assessment for Cohort D

Time point	Population	Assessment timing	Assessment Window
Baseline	All subjects	Screening	Within 28 days prior to first dose
End-of-monotherapy assessments when four nivolumab monotherapy doses are not completed[a]	Only subjects who have early discontinuation of nivolumab monotherapy during monotherapy phase and who enter combination phase	at the end of monotherapy	anytime between the last monotherapy dose and first Combocycle dose
Post-Monotherapy dose 4 assessments	All subjects who completed 4 doses of nivolumab monotherapy	after monotherapy dose 4 and before entering combination phase	anytime between the monotherapy dose 4 and first Combocycle dose
Post-Combocycle 2 assessments	All subjects who have completed Combocycle 2	after Combocycle 2 and before Combocycle 3	anytime between Combocycle 2 and Combocycle 3
End-of-therapy radiographic assessments	All subjects	9 weeks from the last dose, which is between Follow-up visit 1 and Follow-up visit 2.	± 14 days
FU/Observational visit 04 (39 weeks)	All subjects	39 weeks from the last dose	± 21 days
FU/Observational visit 06 (65 weeks)	All subjects	65 weeks from the last dose	± 21 days
FU/Observational visit 09 (104 weeks)	All subjects	104 weeks from the last dose	± 21 days

[a] CT (preferred) or MRI will be required if previous assessment was conducted > 4 weeks ago.

Table 5.4.1.2-2: Schedule of FDG-PET Tumor Assessments for Cohort D

Time point	Population	Assessment timing	Assessment Window
Baseline	All subjects	Screening	Within 28 days prior to first dose
End-of-monotherapy assessments when four nivolumab monotherapy doses are not completed.[a]	Only subjects who have not completed 4 dose of nivolumab monotherapy, and who enter Combination phase	at the end of monotherapy	anytime between the last monotherapy dose and first Combocycle dose. Preferably at least 10 days after last monotherapy dose
Post-Monotherapy dose 4 assessments	All subjects who completed 4 doses of nivolumab monotherapy	after monotherapy dose 4 and before entering Combination phase	After monotherapy Dose 4 and at least 4 days prior to first Combocycle dose (4 days excluding the day of subsequent cycle)
Post-Combocycle 2 assessments[b]	All subjects who have completed Combocycle 2	after Combocycle 2 and before Combocycle 3	At least 4 days before the start of Combocycle 3 (4 days excluding the day of subsequent cycle).
End-of-therapy radiographic assessments	All subjects	nine weeks from the last dose, which is between Follow-up visit 1 and Follow-up visit 2.	± 14 days

a FDG-PET scan will be required if a previous assessment was conducted > 4 weeks ago.

b Post-Combocycle 2 PET scan is optional if previous PET was negative

5.4.2 Assessment of Overall Tumor Burden and Measurable Disease

To serially evaluate tumor response to therapy, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows in Sections 5.4.2.1 and 5.4.2.2.

5.4.2.1 Measurable Lesions

Measurable lesions must be accurately measured in at least two perpendicular dimensions based on 2007 IWG criteria.[89] The following lesions should be considered as measurable lesions.

- Lesion(s) with the long axis > 15 mm regardless of the short axis, and
- Lesion(s) with the long axis 11 - 15 mm and with short axis > 10 mm.

Please note that, to be eligible for this study, a subject must have at least one lesion that is > 15 mm (1.5 cm) in the longest diameter on cross-sectional imaging and measureable in two perpendicular dimensions on CT (or MRI). Refer to inclusion criteria Section 3.3.1.

If possible, nodes or masses should be from disparate regions of the body and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

5.4.2.2 Non-Measurable Lesions

All other lesions, including small lymph nodes (longest diameter < 10 mm) as well as truly non-measurable lesions.

Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

5.4.3 Specifications by Method of Assessment

5.4.3.1 Measurement of Lesions

All measurements should be recorded in mm. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of treatment.

5.4.3.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical

5.4.3.3 CT or MRI Scan

CT or MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT or MRI scan is based on the assumption that CT or MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Note on PET/CT scans: Combined modality scanning such as with PET/CT is increasingly used in clinical care. Low dose or attenuation correction CT portions of a combined PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based measurements. However, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for measurements.

5.4.3.4 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. As previously noted, when lesions can be evaluated both by clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed by the IRRC.

5.4.3.5 FDG-PET scan

For Cohorts A, B, and C, a baseline FDG-PET scan is required for each treated subject at screening (within 28 days prior to first dose) 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 time points where FDG-PET is not otherwise scheduled; this FDG-PET scan should be performed within 4 weeks of a CT scan.

For Cohort D, a baseline FDG-PET scan is required for each treated subject at screening (within 28 days prior to first dose). Two interim FDG-PET scans are planned: post-monotherapy dose 4 and post-Combocycle 2. The interim FDG-PET scan post-monotherapy dose 4 is required for each treated subject while the interim FDG-PET scan post-Combocycle 2 is optional if a previous scheduled or unscheduled FDG-PET scan after the first dose was negative based on the investigator's assessment. These interim PET studies should be scheduled at least 4 days before the start of the subsequent cycle (4 days excluding the day of subsequent cycle). The end-of-therapy FDG-PET should be conducted 9 weeks (± 14 days) from the last study treatment.

5.4.4 Baseline Documentation of "Target" and "Non-Target" Lesions

5.4.4.1 Target Lesions

At baseline, up to 6 of the largest dominant nodes or nodal masses meeting the criteria for measurable lesions given in Section 5.4.2.1 should be identified as target lesions and their measurements recorded.

Target lesions should be selected according to the definitions of abnormal lesion in 2007 IWG criteria.

- Lesion(s) with the long axis > 15 mm regardless of the short axis, or
- Lesion(s) with the long axis 11 to 15 mm and with short axis > 10 mm.

Other measurable lesions will be designated as non-target lesions.

A sum of the product of the diameters (SPD) will be calculated for all target lesions and recorded as the baseline SPD. The baseline SPD will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

5.4.4.2 Non-Target Lesions

All other lesions (or sites of disease) including non-measurable lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or multiple liver nodules').

5.4.5 Bone Marrow Assessments

To determine the extent of disease involvement of the bone marrow, a bone marrow biopsy/aspirate performed at screening or within 90 days prior to enrolment must be documented. Subjects may start the study drug before bone marrow biopsy results become available; results must be documented in the subject's medical record when becoming available.

If a bone marrow biopsy/aspirate needs to be performed during the screening period, an aspirate sample for biomarker analyses as per Table 5.6-1 must be submitted.

For subjects with marrow involvement at screening, a bone marrow biopsy and aspirate will be required to confirm a CR, and submission of bone marrow aspirate samples is mandatory as detailed in Table 5.6-1.

For Cohorts C and D, FDG-PET at baseline can be used in lieu of a bone marrow biopsy/ aspirate. No evidence of FDG-avid disease in the bone marrow will be required to confirm CR for all subjects regardless of FDG-PET results in the bone marrow at baseline.

5.4.6 Disease Response Evaluation

The determination of disease response to study treatment will be made using 2007 IWG criteria (Appendix 2).

For Cohorts C and D, bone marrow assessment will be based on 2014 Lugano classification in which FDG-PET can be used in lieu of bone marrow aspirate/ biopsy.[90]

The 2007 IWG criteria define relapsed disease or progressive disease based largely on the evaluation of nodal masses, spleen/liver, and bone marrow (Appendix 2). The criteria also stipulate that disease that is only assessable but not measureable (eg, pleural effusion or bone lesion) will be recorded as "present" or "absent", unless such an assessable abnormality, noted by imaging studies or physical examination, is confirmed to be histologically negative. For purposes of protocol-defined disease progression, the appearance of new sites of assessable but not measureable disease while on treatment meets protocol criteria for disease progression if histological results are documented (eg, the presence of lymphoma cells in a pleural effusion or spinal fluid).

Immunotherapeutic agents produce atypical clinical response patterns which are not usually observed in conventional chemotherapy. Two distinct non-conventional patterns have been reported: a reduction in total tumor burden despite of the appearance of new lesion(s), and

responses after a transit increase in total tumor burden in an initial phase, followed by subsequent tumor shrinkage.[91] These two patterns have also been recognized in the subjects who were treated with nivolumab monotherapy in the CA209039 Phase 1 study (Figure 1.4.3.4-1). Therefore, appearance of new lesions during nivolumab monotherapy may not necessarily indicate true disease progression although this should be reported as disease progression according to 2007 IWG criteria for all four cohorts in this study.

5.5 Pharmacokinetic Assessments

Samples for pharmacokinetic and immunogenicity assessments will be collected for all subjects receiving nivolumab. Table 5.5-1 lists the sampling schedule to be followed for pharmacokinetics and immunogenicity for Cohorts A, B, and C. Table 5.5-2 lists the sampling schedule to be followed for pharmacokinetics and immunogenicity for Cohort D. All time points are relative to the start of nivolumab infusion. All on-treatment PK time points are intended to align with days on which nivolumab is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. Further details of blood collection and processing will be provided in the procedure manual.

Table 5.5-1: Sampling Schedule for Cohorts A, B, and C

Study Day[a]	Event	Time (Relative to Start of Nivolumab Infusion) Hour: Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 1	predose[a]	00:00	X	X
Cycle 3 Day 1	predose[a]	00:00	X	X
Cycle 7 Day 1	predose[a]	00:00	X	X
Cycle 13 Day 1	predose[a]	00:00	X	X
Day 1 of every 12th cycle up to Cycle 49	predose[a]	00:00	X	X

[a] Predose samples should be taken just prior to the start of Nivolumab infusion (preferably within 30 minutes, however predose collection up to 4 hours before study drug administration would be acceptable). If the infusion is delayed and a predose sample was already collected, there is no need to collect an additional predose sample.

Table 5.5-2: Sampling Schedule for Cohort D

Study Day	Event	Time (Relative to Start of Nivolumab Infusion) Hour: Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Monotherapy Dose 1	Predose[b]	00:00	X	X
Monotherapy Dose 3	Predose[b]	00:00	X	X
Combocycle 1 Day 1[a]	Predose[b]	00:00	X	X
Combocycle 4 Day 1	Predose[b]	00:00	X	X
First 2 Follow-up Visits FU1 & FU2			X	X

[a] For subjects who discontinue nivolumab monotherapy before the end of monotherapy dose 4, blood samples for nivolumab will be collected at the start of combination cycle.

[b] Predose samples should be taken just prior to the start of Nivolumab infusion (preferably within 30 minutes, however predose collection up to 4 hours before study drug administration would be acceptable). If the infusion is delayed and a predose sample was already collected, there is no need to collect an additional predose sample.

5.5.1 Pharmacokinetic Sample Analysis

Serum samples will be analyzed for nivolumab concentrations by a validated method. In addition, selected samples may be analyzed by an exploratory analytical method that measures nivolumab for technology exploration purposes; exploratory results will not be reported.

5.6 Biomarker Assessments

Peripheral blood and tumor tissue will be collected prior to therapy and at selected time points on treatment as outlined in Table 5.6-1 for Cohorts A, B, and C and Table 5.6-2 for Cohort D, unless restricted by local requirements.

Tumor Biopsy

Minimum of 1 FFPE tumor tissue block (preferred) OR minimum of 10 FFPE unstained sections are required for assessment of PD-L1 status and other biomarker evaluations. For Cohort D, a minimum of 15 unstained slides, preferably 20, is required.

Tumor samples obtained from bone metastases are not considered acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step. For any cases where the only tumor tissue available is from a bone metastasis lesion, please discuss further with the study Medical Monitor.

Exploratory Analysis for Tumor Biopsy during Nivolumab Monotherapy in Cohort D (Optional)

In order to assess the immune response to nivolumab therapy, patients will undergo tumor biopsies during screening and, optionally, at any time during the monotherapy phase (ideally, approximately 3 weeks following the initiation of nivolumab monotherapy) if the procedure is deemed as safe by investigators. Tumor biopsies can be either excisional, incisional, or core needle. Excisional or incisional biopsies are encouraged whenever possible. **In addition to preparing a FFPE tumor tissue block or 15 unstained slides per standard protocols, the remaining tumor biopsy specimen should be sent en bloc in media on ice.** Please refer to laboratory manual for the shipping address and procedural details. Viable tumor cell suspensions will be prepared for comprehensive CyTOF analysis and single cell RNAseq. The receiving laboratory should be contacted on the day before the planned biopsy procedure regarding the planned shipment. Please note that submission of tumor tissue (FFPE tumor tissue block or a minimum of 15 unstained slides, preferably 20, per standard protocols) from a biopsy performed during screening, or within 90 days prior to enrollment is still mandatory for all subjects of Cohort D.

Bone Marrow Aspirates

For Cohorts A and B, samples from bone marrow aspirates performed at screening and during CR evaluation (only for subjects who had marrow involvement at study entry) must be submitted for biomarker assessment. These will be utilized to assess the phenotypic and functional status of immune cells and tumor cells.

In all cohorts, for subjects who had bone marrow biopsies performed at any time during therapy, if clinically indicated, submission of the bone marrow aspirates is strongly encouraged.

Bone marrow aspirates will be obtained using institutional standards for these procedures.

A schedule of biomarkers evaluations is provided in Table 5.6-1.

Soluble Biomarkers

Soluble factors, such as cytokines, chemokines, soluble receptors, and antibodies to tumor antigens will be characterized and quantified by immunoassays in serum. Analyses may include, but not necessarily be limited to, soluble CD25, soluble PD-1, soluble LAG-3, and CXCL-9. Collected serum samples will also be used for the assessment of tumor antigen-specific responses elicited following treatment with study therapy to explore which antitumor antibodies are most associated with clinical response. Antibody levels to cancer test antigens will be assessed by multiplex assays and enzyme-linked immunosorbent assay (ELISA).

Immunophenotyping of PBMC and Bone Marrow Aspirates

The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory markers in PBMC preparations will be quantified by flow cytometry. Analyses may include, but not necessarily be limited to, the proportion of T, B, and NK cells, proportion of memory and effector T cell subsets, and expression levels of PD-1, PD-L1, PD-L2, ICOS, and Ki67.

Ex vivo Functional Assays

To explore whether nivolumab will restore T cell activation and function, PBMCs will be isolated and cryopreserved. Assays of the functional status of effector T cells will be performed, including but not limited to, assays for IFN-γ and CD107.

Peripheral Blood Gene Expression

The expression level of genes and miRNA related to response to nivolumab monotherapy will be quantified molecular methods such as Affymetrix by microarray and/or quantitative RT-PCR analysis in whole blood samples. Analysis may include, but not necessarily be limited to, genes associated with immune-related pathways, such as T cell activation and antigen processing and presentation.

T cell Repertoire Analysis

Low diversity of the peripheral T cell compartment has been shown to correlate with poor OS in metastatic breast cancer. A standing theory in immuno-oncology suggests a diverse and activated immune environment is better adept at eradicating tumor compared to a skewed repertoire of naïve and tolerized T cells. In order to explore whether a diverse T cell repertoire is predictive of response to therapy, next generation, high-throughput, Deoxyribonucleic acid (DNA) sequencing will be performed on DNA isolated from peripheral blood and tumor tissue to quantitate the composition of the T cell repertoire prior to, and during, monotherapy.

SNP Analysis

In order to identify potential polymorphisms associated with safety and efficacy of nivolumab, selected genes will be evaluated for single nucleotide polymorphisms (SNP). Analysis will be limited to sequence polymorphisms linked to genes associated with the PD-1/PD-L1 pathway and activated T cell phenotype, including PD-1, PD-L1, PD-L2, and CTLA-4. A blood sample will be obtained at Day 1, unless restricted by local requirements.

Tumor-Based Biomarker Measures

Tumor biopsy specimens will be obtained from consenting subjects prior to nivolumab to characterize immune cell populations and expression of selected tumor markers. Submission of tumor biopsy is mandatory for subjects with accessible lesions prior to therapy and on-treatment biopsy samples are optional.

Submission of tumor tissue from a biopsy performed during screening is mandatory for biomarker analysis. If this is not possible, archival tissue from a previous biopsy can be used.

For subjects who had tumor biopsies performed at any time during therapy, if clinically indicated, submission of the biopsy samples is strongly encouraged.

Biopsy samples may be used for the following assessments:

Characterization of TILs and tumor antigens IHC will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within

FFPE tumor tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.

Characterization of tumor genotype and phenotype

Gene mutations, chromosomal translocations, aberrant expressions, and epigenetic modifications within tumor cells will be characterized and explored by IHC and RNA/DNA analysis of tumor biopsies. Associations of altered tumor cell genetic structure with nivolumab efficacy will be performed.

Characterization of T cell repertoire

As described above, DNA sequencing will be performed on pre- and post treatment tumor tissue to assess the composition of the T cell repertoire. DNA will be isolated from either the FFPE tumor block or from RNAlater or equivalent preparations.

Gene expression profiling

Tumor biopsies that are collected in RNAlater or equivalent fixative will be examined for mRNA and miRNA gene expression by Affymetrix gene array technology and/or quantitative real-time polymerase chain reaction (qPCR) to detect expression of selected immune-related genes and regulatory pathways.

Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate procedure manual at the time of study initiation.

Plasma samples

Plasma samples will be collected for subjects in Cohorts C and D for, but not limited to, the determination of Minimal Residual Disease (MRD). For this purpose, novel sequencing-based methods can detect circulating tumor DNA (ctDNA) in plasma isolated from whole blood of subjects with great sensitivity which opens new opportunities for molecular monitoring before, during, and after therapy. Beyond monitoring, ctDNA can also be used as a “liquid biopsy” to assess for molecular changes during the course of the therapy that may identify the emergence of treatment-resistant clones in the subjects at risk of relapse.

Table 5.6-1: CA209205 Biomarker Sampling Schedule for Cohorts A, B, and C

Collection Time	Serum	PBMC		Tumor Biopsy	Bone Marrow Biopsy	Bone Marrow Aspirate	Whole Blood		Plasma (ctDNA)[a]
Study Day[b]	Soluble Biomarker	Immuno-phenotyping	Ex-vivo Functional				Gene Expression	SNP	
Screening				X[c]	X[d]	X			X
Cycle 1 Day 1	X	X	X				X	X	
Cycle 2 Day 1	X	X					X		
Cycle 3 Day 1	X	X					X		
Cycle 4 Day 1	X	X	X						X
Cycle 7 Day 1	X	X							X
Cycle 11 Day 1									X
Cycle 15 Day 1									X
Cycle 19 Day 1									X
Cycle 23 Day 1									X
Cycle 27 Day 1									X
Cycle 68 Day 1									X
Cycle 81 Day 1									X
CR Evaluation	X	X		X[e]	X[e]	X	X		X
During Treatment (when clinically indicated)				X[f]	X[f]	X[f]			
At Study Drug Discontinuation									X[g]
Safety FU X02									X[g]
FU/Observational 1									X[g]
FU/Observational 2									X[g]

Table 5.6-1: CA209205 Biomarker Sampling Schedule for Cohorts A, B, and C

Collection Time	Serum	PBMC		Tumor Biopsy	Bone Marrow Biopsy	Bone Marrow Aspirate	Whole Blood		Plasma (ctDNA)[a]
Study Day[b]	Soluble Biomarker	Immuno-phenotyping	Ex-vivo Functional				Gene Expression	SNP	
FU/Observational 3									X[g]
FU/Observational 4									X[g]
FU/Observational 5									X[g]
FU/Observational 6									X[g]
Upon Progression[h]	X (optional)	X (optional)	X (optional)	X (optional)		X (optional)	X (optional)		X (strongly recom-mended)

[a] Plasma (ctDNA) sample collection is only applicable to Cohort C subjects.

[b] On-treatment biomarker samples will be collected prior to administration of study drug and may be obtained ± 3 days of the indicated time (except for Cycle 1 Day 1).

[c] Submission of tumor tissue from a biopsy performed during screening is mandatory (see the details in Section 3.1 and Table 5.1.1-1).

[d] For Cohorts A and B, extent of disease involvement in the bone marrow must be documented at screening based on the results of a bone marrow biopsy/aspirate performed within 90 days prior to enrolment or a bone marrow biopsy/aspirate performed during the screening period. If bone marrow biopsy/aspirate is performed during screening (after obtaining informed consent), submission of bone marrow aspirate is mandatory. Submission of bone marrow biopsy specimen is not required at any point in the study. For Cohort C, performing a bone marrow biopsy/aspirate is optional and submission of bone marrow aspirate, if performed, is optional.

[e] For Cohorts A and B, if the bone marrow was involved by lymphoma at baseline, a bone marrow biopsy and aspirate will be required to confirm a CR. Submission of bone marrow aspirate is mandatory in this case.

[f] All subjects may volunteer to undergo tumor and/or bone marrow biopsies at any time during therapy if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy is strongly encouraged. When bone marrow biopsy is done, submission of bone marrow aspirate is strongly encouraged.

[g] Only for those Cohort C subjects who discontinued study drug due to persistent CR for one year.

[h] Sample submission upon progression is optional (except for plasma, which is strongly recommended) and can be taken ± 7 days at the discretion of the investigator.

Table 5.6-2: CA209205 Biomarker Sampling Schedule for Cohort D

Collection Time[a]	Serum	PBMC	Tumor Biopsy	Whole Blood	Plasma (ctDNA)
Study Day	**Soluble Biomarker**	**Immuno-phenotyping**		**SNP**	
Screening			X[b]		
Monotherapy Dose 1	X	X		X	
Monotherapy Dose 3	X	X			
Tumor biopsy during monotherapy phase			X (optional)[c]		
Combocycle 1 Day 1	X	X			
Combocycle 3 Day 1	X	X			
Combocycle 5 Day 1	X	X			
Tumor biopsy during combotherapy phase			X (optional)[d]		
Safety Follow up 1	X	X			X
Upon Progression[e]	X (optional)	X (optional)	X (optional)		

[a] On-treatment biomarker samples will be collected prior to administration of study drug and may be obtained ± 3 days of the indicated time (except for Monocycle 1 Day 1).

[b] Submission of tumor tissue from a biopsy performed during screening is mandatory (see the details in Section 3.1.2 and Table 5.1.2-1).

[c] All subjects may volunteer to undergo tumor biopsies for exploratory analysis at any time during monotherapy phase if the procedure is deemed as safe by investigators. When tumor biopsy is performed, specimen of tumor biopsy should be submitted.

[d] All subjects may volunteer to undergo tumor biopsies at any time during therapy if clinically indicated.

[e] All sample submission upon progression is optional up to 3 years from the last dose of study treatment at the discretion of the investigator.

5.7 Outcomes Research Assessments

Outcomes research data including health-related quality of life and patient reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the subjects' perspective. These data offer insights into the patient experience that may not be captured through physician reporting. Generic health-related quality of life scales provide data necessary in calculating utility values for health economic models. The EQ-5D will be collected in order to assess the impact of nivolumab on generic health-related quality of life and the data will be used for populating health economic models most notably, cost effectiveness analysis. The EORTC QLQ-C30 will be collected in order to assess cancer specific health-related quality of life. The combination of the generic scale for general health status and economic evaluation and the cancer specific scale will provide a robust outcomes research package.

The EORTC QLQ-C30 is one the most commonly used QoL instrument in oncology studies. The EORTC QLQ-C30 is a 30-item instrument comprising six functional scales (physical functioning, cognitive functioning, emotional functioning, role functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

All QoL assessments will be administered as outlined in Table 5.1.1-2, Table 5.1.1-3, Table 5.1.1-4, Table 5.1.2-2, Table 5.1.2-3 and Table 5.1.2-4. EORTC-QLQ-C30 will be collected for Cohorts A, B, and C. EQ-5D will be collected for Cohorts A, B, C, and D.

Outcomes research data will not be collected for subjects who re-initiate study therapy (Cohort C subjects).

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Serum samples collected at time points identified in Table 5.5-1 (Cohorts A, B, and C) and Table 5.5-2 (Cohort D) will be analyzed by a validated immunoassay. Additional characterization (ie, neutralizing antibodies) for any detected anti-drug antibodies (ADA) response to nivolumab may also be performed using a validated functional cell-based assay. All on-treatment immunogenicity assessment time points are intended to align with days on which nivolumab is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is

subsequently delayed, an additional predose sample should not be collected. Selected serum samples may be analyzed by an exploratory method that measures anti-nivolumab antibodies for technology exploration purposes; exploratory results will not be reported.

In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, if there is insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AE).

5.9 Results of Central Assessments

The primary endpoint for Cohorts A, B, and C is ORR, as determined by the IRRC.

For Cohort D, OR and CR for secondary and exploratory endpoints are also determined by the IRRC.

Site will be informed of quality issues or needs for repeat scanning via queries from the corelab. Results of central Imaging analysis will not be returned to the site.

For Cohort D, histology of cHL will be confirmed later by a central pathological laboratory; subjects may start the first dose after cHL histology is confirmed by a local pathological laboratory.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

For the Cohort C subjects who discontinue treatment after persistent one-year CR, SAEs will be collected for a maximum of two years and a minimum of 100 days after last dose during safety and FU/Observational visits. After, only study procedures-related SAEs will need to be reported and collected.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

For the Cohort C subjects who discontinue treatment after persistent one-year CR, NSAEs will be collected for a maximum of two years and a minimum of 100 days after last dose during safety and FU/Observational visits.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with the SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Surveillance form

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. Aminotransaminases (AT) (ALT or AST) elevation > 3 times ULN
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An IRRC will be utilized in this study for determination of IRRC-assessed endpoints such as ORR, CR rate, PR rate and associated durations. 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.

The subjects' safety will be monitored on an ongoing basis. The BMS medical monitor is a physician responsible for reviewing, on a systematic and continuous basis, the safety of subjects on this study. This includes a review of serious and non-serious adverse events, including all hematological and non-hematological events. In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab. The MST is independent from the BMS medical monitor. The MST has the primary responsibility within BMS for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk management plans. The MST is responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

For Cohort D, when required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation. In addition, safety conference calls with investigators and representatives of the sponsor will be held regularly until all subjects have entered the FU/observational phase or discontinued the study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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), and treatment with brentuximab vedotin at any time point (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.[23]

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 8.1-1 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 8.1-1: 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[92] 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 8.1-2 summarizes the 95% exact CI for a range of incidence rates.

Table 8.1-2: 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.[12,15,93] Table 8.1-3 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 8.1-3: 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

8.2 Populations for Analyses

Within each cohort the following populations will be defined.

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Treated Subjects: All subjects who received at least one dose of nivolumab. This is the primary population for safety and efficacy analyses.
- PK subjects: All subjects with available serum time-concentration data from subjects dosed with nivolumab
- Immunogenicity Evaluable Subjects: All treated subjects with baseline and at least 1 postbaseline immunogenicity assessment.

8.3 Endpoints

8.3.1 Cohorts A, B, and C

8.3.1.1 Primary Endpoint(s) for Cohorts A, B, and C

The primary objective will be measured by the primary endpoint of IRRC-assessed ORR. It is defined as the number of subjects with a BOR of CR or PR, according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. Only for Cohort C, FDG-PET can be used in lieu of bone marrow aspirate/ biopsy for bone marrow assessment. 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 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). Primary analysis will be performed separately for each cohort (ie, at separate time points) upon completion of a pre-specified amount of follow-up (Table 8.3.1.1-1) after last patient first treatment (LPFT).

Table 8.3.1.1-1: CA209205 Schedule of Analyses

Cohort	Follow-Up Requirement for Primary Endpoint Analysis
Cohort A	Primary ORR analysis after approximately 9 months minimum follow up in all Cohort A subjects
Cohort B	Primary ORR analysis after approximately 6 months minimum follow-up in all Cohort B subjects
Cohort C	Primary ORR analysis after approximately 6 months minimum follow-up in all Cohort C subjects

8.3.1.2 Secondary Endpoint(s) for Cohorts A, B, and C

Secondary endpoints will be analyzed at the same time as the primary endpoint.

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 assessments prior to initiation of the subsequent anticancer therapy. This endpoint will only be evaluated in subjects with objective response of CR or PR.

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.

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.

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, but will be assessed per investigator.

8.3.1.3 Exploratory Endpoint(s) for Cohorts A, B, and C

Exploratory efficacy objectives will be measured by exploratory endpoints of PFS based on IRRC assessment and OS.

PFS is defined as the time from first dosing date to the date of the first documented progression using the 2007 IWG criteria, as determined by IRRC, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study assessments and did not die will be censored on the first dosing date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

OS is defined as the time from first dosing date to the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

The safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths and laboratory abnormalities.

The PK samples collected will be used to determine summary measures of nivolumab exposure (see Section 8.4.4).

Other exploratory endpoints for pharmacodynamics, outcomes research and immunogenicity are discussed in detail in Sections 5.6, 5.7 and 5.8.

For Cohort C, clinical course of the subjects who discontinued after persistent CR for 1 year will be evaluated in a descriptive fashion.

8.3.2 Cohort D

8.3.2.1 Primary Endpoints for 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.

8.3.2.2 Secondary Endpoints for Cohort D

- 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).
- 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.
- 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.

8.3.2.3 Exploratory Endpoints for Cohort D

- The OR rate at the planned end of study therapy based on IRRC assessments, and the CR and OR rates based on investigator assessments, are defined as follows:
  - The CR rate at the planned end of study therapy (investigator-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.
  - The OR rate at the planned end of study therapy (IRRC-assessed or investigator-assessed) is defined as the number of subjects who have CR or PR 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 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).
- The CR and OR rates at the planned end of nivolumab monotherapy therapy based on IRRC assessments or based on investigator assessments, are defined as follows:
  - The CR rate at the planned end of nivolumab monotherapy (IRRC-assessed or investigator-assessed) is defined as the number of subjects who are CR according to the 2007 IWG criteria at the planned end of nivolumab monotherapy radiographic tumor assessment, divided by the number of subjects who have received at least one dose of nivolumab monotherapy.
  - The OR rate at the planned end of nivolumab therapy (IRRC-assessed or investigator-assessed) is defined as the number of subjects who have CR or PR according to the 2007 IWG criteria at the planned end of nivolumab monotherapy radiographic tumor assessment, divided by the number of subjects who have received at least one dose of nivolumab monotherapy.
- The CR and OR rates at the planned end of two Combocycles based on IRRC assessments or based on investigator assessments, are defined as followed:
  - The CR rate at the planned end of two Combocycles (IRRC-assessed or investigator-assessed) is defined as the number of subjects who are CR according to the 2007 IWG

criteria at the planned end of two Combocycles radiographic tumor assessment, divided by the number of subjects who have received at least one dose of nivolumab monotherapy.

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

- The PFS IRRC-assessed is defined as the time from first dosing date to the date of the first documented progression using the 2007 IWG criteria, as determined by IRRC or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study assessments and did not die will be censored on the first dosing date. Subjects who initiate a subsequent anti-cancer therapy will contribute as an event to PFS analysis at the date of the start of their subsequent anti-cancer therapy.
- The PFS investigator-assessed is defined similarly as for IRRC-assessed PFS.
- OS is defined as the time from first dosing date to the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.
- The safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths and laboratory abnormalities.
- The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a PPK model (see Section 8.4.4).
- Other exploratory endpoints for pharmacodynamics, pulmonary function outcomes research and immunogenicity are discussed in detail in Sections 5.6, 5.7, and 5.8.
- Other exploratory endpoints are discussed in details in the statistical analysis plan.

8.4 Analyses

All analyses will be performed separately for each cohort.

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized using descriptive statistics for all treated subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Complete Response, Partial Response and Objective Response Rates

The IRRC-assessed and investigator-assessed CR, PR, and ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CI using the Clopper-Pearson method.

For Cohorts A and B, the null hypothesis will be rejected if the 2-sided 95% CI lower bound for the ORR IRRC-assessed estimate is greater than 20%. This translates in observing at least 19 responders out of 60 treated subjects.

8.4.2.2 Duration of Response

The IRRC-assessed DOR will be summarized by cohort for subjects who achieve PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CIs (based on the log-log transformation) and range, will also be calculated. The same analysis will be performed for the duration of PR and CR, as well as DOR per investigator.

For Cohorts A and B, the IRRC-assessed CR and PR rates and investigator-assessed ORR will be summarized by binomial response rates and their corresponding two-sided 95% CI using the Clopper-Pearson method.

8.4.2.3 Progression Free Survival and Overall Survival

The IRRC-assessed and investigator-assessed PFS and OS will be summarized by the Kaplan-Meier product-limit method. Median values along with two-sided 95% CIs based on the log-log transformation, will be calculated. PFS and OS will be evaluated in all treated subjects.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

In addition to separate analyses per cohort, safety analyses will be performed on combined cohorts for Cohorts A, B, and C.

For Cohort D, in addition to analyses described above, the treatment discontinuation rate, the treatment discontinuation rate of Nivolumab monotherapy, the treatment discontinuation rate of the Nivolumab-AVD combination therapy and the treatment discontinuation rate of combination therapy (AVD ± Nivolumab), as defined in Section 8.3.2.2, will be provided with exact 95%CI using the Clopper-Pearson method.

8.4.4 Pharmacokinetic Analyses

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a PPK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model determined exposures may be used for E-R analyses. Results of PPK and E-R analyses will be reported separately.

8.4.5 Biomarker Analyses

Methodology for exploratory biomarker analyses will be described in the statistical analysis plan.

8.4.6 Outcomes Research Analyses

8.4.6.1 EQ-5D

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

8.4.6.2 EORTC QLQ-C30

The analysis of EORTC QLQ-C30 will be performed in all treated subjects who have an assessment at baseline and at least one subsequent assessment. The analysis will be conducted separately for Cohorts A, B, and C.

All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, and higher scores for a symptom scale representing higher level of symptoms.

Baseline and change from baseline in EORTC QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). In addition, the percentage of subjects demonstrating a clinically meaningful deterioration (defined as a 10 point change from baseline) will be presented for each scale at each assessment time point. Percentages will be based on number subjects assessed at assessment time point.

8.4.7 Other Analyses

8.4.7.1 Immunogenicity Analysis

Immunogenicity may be reported for ADA positive status (such as persistent positive, neutralizing positive, only last sample positive, baseline positive and other positive) and ADA negative status, relative to baseline. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the SAP.

8.5 Interim Analyses

Interim analyses may be conducted if it is necessary in order to make decisions regarding further development. Summaries and listings of efficacy and safety will be provided.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area

- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine, where A stands for Adriamycin, which is the trade name of doxorubicin
ADA	Anti-drug antibodies
AE	adverse event
ADC	antibody drug conjugate
AEs	adverse events
AI	accumulation index
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASCT	autologous stem cell transplant
AT	aminotransaminases
AVD	doxorubicin, vinblastine, and dacarbazine, where A stands for Adriamycin, which is the trade name of doxorubicin
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
β-HCG	beta-human chorionic gonadotrophin
BCNU	bis-chloroethylnitrosourea (Carmustine)
BEACOPP	bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone
BEAM	Carmustine, etoposide, cytarabine and melphalan
BID, bid	bis in die, twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BSA	Body surface area
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium

Term	Definition
CBC	complete blood count
CFR	Code of Federal Regulations
cHL	“classic” HL
CI	confidence interval
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CR	complete remission
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CT	Computed tomography
D/C	discontinue
DILI	drug induced liver injury
dL	deciliter
DLBCL	Diffuse Large B-Cell Lymphoma
DLCO	Diffusing capacity or Transfer factor of the lung for carbon monoxide
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	duration of objective response
EA	extent of absorption
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EB	Epstein-Barr
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer

Term	Definition
E-R	exposure–response
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FDG-PET	[18F]-fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FL	Follicular Lymphoma
FSH	follicle stimulating hormone
fT4	Free thyroxine
FU	Follow-up
fu	fraction of unbound drug
g	gram
G	Grade
GCP	Good Clinical Practice
GVHD	graft-versus-host-disease
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
HR	heart rate
hrs	Hours
HRT	hormone replacement therapy
IB	Investigator Brochure
ICE	ifosfamide, carboplatin, etoposide
ICF	Informed Consent

Term	Definition
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IPS	International Prognostic Score
IRB	Institutional Review Board
ID	Infectious Disease
I-O	Immuno-oncology
IRRC	independent radiologic review committee
ITIM	immunoreceptor tyrosine inhibitory motif
ITSM	immunoreceptor tyrosine-based switch motif
IU	International Unit
IV	intravenous
IVRS	Interactive Voice Response Service
IWG	International Working Group
K	slope of the terminal phase of the log concentration-time curve
KM	Kaplan-Meier
K+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LFT	Liver function tests
mAbs	monoclonal antibodies
MDS	Myelodysplastic syndrome
mg	milligram
mg/kg	Milligram per kilogram
Mg++	magnesium
min	minute

Term	Definition
mL	milliliter
MLR	mixed lymphocyte reaction
MMAE	monoethyl auristatin E
mmHg	millimeters of mercury
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
NCI CTCAE v4	National Cancer Institute Common Terminology Criteria for Adverse Event version 4
ng	nanogram
NSAE	Non-Serious Adverse Event
NSCLC	non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamics
PFS	progression free survival
PFSR	progression-free survival rate
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PPK	population pharmacokinetic
PR	partial remission
Q2W	every 2 weeks
Q4W	every 4 weeks
QD, qd	quaque die, once daily
QLQ	Quality of Life Questionnaire
RBC	red blood cell

Term	Definition
RCC	renal cell carcinoma
RNA	Ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SCT	stem cell transplant
SD	Stable Disease
SNP	single nucleotide polymorphisms
SOP	Standard Operating Procedures
SPD	sum of the product of the diameters
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
Tmax, TMAX	time of maximum observed concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VAS	visual analog rating scale
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

12 REFERENCES

1 Braeuninger A, Kuppers R, Strickler JG, et al. Hodgkin and Reed-Sternberg cells in lymphocyte predominant Hodgkin disease represent clonal populations of germinal center-derived tumor B cells. Proc Natl Acad Sci USA 1997;94:9337-42.

2 Gobbi PG, Ferreri AJ, Ponzoni M, et al. Hodgkin Lymphoma. Crit Rev Oncol/Hematol 2012;85:216-37.

3 Chang KC, Huang GC, Jones D, et al. Chang Distribution Patterns of Dendritic Cells and T Cells in Diffuse Large B-Cell Lymphomas Correlate with Prognoses. Clin Cancer Res 2007;13:6666-6672.

4 http://seer.cancer.gov/statfacts/html/hodg.html.

5 Armitage JO. Early-Stage Hodgkin's Lymphoma. N Engl J Med 2010;363:653-662.

6 Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory lymphoma. Blood 2011;117:4208-4217.

7 Younes A, Gopal AK, Smith SC, et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. J Clin Oncol 2012;30:2183-2189.

8 Gopal AK, Chen R, Smith S, et al. The three-year follow-up data and characterization of long-term remissions from an ongoing Phase 2 study of Brentuximab Vedotin in patients with relapsed or refractory Hodgkin Lymphoma. ASH 2013;Abstract number 4382.

9 Kuruvilla J. Standard therapy of advanced Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2009:497-506.

10 Ansell SM. Induction therapy for advanced-stage Hodgkin lymphoma: late intensification (ABVD chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant only for those who relapse). Hematol Oncol Clin North Am. 2014;28(1):75-86.

11 Avandi R. Optimal therapy of advanced Hodgkin lymphoma. Hematol. 2011;1:310-316.

12 Gordon L, Hong F, Fisher R et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol 2013;31(6):684-91.

13 Shenoy P, Maggioncalda A, Malik N, Flowers CR. Incidence patterns and outcomes for hodgkin lymphoma patients in the United States. Adv Hematol. 2011;2011:725219.

14 Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009;27(27):4548-54.

[15] Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. N Engl J Med. 2011; 365(3):203-212.

[16] Kelly K, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's Oncology Group. Blood 2011; 117(9): 2596–2603.

[17] Crump M. Management of Hodgkin Lymphoma in Relapse after Autologous Stem Cell Transplant. ASH Education Book 2008;1:326-333.

[18] von Tresckow B, Muller H, Eichenhauer DA, et al. Outcome and risk factors of patients with Hodgkin Lymphoma who relapse or progress after autologous stem cell transplant. Leuk Lymph 2014;Epub ahead of print.

[19] Falini B, Pileri S, Pizzolo G, et al. CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. Blood 1995;85:1-14.

[20] Sutherland MS, Sanderson RJ, Gordon KA, et al. Lysosomal Trafficking and Cysteine Protease Metabolism Confer Target-specific Cytotoxicity by Peptide-linked Anti-CD30-Auristatin Conjugates. J Biol Chem 2006;281:10540-10547.

[21] Francisco JA, Cerveny CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood 2003;102:1458-1465.

[22] Younes A, Bartlett NL, Leonard JP, et al. Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas. N Engl J Med 2010;363:1812-1821.

[23] Younes A, Gopal AK, Smith SC, et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. J Clin Oncol 2012;30:2183-2189.

[24] Gopal AK, Chen R, Smith S, et al. The three-year follow-up data and characterization of long-term remissions from an ongoing Phase 2 study of Brentuximab Vedotin in patients with relapsed or refractory Hodgkin Lymphoma. ASH 2013;Abstract number 4382.

[25] Gopal AK, Bartlett NL, Forero-Torres A, et al. Brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30-positive lymphomas: a retrospective evaluation of safety and efficacy. Leuk Lymph 2014, Epub ahead of print.

[26] Schnell R, Barth S, Diehl V, Engert A. Non-Hodgkin's Lymphoma: A Review of Immunotherapeutic Approaches to Treatment. BioDrugs 1997;8(3):216-34.

[27] Kasamon YL, Ambinder RF. Immunotherapies for Hodgkin's lymphoma. Crit Rev Oncol Hematol. 2008;66(2):135-44.

[28] Cheson, BD and Leonard JP. Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma. N Engl J Med 2008;359:613-626.

[29] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39(1):1-10.

[30] Brahmer JR, Drake CG, Wollner I, et al. Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. J Clin Oncol. 2010;28:3167-3175.

[31] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. The New England Journal of Medicine 2012;366:2443-2454.

[32] Francisco LM, Sage PT and Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219-42.

[33] Keir ME, Butte MJ, Freeman GJ and Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

[34] CA209039 data cutoff date *18-Nov-2014 (data lock date 09-Jan-2015).

[35] Younes A, Gopal AK, Smith SC, et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. J Clin Oncol 2012;30:2183-2189.

[36] Ng AK. Current survivorship recommendations for patients with Hodgkin lymphoma: focus on late effects. Blood. 2014; 124(23):3373-9.

[37] Delwail V, Jais JP, Colonna P, Andrieu JM. Fifteen-year secondary leukaemia risk observed in 761 patients with Hodgkin's disease prospectively treated by MOPP or ABVD chemotherapy plus high-dose irradiation. Br J Haematol. 2002; 118(1):189-94.

[38] Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015; 372(4):320-30.

[39] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015; 373(1):23-34.

[40] Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med. 1992; 327:1478-1484.

[41] Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an intergroup trial. J Clin Oncol. 2003; 21:607-614.

[42] Canellos GP, Duggan D, Johnson J, Niedzwiecki D. How important is bleomycin in the adriamycin + bleomycin + vinblastine + dacarbazine regimen? J Clin Oncol. 2004; 22(8):1532-3.

[43] Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol. 2005;23(30):7614-7620.

[44] Johnson PW, Federico M, Fossa A, et al. Response-adapted therapy based on interim FDG-PET scans in advanced Hodgkin lymphoma: first analysis of the safety of de-escalation and efficacy of escalation in the international RATHL study (CRUK/07/033).Hemaol Oncol. 2015; 33:102.

[45] Opdivo (nivolumab) Package Insert. http://packageinserts.bms.com/pi/pi_opdivo.pdf. Last accessed 28 July 2015.

[46] Ngeow J, Tan IB, Kanesvaran R, et al. Prognostic impact of bleomycin-induced pneumonitis on the outcome of Hodgkin's lymphoma. Ann Hematol. 2011; 90(1):67-72.

[47] Sleijfer S. Bleomycin-induced pneumonitis. Chest. 2001; 120(2):617-24.

[48] Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study.Lancet Oncol. 2013;14(13):1348-1356.

[49] Antonia SJ, Brahmer JR, Gettinger SN, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2014; 32:5s (suppl; abstr 8113).

[50] Gettinger S, Rizvi N, Chow LQ. Nivolumab (Anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based duplet chemotherapy (PT-DC) or erlotinib (ERL) in advanced non-small cell lung cancer (NSCLC). Ann Oncol. 2014; 25(suppl 4):iv361-iv372.

[51] Adriamycin (Doxorubicin) Package Insert. Doxorubicin http://bidocs.boehringer-Ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Ben+Venue_Bedford+Labs/55390-237-01+ADR+50MG/5539023701. Last accessed 27 July2015.

[52] Vinblastine Package Insert. Vinblastine http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Ben+Venue_Bedford+Labs/55390-091-10+VIN+10MG/5539009110. Last accessed 28 July 2015.

[53] DTIC-Dome (dacarbazine) Package Insert. http://www.univgraph.com/bayer/inserts/dtic-dome.pdf. Last accessed 27 July 2015.

[54] Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2004;23:515-48.

[55] Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027-34.

[56] Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001;2(3):261-8.

[57] Carter LL, Fouser LA, Jussif J, et al. PD-1:PD-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. Eur J Immunol 2002;32(3):634-43.

[58] Chemnitz JM, Parry RV, Nichols KE, et al. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173(2):945-54.

[59] Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKC-theta. FEBS Letters 2004;574(1-3):37-41.

[60] Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol. 2001;22:265-8.

[61] Nishimura H, Nose M, Hiai H, et al. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity. 1999;11:141-51.

[62] Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291:319-22.

[63] Okazaki T, Tanaka Y, Nishio R, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1 deficient mice. Nat Med. 2003;9:1477-83.

[64] Salama AD, Chitnis T, Imitola J, et al. Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. J Exp Med. 2003;198:71-8.

[65] Blazar BR, Carreno BM, Panoskaltsis-Mortari A, et al. Blockade of programmed death-1 engagemet accelerates graft-versus-host disease lethality by an IFN-γ-dependent mechanism. J Immunol. 2003;171:1272-7.

[66] Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int Immunol. 2004;17:133-44.

[67] Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-1 blockade. Proc Natl Acad Sci USA. 2002;99:12293-7.

[68] Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 2003;63:6501-5.

[69] Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8:793-800.

[70] Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65:1089-96.

[71] Blank C, Brown, I, Peterson AC, et al. PD-L1/B7-H1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res 2004;64:1140-45.

[72] Konishi J, Yamazaki K, Azuma M, et al. B7-H1 expression on non-small cell lung cancer and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clin Cancer Res 2004;10:5094-100.

[73] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory B7-H1 in renal cell carcinoma subjects: indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci USA 2004;101:7174-9.

[74] Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res. 2005;11:2947-53.

[75] Tsushima F, Tanaka K, Otsuki N, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol. 2006;42:268-74.

[76] Thompson RH, Weber, WS, Cheville JC, et al. B7-H1 glycoprotein blockade: a novel strategy to enhance immunotherapy in subjects with renal cell carcinoma. Urology 2005;66:10-4.

[77] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer 2005;104:2084-91.

[78] Azuma T, Yao S, Zhu G, et al. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood. 2008;111:3635-43.

[79] Andorsky DJ, Yamada RE, Said J, et al. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res. 2011 Jul 1;17(13):4232-44.

[80] Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res. 2013;19(13):3462-73.

[81] Non-Clinical Expedited Safety Report for Nivolumab (Ad Hoc CARES #54344.1). BMS; 2013. Document Control No. 930067627 1.0.

[82] Effect of MDX-1106 on CD4+ T cells during an allogeneic mixed lymphocyte reaction (MLR) (Medarex Study no. MDX-1106-026-R). Bristol-Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930046581.

[83] Kuppers R. The biology of Hodgkin's lymphoma. Nat Rev Cancer 2009;9:15-27.

[84] Juszczynski P, Ouyang J, Monti S, et al. The AP1-dependent secretion of galectin-1 by Reed Sternberg cells fosters immune privilege in classical Hodgkin lymphoma. Proc Natl Acad Sci U S A 2007;104(32):13134-9.

[85] Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma Blood 2010;116(17):3268-77; PMCID: PMC2995356.

[86] Green MR, Rodig SJ, Juszczynski P, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. Clin Cancer Res 2012;18(6):1611-8.

[87] Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res 2013:1-12.

[88] Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989 Nov;7(11):1630-6. Erratum in: J Clin Oncol 1990 Sep;8(9):1602.

[89] Cheson BD, Pfistner B, Juweld ME, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol 2007;25(5):579-586.

[90] Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014 Aug 11.

[91] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009; 52(23): 7412-7420.

[92] Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin’s lymphoma when high-dose salvage is planned. N Engl J Med 2011;365:203-12.

[93] Federico M, Luminari S, Iannitto E, et al; HD2000 Gruppo Italianoper lo Studio dei Linfomi Trial. ABVD compared with BEACOPP compared with CEC forthe initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. J Clin Oncol. 2009;27(5):805-811.

APPENDIX 1 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

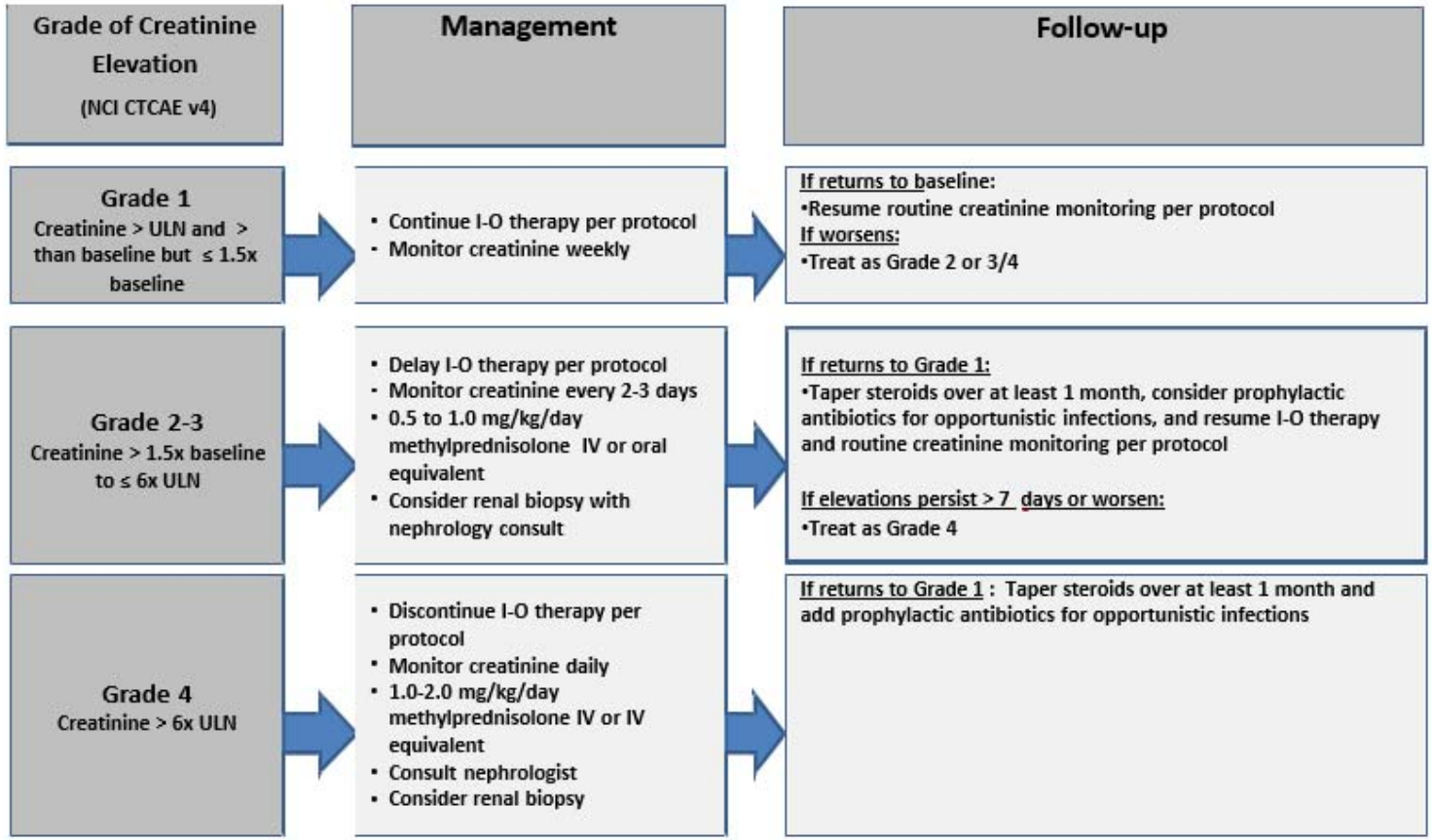
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

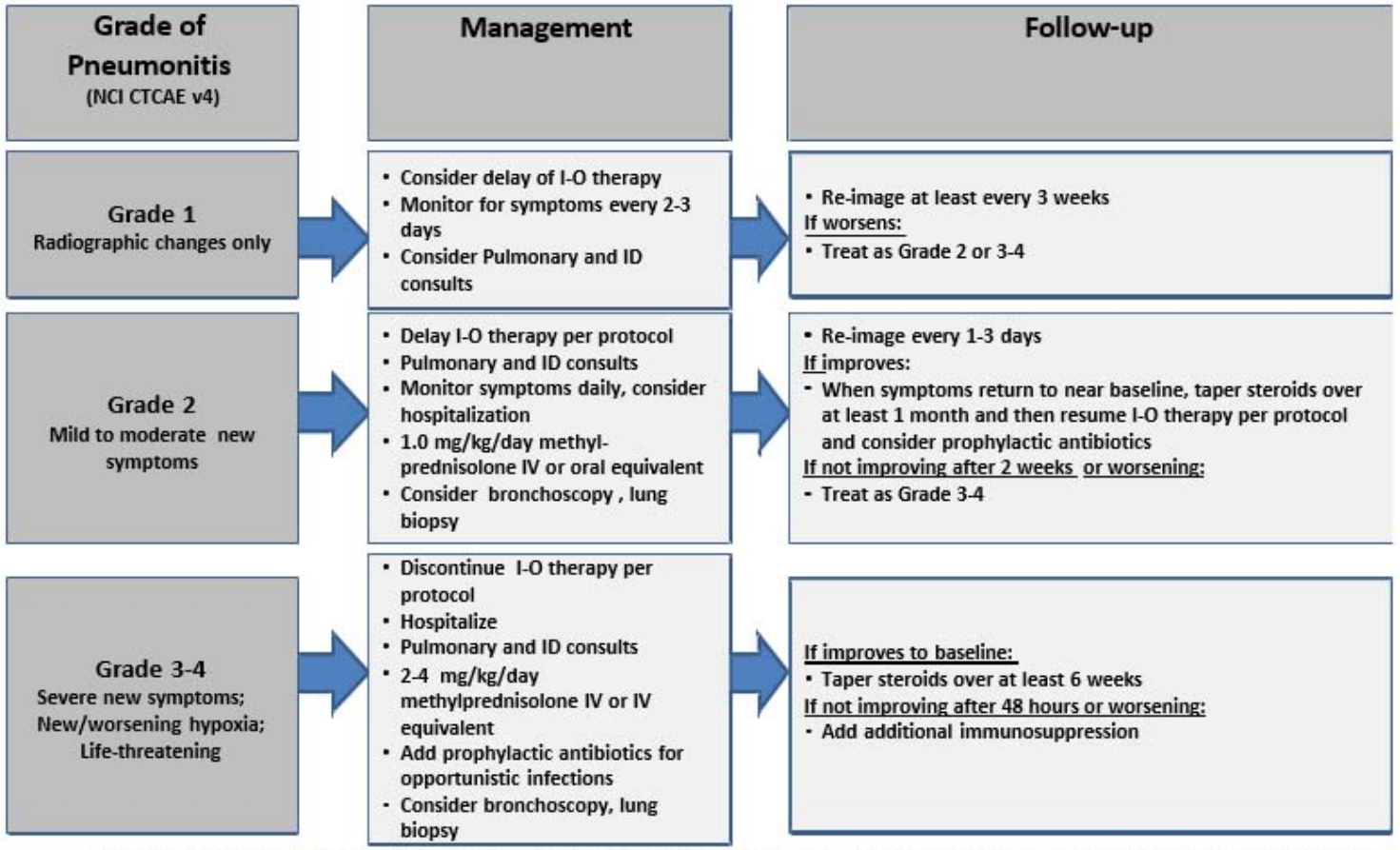


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

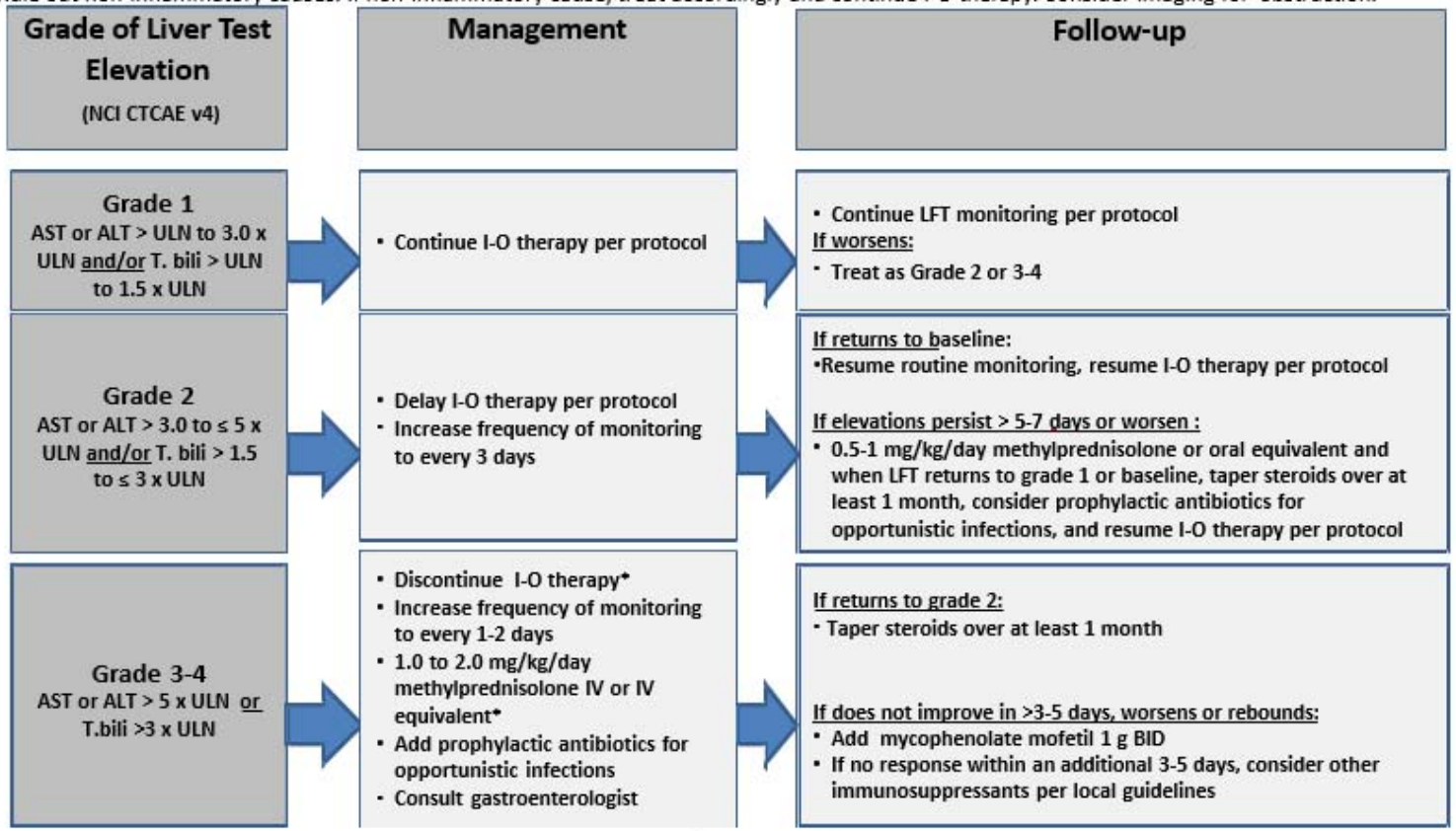


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

27-Jun-2019

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



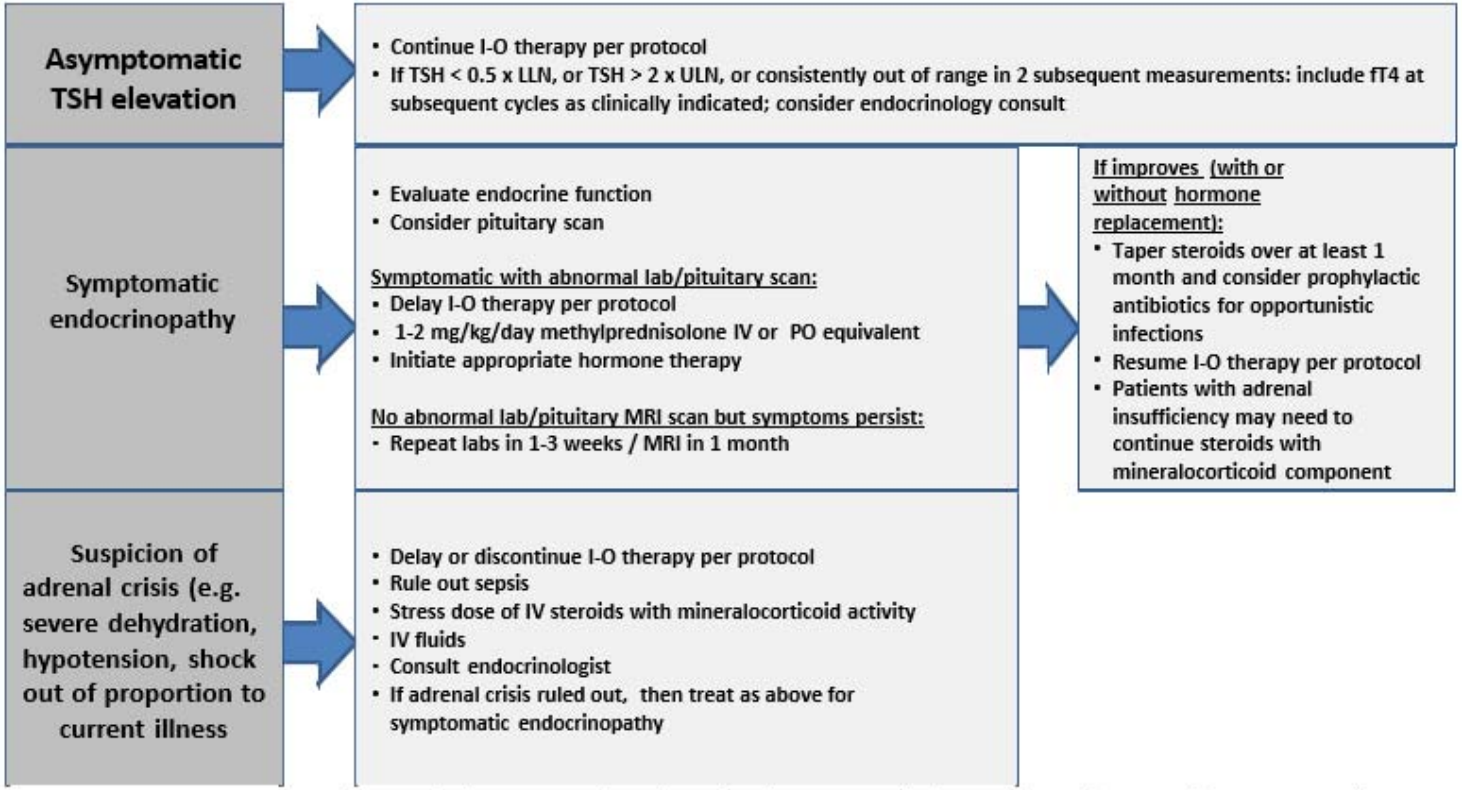
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

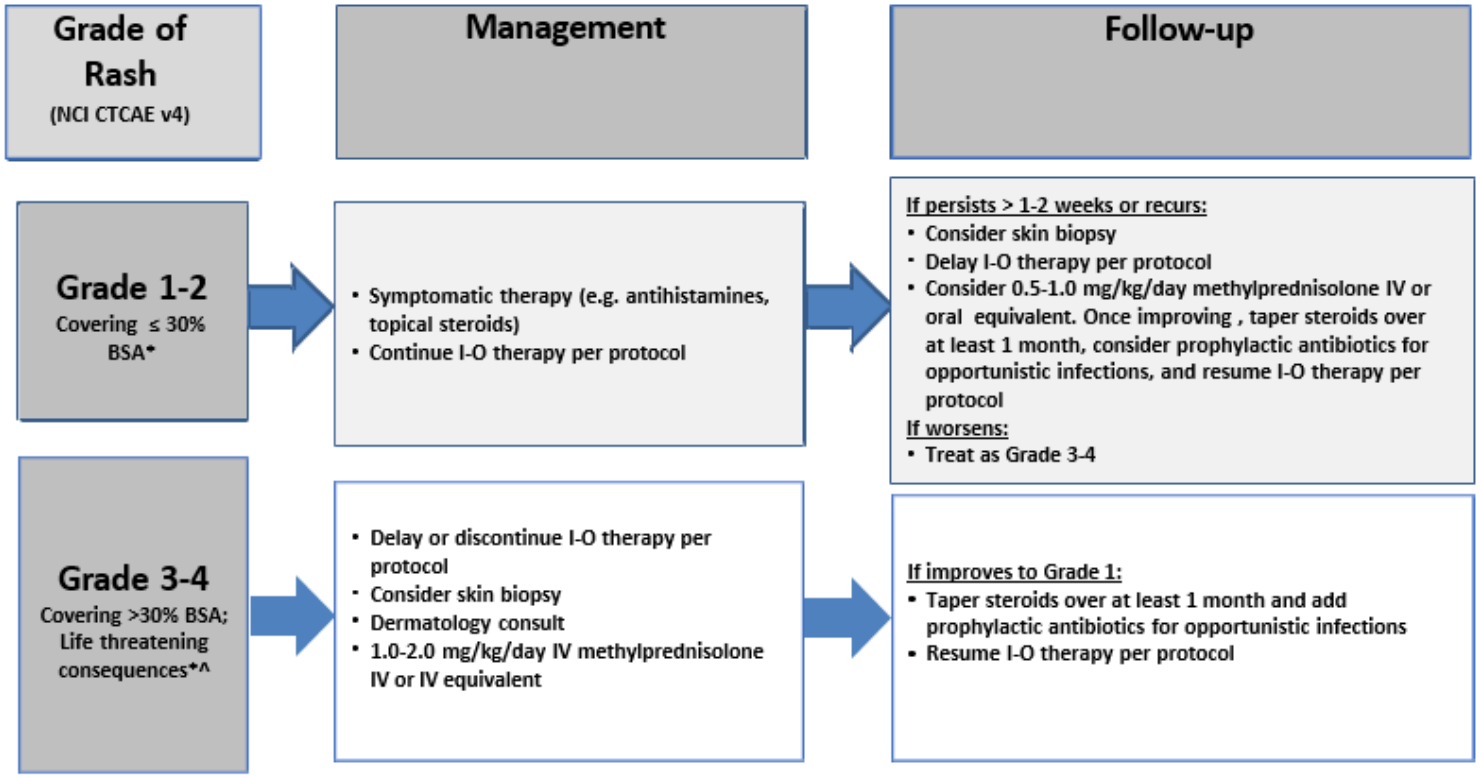


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

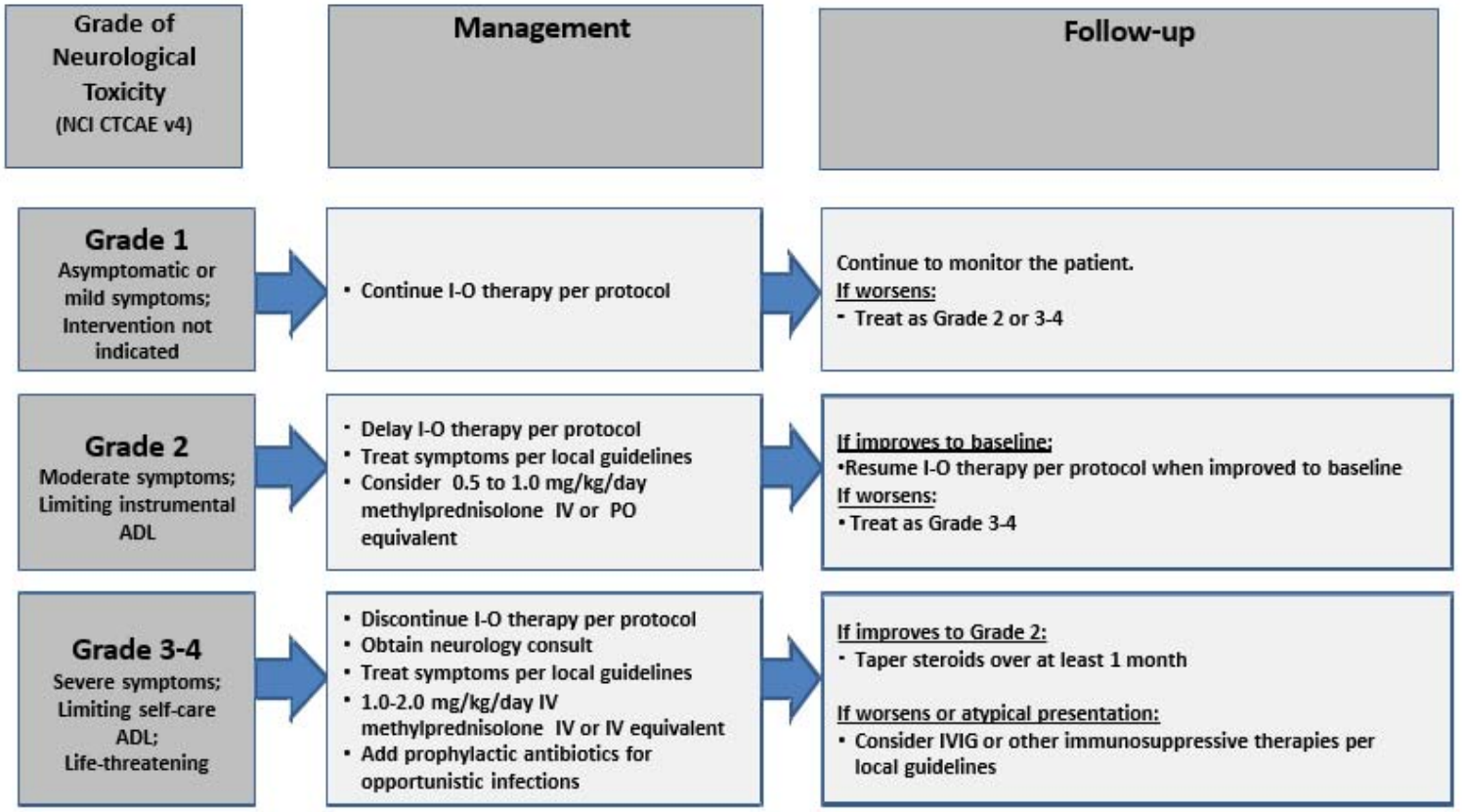
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

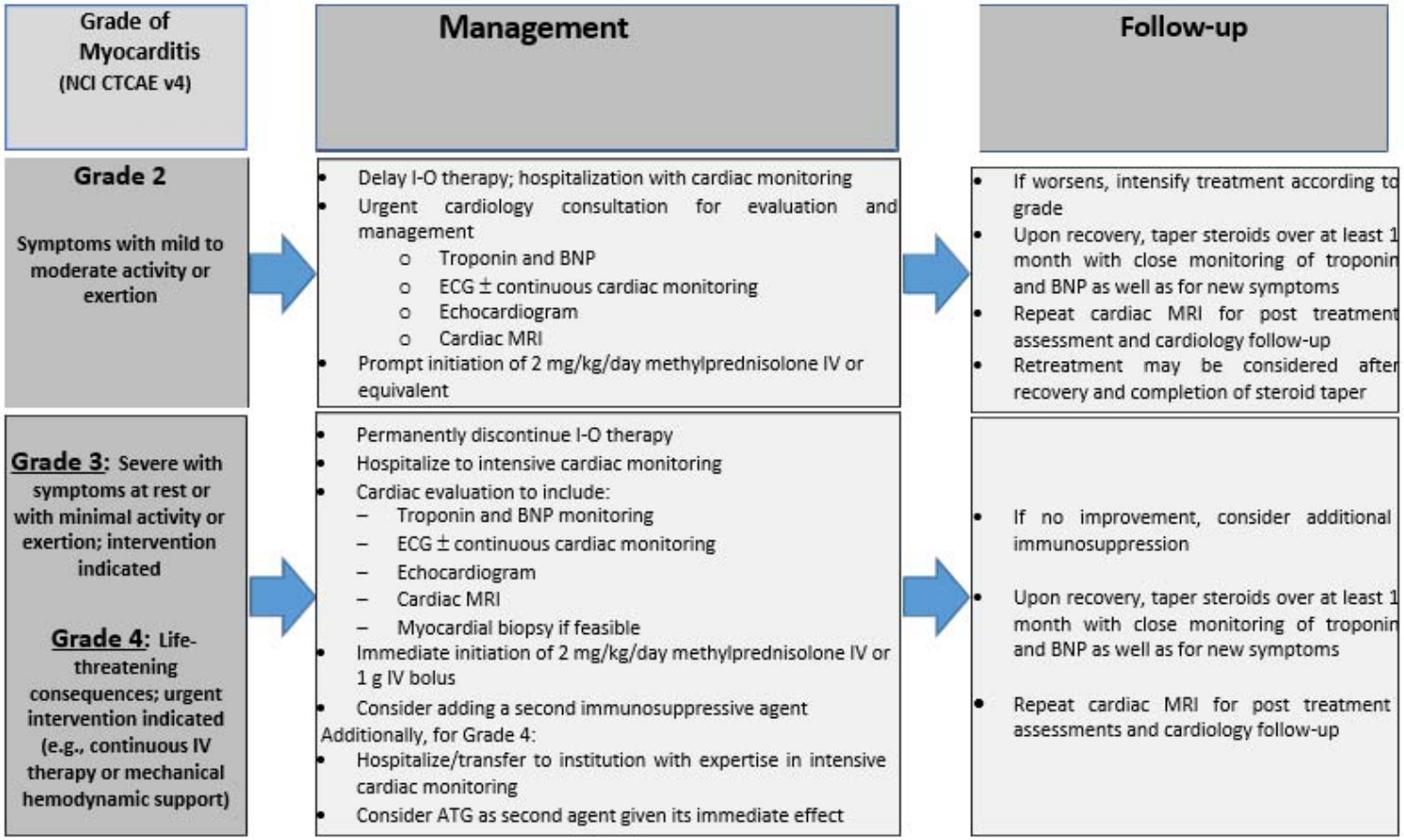
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 2 INTERNATIONAL WORKING GROUP CRITERIA FOR MALIGNANT LYMPHOMA

2007 IWG Response Criteria for Malignant Lymphoma				
Response	**Definition**	**Nodal masses**	**Spleen, Liver**	**Bone marrow**
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; residual mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative [Cohort C only] No evidence of FDG-avid disease in bone marrow
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses (index lesions); no increase in size of other nodes (non-index lesions) (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT	N/A	N/A
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node (index lesions), or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Key: CR = complete remission CT = computed tomography; FDG = [18F] fluorodeoxyglucose; IWG = International Working Group; NA = Not applicable; PD = progressive disease; PET = positron-emission tomography; PR = partial remission; SD = stable disease; SPD = sum of the product of the diameters.

CR (Complete Remission)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.
2. a. Typically [^{18}F] fluorodeoxyglucose (FDG)-avid lymphoma: in patients with no pretreatment positron emission tomography (PET) scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

   b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on computed tomography (CT) scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
4. For cohort A and B, if the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.
5. For cohort C, no evidence of FDG-avid disease in bone marrow will be required in all patients in lieu of bone marrow aspirate/ biopsy.

PR (Partial Remission)

The designation of PR requires all of the following:

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR, if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least 1 previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders

SD (Stable Disease)

SD is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

PD: Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered abnormal for relapse or progressive disease.

1. Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Reference: Cheson BD, Pfisner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. Journal of Clinical Oncology 2007;25:579-586.

APPENDIX 3 HASENCLEVER-INDEX FOR HODGKIN'S DISEASE ALSO KNOWN AS INTERNATIONAL PROGNOSTIC SCORE (IPS)

Composite score determined by assigning 1 point for each of the following factors;

- Age ≥ 45 yrs
- Serum albumin < 40 g/L
- Disease Stage 4
- Gender is male
- Hemoglobin level < 105 g/L
- White Blood Cells ≥ 15G/L
- Lymphocytes < 0.6 G/L or < 8% of White Blood Cells

Reference: Hasenclever D and Diehl V. **A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease.** NEJM 1998;339:1506-14.

APPENDIX 4 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 5 ACUTE GVHD GRADING AND STAGING

Table 1: Extent of Organ Involvement

Stage	Skin	Liver	Gut
1	Rash on < 25% of skin[a]	Bilirubin 2 - 3 mg/dL[b]	Diarrhea > 500 mL/day[c] or persistent nausea[d]
2	Rash on 25 - 50% of skin	Bilirubin 3 - 6 mg/dL	Diarrhea > 1000 mL/day
3	Rash on > 50% of skin	Bilirubin 6 - 15 mg/dL	Diarrhea > 1500 mL/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1 - 2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	--	Stage 2 - 3 or	Stages 2 - 4
IV[f]	Stage 4	Stage 4	--

[a] Use "Rules of Nines" (Table 2) or burn chart to determine extent of rash.

[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[c] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

[d] Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.

[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[f] Grade IV may also include lesser organ involvement with an extreme decrease in performance status.

Table 2: Percent Body Surfaces

Body Area	Percent	Total Percentage
Each Arm	9%	18%
Each Leg	18%	36%
Chest & Abdomen	18%	18%
Back	18%	18%
Head	9%	9%
Pubis	1%	1%

Ref.: Przepiorka et al. Bone Marrow Transplant 1995;15(6):825.

Stage of Chronic GVHD

Limited: Localized skin involvement resembling localized scleroderma with or without liver involvement; no other organ involvement.
Extensive: Generalized skin and/or multiple organ involvement.

Ref. Sullivan KM, Blood 1981;57:267.

APPENDIX 6 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 04b, 14-Sep-2018

The purpose of this revision is to clarify language surrounding the timing of biomarker sample collection, specifically plasma ctDNA. Additional changes were made to align text with nivolumab program standards and to align text concerning contraception with the Investigator's Brochure (IB) for nivolumab.

Revisions apply to all participants currently enrolled.

Summary of key changes of Revised Protocol 04b		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.1.2.1, Rationale for Cohort C	Added rationale for why plasma samples will be collected (for molecular monitoring of the disease).	To clarify text.
Section 1.4.3.5, Nivolumab Monotherapy Clinical Pharmacology Summary	In reference to the current IB, "additional information" was changed to "full details on the clinical pharmacology aspects of nivolumab."	To clarify text.
Figure 3.1.2-2: Treatment and Follow-up Phase for Cohort D	In top figure, the last bullet was corrected: "...survival visits continue every 3 months" was changed to 6 months.	To be consistent with the language in the Follow-up (FU)/Observational Phase subsection on the previous page.
Section 3.3.1, Inclusion Criteria: #3, Age and Reproductive Status	Changes to contraception wording.	To align with IB for nivolumab.
Section 3.4.1, Prohibited and/or Restricted Treatments	Added 3rd bullet: • Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.	To align with nivolumab program standards.
Table 5.1.1-4: Follow-Up Assessments for Cohort C Subjects who Discontinued due to CR (CA209205) or After Re-Initiation of Nivolumab	Added "or After Re-Initiation of Nivolumab" to the table title.	To clarify that follow-up assessments also apply to patients in Cohort C who discontinue after re-initiation of nivolumab.
Section 5.4, Efficacy Assessments	Sentence added to specify that for Cohort D, additional assessments, for example, Deauville scoring, may also be performed.	Since the predictive value of interim PET Deauville score in the prognosis of patients with Hodgkin's lymphoma using I-O (Nivolumab-AVD) in a first-line setting is of limited value, as opposed to when chemotherapy is used, the predictive value of EOT PET Deauville score might be more helpful.

Summary of key changes of Revised Protocol 04b		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.5-1: Sampling Schedule for Cohorts A, B, and C	In the Day 1 of every 12th cycle row, instead of samples being collected until discontinuation of study treatment, text was changed to "up to Cycle 49."	PK/IMG sample collection beyond Cycle 49 from subjects randomized to Cohorts A, B, or C is not required. Samples collected from subjects beyond Cycle 49 will not be used in PK/statistical analyses, tables, listings, or figures.
Section 5.6, Biomarker Assessments	In the last subsection, "Plasma samples," text was added that describes "novel sequencing-based methods" that "can detect circulating tumor DNA (ctDNA)."	ctDNA opens new opportunities for molecular monitoring before, during, and after therapy. It can also be used as a "liquid biopsy" to assess for molecular changes during the course of the therapy that may identify the emergence of treatment-resistant clones in the subjects at risk of relapse.
Table 5.6-1: CA209205 Biomarker Sampling Schedule for Cohorts A, B, and C	• "(ctDNA)" added after "Plasma" in last column heading and in table footnote a. • For plasma (ctDNA) collection times after Cycle 27, "Thereafter, every 6 cycles" was changed to "Cycle 68 Day 1" and "Cycle 81 Day 1." • Plasma (ctDNA) collection changed from "optional" to "strongly recommended" in the "Upon Progression" collection time row and in table footnote h.	• To be consistent with changes made in Section 5.6. • Collection of plasma/ctDNA after C27 was stopped since it is not expected that the emergence of any treatment resistance clones/mutations earlier than C68 will be identified. Plasma will be collected at C81 to confirm the presence and/or the selection of the mutations/clones at a later phase of the treatment course. • This time point is extremely important to identify emergence of therapy resistance clone; therefore, it has been specified as "strongly recommended."

Summary of key changes of Revised Protocol 04b		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.6-2: CA209205 Biomarker Sampling Schedule for Cohort D	"(ctDNA)" added after "Plasma" in last column heading.	To be consistent with changes made in Section 5.6.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized.