Protocol for

Official Title of Study

A Phase I/ II Study to Evaluate the Safety and Preliminary Efficacy of Nivolumab in Combination with Brentuximab Vedotin in Subjects with Relapsed Refractory Non Hodgkin Lymphomas with CD30 Expression CheckMate 436: CHECKpoint pathway and nivolumab clinical Trial Evaluation

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Incorporates Amendment: 04

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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 01	14-Sep-2016	Incorporates Amendment 04
Amendment 04	14-Sep-2016	This amendment will allow additional cohorts in subjects with relapsed PMBL & MGZL to participate in the expansion cohort. Additionally, the amendment will also provide defined Indeterminate response (IR) criteria along with changes in the biomarker section. Minor clarification in the inclusion, exclusion criteria and clarification of dose adjustment for brentuximab vedotin for grade 3 neurological toxicity has also been updated
Original Protocol	05-Aug-2015	Not applicable

SYNOPSIS

Clinical Protocol CA209436

Protocol Title: A Phase I/ II Study to Evaluate the Safety and Preliminary Efficacy of Nivolumab in Combination with Brentuximab Vedotin in Subjects with Relapsed Refractory Non Hodgkin Lymphomas with CD30 Expression CheckMate 436: CHECKpoint pathway and nivolumab clinical Trial Evaluation

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Brentuximab vedotin 1.8 mg/kg is to be administered as a 30-minute intravenous infusion on day 1 of every 3-week cycle during the Dose Evaluation Phase (Cohort A). The brentuximab vedotin dose for the Expansion Phase (Cohort B) will be determined once the Dose Limiting Toxicity (DLT) period in Cohort A is complete.

Nivolumab dose will be 240 mg flat administered intravenously over a 30-minute infusion throughout Cohort A and Cohort B. Nivolumab is to be administered on Cycle 1, day 8. Subsequent to cycle 1, both drugs will be administered on the Day 1 of every 3-week cycle.

Study Phase: Phase I/II

Research Hypothesis: The study will investigate the hypothesis that brentuximab vedotin can be safely combined with nivolumab. Additionally, the study will investigate that the combination can result in a clinical meaningful ORR in subjects with relapsed/refractory Diffuse Large B Cell Lymphoma (DLBCL), relapsed/refractory Peripheral T Cell Lymphoma (PTCL) (all subtypes excluding Anaplastic Large Cell Lymphoma), relapsed/refractory Primary Mediastinal B Lymphoma (PMBL), relapsed/refractory Mediastinal Gray Zone Lymphoma (MGZL) and relapsed/refractory Cutaneous T Cell Lymphoma (CTCL) Mycosis Fungoides/Sezary Syndrome (MF/SS).

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of the combination of nivolumab and brentuximab in subjects with the diagnosis of relapsed, refractory DLBCL, PTCL (all subtypes excluding ALCL), CTCL (MF/SS), PMBL and MGZL.
- To assess the clinical benefit of nivolumab and brentuximab vedotin combination regimen in subjects with the diagnosis of relapsed/refractory DLBCL, relapsed/refractory PTCL (excluding ALCL), relapsed refractory CTCL, relapsed/refractory PMBL, and relapsed/refractory MGZL (MF/SS) (CD30 expression ≥ 1% by immunohistochemistry (IHC) is a prerequisite for all subjects participating in this study), as measured by ORR, defined as the proportion of subjects achieving either a PR or CR. In subjects with relapsed/refractory DLBCL, relapsed/refractory PTCL, relapsed/refractory PMBL, and relapsed/refractory MGZL, the response will be assessed according to Lugano Classification 2014. For subjects with relapsed/refractory CTCL, response will be assessed according to consensus Global Response Score as per the consensus statement of the International Society for Cutaneous Lymphoma.

Secondary Objectives:

- To assess overall duration of response (DOR) of the brentuximab vedotin and nivolumab combination regimen based on investigators assessments
- To assess the complete response rate (CRR) with the combination regimen and the duration of CR based on investigators assessments.
- To assess progression free survival (PFS) based on investigators assessments and overall survival (OS) of the brentuximab vedotin and nivolumab combination regimen.

Exploratory Objectives:

- To assess the Indeterminate response (IR) per Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) in subjects with DLBCL, PTCL, PMBL, MGZL and CTCL (if applicable)

- To assess CD30 expression and correlate with response, and to assess PD-L1/L2 status and correlate it with response
- To characterize the molecular effects of the brentuximab vedotin and nivolumab combination regimen on tumor cells and the immune response; and identify biomarkers of response or resistance to the combination
- To assess tumor microenvironment and peripheral immune status
- To characterize pharmacokinetics of nivolumab and brentuximab and explore exposure response relationships
- To characterize the immunogenicity of nivolumab and brentuximab following combination therapy
- To evaluate changes in general health status assessed by the EQ-5D 3L (Cohort B only)

Study Design:

This is an open-label, multicenter phase I/II study of nivolumab in combination with brentuximab vedotin designed to evaluate the safety and efficacy in subjects with the diagnosis relapsed/refractory of DLBCL, PTCL (excluding ALCL) , CTCL (MF/SS), PMBL and MGZL.

The study will consist of three phases: Screening, Treatment and Follow-up. The treatment phase is divided in two parts: Cohort A consists of the Dose Evaluation Phase and Cohort B is the Expansion Phase.

It is anticipated that 170 subjects will be enrolled in the United States, Canada and Europe for the entire study (Cohort A and Cohort B combined). All subjects will undergo a screening period to determine eligibility within 28 days prior to initial dosing.

Dose Evaluation Phase (Cohort A)

The Dose Evaluation Phase (Cohort A) will include a dose limiting toxicity (DLT) evaluation for the dose level of brentuximab vedotin 1.8 mg/kg intravenously in combination with nivolumab 240 mg flat dose intravenously in a q 3 week cycle. Refer to section 4.5.1 for further details.

In cycle 1, brentuximab vedotin 1.8mg/kg will be administered on day 1 nivolumab 240 mg flat dose will be administered on day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30-minute rest. Nivolumab will then be administered also as a 30-minute infusion.

The DLT evaluation period, which consists of the first dose of study drug through the first 6 weeks of treatment, will be conducted in the first 6 treated subjects (all comers). Decisions to enroll up to 6 additional subjects onto the same dose of brentuximab vedotin 1.8 mg/kg in combination with nivolumab 240 mg flat dose intravenously every 3 weeks or at a reduced dose of brentuximab vedotin at 1.2 mg/kg will be based on the safety data reviewed throughout the DLT evaluation period.

If any of the first 6 treated subjects discontinue treatment for reasons other than a DLT but prior to completing the DLT evaluation period, then they will be replaced. Subjects enrolled to Cohort A will be monitored for DLT throughout the DLT evaluation period. Refer to section 4.5.1 for DLT definition.

After 6 DLT-evaluable subjects have been followed through the first 6 weeks of treatment, or at the point that 2 or more subjects experience a DLT, whichever comes first, the study team will review the available data and provide any of the following recommendations, but not limited to:

1. If one or none (≤ 1) of the 6 subjects experience a DLT, the expansion cohort will begin with brentuximab vedotin 1.8 mg/kg Cycle 1 Day 1 and nivolumab 240 mg flat dose on Cycle 1 Day 8.
2. If two or more (≥ 2) of the 6 subjects are determined to have had a DLT based on the protocol definition (refer to section 4.5.1) , the following options will be considered
    a. To repeat Cohort A of the study and treat up to 6 additional subjects at the same drug doses and schedule previously tested
    b. To repeat Cohort A of the study and treat up to 6 additional subjects at a reduced dose of brentuximab vedotin 1.2 mg/kg
    c. Administration of the combination treatment on Day 1 of every cycle, including cycle 1
    d. To close the study to additional enrollment

NOTE: Doses may not be increased to above 1.8 mg/kg brentuximab vedotin or nivolumab 240 mg flat dose.

On review of all available data, the study team may determine that the classification of DLT was not appropriate for one or more of the subjects, in which case enrollment may resume if the target of 6 DLT-evaluable subjects has not yet been reached. However, if 2 or more subjects were determined to have experienced DLTs, then expansion will not occur as the next step. Based on the study team's recommendations, up to 6 additional subjects may be enrolled in Cohort A at the same drug dose levels and schedule or at a modified treatment (described above in this section). These additional subjects will then be assessed for DLT in the same manner described above to determine if it is appropriate to move to the Expansion Phase (Cohort B). If it is determined by the study team that due to safety concerns no additional dose levels or schedules should be enrolled, then the study will be closed to enrollment.

There is no planned interim analysis (IA). However, all available efficacy and safety data will be used to select the recommended brentuximab vedotin dose and treatment schedule that will be further evaluated in the Expansion Phase (Cohort B).

Expansion Phase (Cohort B)

The Expansion Phase will assess the combination of nivolumab and brentuximab vedotin and will consist of a single-arm phase II study which will expand enrollment at the recommended dose level and treatment schedule as deemed safe by the study team in Cohort A. An additional 40 subjects in DLBCL (cohort B1), 30 subjects in PTCL (cohort B2), 20 subjects in CTCL (cohort B3), 30 subjects in PMBL (cohort B4) and 10 subjects MGZL (cohort B5) will be enrolled to complete this evaluation.

If one or none (≤ 1) of the 6 subjects experience a DLT, the expansion cohort will begin with brentuximab vedotin 1.8 mg/kg Cycle 1 Day 1 and nivolumab 240 mg flat dose on Cycle 1 Day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30-minute rest. Nivolumab will be then be administered as a 30-minute infusion. If two or more (≥ 2) of the 6 subjects are determined to have had a DLT based on the protocol definition (refer to section 4.5.1) treatment modification or enrollment closure will be considered, as described above.

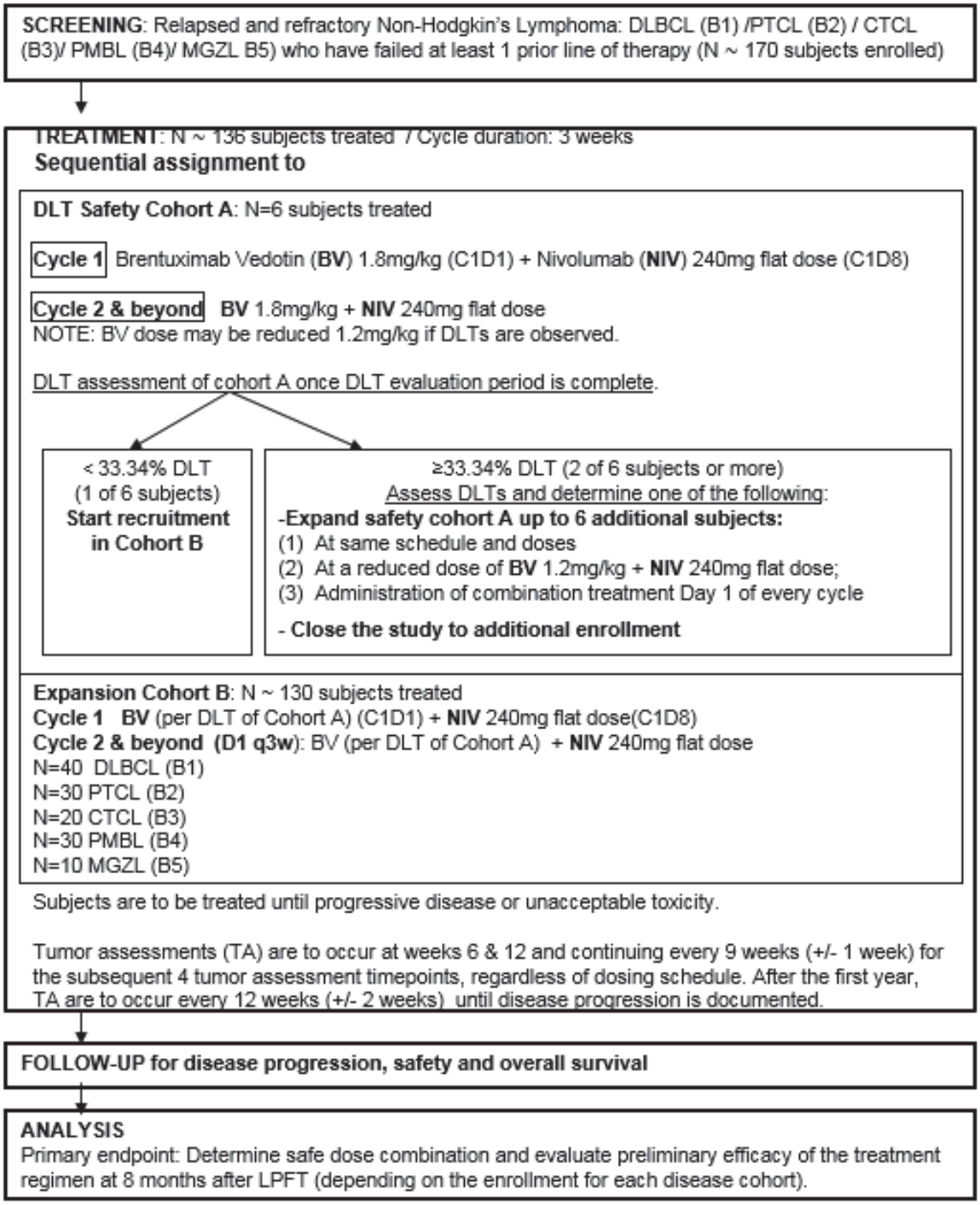
All subjects in Cohort A and Cohort B will be allowed to be treated until disease progression or unacceptable toxicity as described in Section 4.5.3 and Section 4.5.5. If during therapy it appears that a subject is benefiting from the combination but experiencing toxicities related to one agent that would require permanent treatment discontinuation, then they have the option to continue therapy with the single agent not attributing to toxicities.

Subjects that present progressive disease during treatment may be allowed to be treated beyond progression until further progression is observed. Refer to Section 4.5.9 for further details.

Once subjects discontinue from study treatment for any reason, subjects will enter the follow-up phase of the study. During follow-up, long-term safety, survival status, disease progression, subsequent anticancer therapy and occurrence of other primary malignancy data will be collected. Follow-up visit 1 (X01) and follow-up visit 2 (X02) will be in person visits and all subsequent follow-up visits may be done in person or by phone. All treated subjects will be followed for survival at least every 3 months until death or lost to follow-up. Subjects with residual toxicity G ≥ 2 at the time of discontinuation must follow these until resolved to at least G1, end of study or deemed irreversible, whichever occurs first. Subjects who discontinue for reasons different than progressive disease must continue to perform tumor assessments as described in Section 5.4 until disease progression is documented.

The primary endpoint for Cohort B will be investigator-assessed ORR for all five tumor types. This analysis will occur 8 months after the last patient receives their first treatment (LPFT). Depending on the enrollment for each disease cohort, the analysis may be done at different times for each cohort or at the same time for the five cohorts.

The study design schematic is presented below.



Study Population: Subjects with pathologically confirmed non-hodgkin lymphoid malignancies. The types of lymphoma for key eligibility criteria include; Diffuse Large B cell Lymphoma (DLBCL), Peripheral T cell Lymphoma (PTCL, all subtypes excluding Anaplastic Large Cell Lymphoma), Primary Mediastinal B Lymphoma (PMBL), Mediastinal Gray Zone Lymphoma (MGZL) and Cutaneous T cell Lymphoma (Mycosis Fungoides and Sezary Syndrome) that have failed at least one prior line of chemotherapy, along with measurable disease and confirmed CD30 expression ≥ 1%. Subjects must have an eastern cooperative oncology group (ECOG) score of 0-1, along with laboratory criteria as outlined in Section 3.3.

Study Drug include both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA209436		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	100mg (10mg/dL)	IP
Brentuximab Vedotin	50mg	IP

Study Assessments:

Safety Evaluation: Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.03. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Efficacy Assessments: Primary efficacy endpoint in this study is Objective Response Rate. Subjects will perform tumor assessments at week 6 and week 12 continuing every 9 weeks (+/- 1 week) for the subsequent 4 tumor assessment timepoints, regardless of dosing schedule. After the first year, tumor assessments are to occur every 12 weeks (+/- 2 weeks) until disease progression is documented. Subjects with DLBCL, PTCL, PMBL, and MGZL will follow the Lugano Classification 2014 and perform FDG PET-CT at the tumor assessment time points. Subjects with CTCL will follow the mSWAT and Global Response Score and will perform CT/MRI along with whole blood and medical photography (as appropriate) at the tumor assessment time points described in Section 5.4.

Statistical Considerations:

Sample Size: In the Dose Evaluation Phase (Cohort A), 6 -12 subjects will be treated. The number of subjects is not based on statistical power considerations. If less than 1/3 of 6 subjects experience a DLT, the upper limit of the 80% 1-sided exact confidence interval for the true DLT rate will not be greater than 42%. If less than 1/3 of 12 subjects experience a DLT, the upper limit of the 1-sided 80% exact confidence interval (CI) for the true DLT rate will not be greater than 41.2%.

In the Expansion Phase (Cohort B), a total of 130 subjects will be treated, with 40 subjects in cohort B1 (DLBCL), 30 subjects in cohort B2 (PTCL), 20 subjects in B3 (CTCL), 30 subjects in cohort B4 (PMBL) and 10 subjects in cohort B5 (MGZL).

- Given 40 subjects in DLBCL, the one-sided 90% confidence interval (ie, two-sided 80% confidence interval) for the ORR is 48.6% - 70.6% if we assume an observed ORR rate of 60%. The lower bound of the 90% CI excludes 40%, which is the null hypothesis ORR rate for PTCL.
- Given 30 subjects in PTCL, the one-sided 90% confidence interval (ie, two-sided 80% confidence interval) for the ORR is 46.7% - 72.3% if we assume an observed ORR rate of 60%. The lower bound of the 90% CI excludes 40%, which is the null hypothesis ORR rate for PTCL.
- Given 20 subjects in CTCL, the one-sided 90% confidence interval (ie, two-sided 80% confidence interval) for ORR is 63.9% - 91.0% if we assume an observed ORR rate of 80%. The lower bound of the 90% CI excludes 60%, which is the null hypothesis ORR rate for CTCL.
- Given 30 subjects in PMBL, the one-sided 90 % confidence interval (ie, two-sided 80% confidence interval) for the ORR is 37.0% - 63.0% if we assume an observed ORR rate of 50%. The lower bound of the 90% CI excludes 30%, which is the null hypothesis ORR rate for PMBL.
- Given 10 subjects in MGZL, the one-sided 90 % confidence interval (ie, two-sided 80% confidence interval) for the ORR is 11.6% - 55.2% if we assume an observed ORR rate of 50%. The lower bound of the 90% CI excludes 10%, which is the null hypothesis ORR rate for MGZL.

Table below summarizes the 90% exact CI for different targeted ORRs and sample sizes. The targeted ORR of 60% in DLBCL and PTCL and 80% in CTCL, and null hypothesis ORR rate of 40% in DLBCL and PTCL and 60% in CTCL are based on the historical data and the activity of brentuximab vedotin and nivolumab as single agents from phase I and phase II studies.

One-sided 90% Exact CI for different number of subjects in each cohort		
	If the observed ORR rate is 60% in Cohort B1 and B2	**Power**
N=30	[46.7% - 72.3%]	82%
N=40	[48.6% - 70.6%]	87%
	If the observed ORR rate is 80% in Cohort B3	
N=20	[63.9% - 91.0%]	62 %
	If the observed ORR rate is 50% in Cohort B4	
N=30	[37.0% - 63.0%]	81 %
	If the observed ORR rate is 30% in Cohort B5	
N=10	[11.6% - 55.2%]	61%

Also, If we have 20 subjects in Cohort B3, assuming true ORR is 80%, there will be approximately 62% power to reject null hypothesis that the true ORR is <=60%, considering a one-sided alpha of 10%. Given a very low prevalence of CTCL, 20 subjects in cohort B3 is considered as feasible and adequate for a phase II signal detecting trial. Sample size of 30 subjects in Cohort B2 and 40 subjects in Cohort B1 are corresponding to power of 82% and 87% respectively to reject null hypothesis that the true ORR is <=40% assuming true ORR is 60% and considering a one-sided alpha of 10%. If we have 30 subjects in Cohort B4, assuming true ORR is 50%, there will be approximately 81% power to reject null hypothesis that the true ORR is <= 30%, considering a one-sided alpha of 10%. Finally if we have 10 subjects in Cohort B5, assuming true ORR is 30%, there will be approximately 61% power to reject null hypothesis that the true ORR is <= 10%, considering a one-sided alpha of 10%.

Endpoints: The safety endpoints include incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The primary efficacy endpoint is ORR. It is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR 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 or the date of subsequent therapy, whichever occurs first. In subjects with relapsed/refractory DLBCL, relapsed/refractory PTCL, relapsed refractory PMBL and relapsed refractory MGZL the response (CR, PR, PD, and progression) will be assessed according to Lugano Classification 2014. For subjects with relapsed/refractory CTCL, response will be assessed according to consensus Global Response Score as per the consensus statement of the International Society for Cutaneous Lymphoma. The secondary endpoints are DOR, CR rate, duration of CR, PFS and OS.

Analyses: All analyses will be performed separately for each cohort and also for all treated subjects.

Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All on study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.03 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.

The ORR will be summarized by binomial response rates and their corresponding one-sided 90% exact CIs using the Clopper-Pearson method. The same analysis will be performed for CR rate.

The DOR will be summarized by cohort for subjects who achieve confirmed PR or CR using the Kaplan Meier (KM) product-limit method. Median values of DOR, along with one-sided 90% CI using log-log transformation method and range, will also be calculated. The same analysis will be performed for duration of CR, PFS and OS at 1 year.

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1 INTRODUCTION AND STUDY RATIONALE

Treatment with conventional cytotoxic chemotherapy results in promising responses by eliminating tumor cells, however a great majority of subjects relapse with need for therapies that can result in durable responses. The therapeutic efficacy of standard conventional chemotherapeutic treatments is often limited by the emergence of molecular resistance resulting in relapse. Evasion of the host immune responses is an important mechanism for inducing resistance to cancer therapy.[1,2] Over the last several decades drug development in oncology has seen the emergence of immune therapies.[3] The armamentarium includes 1) vaccine approaches to cause strong specific immune responses to tumor antigens 2) adoptive transfer of ex vivo expanded engineered or innate tumor specific lymphocytes 3) therapeutic administration of monoclonal antibodies such as rituximab against CD20 on lymphoid malignant cells, Herceptin® (trastuzumab) directed against HER2 on breast cancer cells and 4) strategies to block molecular and cellular mediators of cancer induced immunosuppression such as Cytotoxic T-Lymphocyte Antigen 4 (CTLA4, CD152), Programmed Death -1 receptor (PD-1, CD279) or T regulatory cells (T reg).[1]

Tumor cells up regulate expression of the immune check point receptors (ICR) such as CTLA4, PD-1 and the ligands (PD-L1, B7-H1/CD274) ICR which effectively attenuates the T-cell proliferation and anti tumor effects.[4] The success of anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) (ipilimumab) in cancer therapy has highlighted the potential role for other check point inhibitors.[4] Analogous to anti-CTLA4, a second immune check point inhibitor, directed against PD-1 has gained interest due to the potential to circumvent multiple immunosuppressive mechanisms emanating in the tumor microenvironment.[5] PD-1 is an immune inhibitory receptor of the CD28/CTLA-4 family which regulates the homeostasis of T cells activation, tolerance and immunopathology.[6] The PD-1/PD-L1 interaction inhibits T lymphocyte proliferation, survival and effector function (cytotoxicity, cytokine release). PD-1 immune check point inhibition has been shown to result in up regulation of genes associated with effector, NK cell function and cytolytic effects.[6] The cardinal biological effects of PD-1immune check point inhibition are manifested by reversal of exhaustive CD8+T cells, averting depletion of memory B cells, depleting Foxp3+iTreg cells and restoring robust Th1 immunity.[6] Targeting PD-1immune check points has the potential to play a major role in cancer therapy by reversing tumor immune escape. Nivolumab is a fully human, IgG4(k) 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), abrogating the inhibitory signals and augmenting host antitumor immune response.[6] Nivolumab has demonstrated efficacy in solid and hematological malignancies.[7,8] Clinical studies are ongoing to further elucidate the efficacy of PD-1 immune check-point inhibition in hematologic malignancies.[9,10]

Nivolumab

Nivolumab is a fully-human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]) that targets PD-1. In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Nivolumab blocks the PD 1 pathway and results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augments IFN- γ secretion from CMV-specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[11] Nivolumab is indicated for the treatment of subjects with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.[12] Nivolumab is indicated for the treatment of metastatic Squamous Non-Small Cell Lung Cancer (NSCLC) with progression on or after platinum-based chemotherapy.[13] Nivolumab is approved in US, Europe and Japan for the treatment of subjects with unresectable or metastatic melanoma following progression on ipilimumab. Nivolumab is approved in US and Europe for the treatment of metastatic Squamous Non-Small Cell Lung cancer (NSCLC).

Nivolumab has demonstrated efficacy in lymphoid malignancies. Results from a phase I trial with heavily pre treated group of lymphoid malignancies demonstrated anti tumor effects of Nivolumab in subjects with relapsed B, T Non Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma (HL). The Overall Response Rate (ORR) in 29 subjects with B NHL was 28% and in 23 subjects with T NHL was 17% respectively.[9] Nivolumab has demonstrated remarkable efficacy in subjects with relapsed refractory HL. In a heavily pre treated group of 23 subjects, therapy with nivolumab demonstrated promising clinical activity. The ORR reported in this study was 87%, Complete Response Rate (CRR) of 17% Partial Response Rate (PRR) of 70% and (13%) of subjects achieved Stable Disease (SD). The Progression Free Survival (PFS) at 24 weeks was reported as 86% Nivolumab has been designated breakthrough therapy for the treatment of relapsed HL after failure of autologous stem cell transplantation and brentuximab vedotin.[8,9] Nivolumab is currently being developed by Bristol Myers Squibb for the treatment of solid tumors and hematological malignancies.

Brentuximab Vedotin

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of 3 components:1) the chimeric IgG1 antibody cAC10, specific for human CD30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The primary mechanism of anticancer activity of brentuximab vedotin is binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage.

Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell.[14]

Additionally brentuximab vedotin has shown to induce Immunogenic Cell Death (ICD).[15] ICD is a distinct cell killing mechanism mediated through toll like receptor ligands which can abrogate the inhibitory effect of tumor immunosuppressive microenvironment and reinitiate the immune responses. Brentuximab vedotin possible immune modulatory properties were demonstrated in a report analyzing brentuximab vedotin's effects in CD30+ Hodgkin Lymphoma cell lines. Brentuximab vedotin was evaluated for its ability to induce Endoplasmic Reticulum Stress (ER). It was shown that brentuximab vedotin in a dose dependent manner up regulated the apoptotic endoplasmic reticulum ER sensor C/EBP homologous protein which resulted in cleavage and activation of ATF6, a transcription factor required for induction of the ER stress. The net results were induction of ER stress and ICD markers. Induction of ICD was associated with activation of immune reaction. It was concluded that exposure of dendritic cells to brentuximab vedotin- killed tumor cells evoked an inflammatory phenotype including an increase in co-stimulatory markers CD86 and Major Histocompatibility Complex (MHC) Class II antigens, and activation of Nuclear Factor kB (NFkB) an intermediate of inflammatory signaling pathway. This suggests additional brentuximab vedotin anti tumor effects by activating the innate immune response, although this effect remains to be validated, as the observations are early and ex vivo.

In a pivotal phase 2 study of 102 subjects with relapsed or refractory Hodgkin lymphoma (HL) following autologous stem cell transplant (SCT), treatment with brentuximab vedotin resulted in an ORR of 75% (95% CI, 64.9%–82.6%). The CRR was 34% (95% CI, 25.2%–44.4%) and the median PFS for all subjects on study was 5.6 months (95% CI, 5.0–9.0 months).[14] Brentuximab vedotin is approved for the therapy of relapsed HL after failure of autologous transplant or after failure of at least two multi agent systemic chemotherapy for subjects who are not candidates for autologous transplant.

Brentuximab vedotin has also demonstrated activity in systemic Anaplastic Large Cell Lymphoma (ALCL). In a trial of 58 subjects with relapsed CD30+ ALCL who had received prior systemic chemotherapy, brentuximab vedotin demonstrated an ORR of 86%, CRR of 57%, and PRR of 29%. The median duration of response was reported as 12.6 months. The most common adverse event reported was peripheral sensory neuropathy, neutropenia, diarrhea, pyrexia, thrombocytopenia, cough and vomiting. [16]

Brentuximab vedotin has also shown efficacy in other lymphoid malignancies. Ongoing trials in different NHL are exploring its full potential. Brentuximab vedotin is currently being developed by Seattle Genetics for the treatment of hematological malignancies.

1.1 Study Rationale

Study CA209436 is an open label, multi center Phase 1/2 study to investigate the safety and efficacy of nivolumab in combination with brentuximab vedotin in subjects with relapsed, refractory Diffuse Large B Cell Lymphoma (DLBCL), Peripheral T Cell Lymphoma (PTCL) all subtypes excluding Anaplastic Large Cell Lymphoma (ALCL), Cutaneous T Cell Lymphoma

(CTCL) Mycosis Fungoides (MF), Sezary Syndrome (SS), Primary Mediastinal B Lymphoma (PMBL) and Mediastinal Gray Zone Lymphoma (MGZL).

Harnessing host immune response is an important antitumor strategy. In this context reversing the effects of exhaustive T cells by checkpoint blockade agents is being actively explored as an effective immune therapy in clinical trials. It has been advocated that optimal T cell-based antitumor immunity requires both CD8+ T cells acting as cytolytic effector cells and CD4+ Th1 cells to sustain antitumor response. Additionally it has been suggested that PD-1 blockade can restore robust Th1 immunity and T cell activation, hence abolish immunosuppression in the tumor microenvironment.[2,5] Although immune therapies including check point blockade appear effective anti cancer therapies, concerns remains for enhancing efficacy due to limitation of single agent activity which has been observed in certain tumor types. Some of the strategies to enhance the efficacy of immune therapies include improving the quality of effector cells and to reveal additional tumor antigens.[2] The MHC class II antigen processing pathway is altered in cancer thereby precluding efficient presentation of T cell epitopes.[2] Hence one strategy to increase efficacy of check point blockade is by combining with agents which possess the ability to enhance the effects of MHC Class II molecules to increase antigen presentation. It is therefore postulated that nivolumab and brentuximab vedotin combination will have additive and synergistic mechanism of actions.

Brentuximab vedotin will mediate its effects through induction of apoptosis.

Brentuximab vedotin may provide synergy by inducing ICD. Induction of ICD may enhance and increase the expression of the co stimulatory molecule CD86 and MHC Class II antigens. These effects may result in augmenting the effects of nivolumab.

Nivolumab by inducing robust Th 1 immunity and T cell activation, will result in augmenting host anti tumor immune response.

Collectively this combination has a high potential of becoming an effective novel therapy in lymphoid malignancies with unmet medical need.

1.1.1 Unmet medical need in DLBCL

DLBCL is the most common form of NHL. With the standard first line chemo immunotherapy (anthracycline based regimen and rituximab), 67% of subjects are alive at a median follow up of 4 years.[17] This implies that approximately 30-40% of subjects either relapse after standard therapy or demonstrate presence of refractory disease. At the time of relapse, the standard of care is to offer high dose therapy with autologous transplant to subjects who demonstrate chemo sensitive disease. The salvage chemotherapy is comprised of platinum or cytarabine based regimens in combination with rituximab. Most studies have demonstrated CRR with salvage regimen ranging from 20-40%.[18,19] The Landmark PARMA study has established autologous transplant as a standard treatment modality in the management of relapsed DLBCL for subjects demonstrating chemo sensitive disease. The PARMA trial demonstrated the rate of Event Free Survival (EFS) of 46% for subjects in the transplant group versus 12% in the group which received chemotherapy

without transplant.[20] Subjects who do not respond to salvage therapy have an extremely poor outcome with a median survival of only 4 months with 4% alive at 1 year.[21] Furthermore, only 20-25% subjects after autologous transplant sustain durable responses. Treatment options following failure of transplant or for chemo refractory subjects are finite. This underscores the urgent need for effective therapy for subjects with relapsed refractory DLBCL. Several novel agents are emerging and have shown activity in relapsed DLBCL.[22] Nivolumab has demonstrated activity as a single agent in subjects with relapsed refractory DLBCL. A total of 11 subjects with relapsed DLBCL were treated with nivolumab. Nivolumab was administered at a dose of 1mg/kg intravenously followed by 3mg/kg intravenously in the expansion cohort until disease progression or unacceptable toxicities. The trial reported an ORR of 36%, CRR of (9%), PRR of (27%), and (27%) SD. The median duration of response was 17 weeks (range 6-44.1+) at a median follow up of 23 weeks (range 3-69.0+). Overall the study treatment was well tolerated and majority of adverse event reported were grades 1-2.[9] Results from a phase II study in subjects with NHL has demonstrated efficacy of brentuximab vedotin in subjects with relapsed DLBCL. There were a total of 49 subjects with relapsed DLBCL, brentuximab vedotin was administered at 1.8 mg/kg intravenously every 3 weeks. Subjects who achieved SD or better could continue treatment until disease progression, unacceptable toxicity or study closure. Subjects with relapsed DLBCL were noted to have an ORR of 44%, with (17%) achieving Complete Remission (CR) in subjects with CD30 expression. The median duration of response was reported as 16.6 months in subjects with CR. Significant activity of brentuximab vedotin was noted across a range of CD 30 expression.[23] An important observation from a majority of the trials of novel agents in relapsed DLBCL is that they have limited single agent activity, suggesting the need of adjuncts to improve quality of response. Trials with novel agent combinations are needed to address an important unmet medical need in this patient population.

1.1.2 Rationale for nivolumab and brentuximab vedotin in relapsed DLBCL

Since the outcome remains dismal for relapsed refractory DLBCL, incorporation of novel agents is key to identify and improve therapy. Research elucidating molecular characterization in DLBCL is emerging to provide insight which can facilitate drug development to improve outcomes. The International Prognostic Index (IPI) is used to delineate subjects into prognostic subgroups based on clinical prognosticators however it lacks biological insight which attributes to the heterogeneity of the disease. Gene- expression profile has yielded important prognostic and biological information for DLBCL. The Leukemia and Lymphoma Profiling Project (L&LPP) using microarray identified two independent groups with distinct gene expression profiles based on hierarchical clustering.[24,25] The two groups based on Cell of Origin (COO) include the Germinal Center subtype (GC) and Activated B Cell like (ABC) or non-Germinal center (non GC) subtype. Subjects with ABC are noted to have inferior outcomes as compared to the GC subtype. In an updated analysis from the L&LPP, in subjects with DLBCL treated with Rituximab, Cyclophosphamide, Adriamycin, Oncovin, Prednisone(R-CHOP) two gene signatures were identified. The favorable signature stromal 1 demonstrated genes related with extracellular matrix and histiocytic infiltration. The stromal signature 2 which was associated with worse prognosis

was reflective of genes linked with angiogenesis and surrounding macrophages.[26,27] This suggests role of tumor microenvironment in DLBCL pathology. Relapsed NHL is often treated with allogeneic transplant, underpinning the role of adaptive immunotherapies in this setting.[28] Eradication of immune tolerance in this patient population may provide an important therapeutic strategy. This is further supported by activity of check point blockade agents such as anti PD1 in relapsed DLBCL. In a phase II trial of subjects with relapsed DLBCL undergoing autologous transplant, pidilizumab an anti PD-1 monoclonal antibody was administered for measurable disease following transplant. The therapeutic benefit of anti-PD1 was manifested by a CRR of 34% and ORR of 51% among subjects with measurable disease.[10] Likewise, Nivolumab has demonstrated activity in heavily pre treated group of subjects with relapsed DLBCL with an ORR of 36%.[9]

CD 30 is a membrane glycoprotein associated with the TNF receptor (TNFR) superfamily. There is suggestion that CD30 stimulation results in cell cycle arrest, apoptosis and activation of the prosurvival transcription factor NF-kB.[29] CD30 is expressed in several lymphoid malignancies. Results from a retrospective analysis of 167 cases of archived tissue from subjects with DLBCL, demonstrated variable CD30 expression measured by immunohistochemistry (IHC). Twenty one percent (95% confidence interval [CI]: 14.8-27.1%) of these cases expressed CD30, and in 52% of samples CD30 expression was noted in > 80% of tumor cells.[30] Multivariate analysis performed in Bcl2+ DLBCL showed that higher frequency of CD30 expression was observed in samples with non- GC subtype, and in subjects < 47 years old. Another group examined CD30 expression in subjects with de novo DLBCL using IHC. A total of 385 cases of formalin fixed paraffin embedded DLBCL in tissue microarray were examined. Using a > 0% cut off, CD30 expression was predicted of superior 5 year progression free within R-CHOP treated germinal center B cell like DLBCL (86% versus 64%, p=0.020). Epstein - Barr virus (EBV) was identified in 11 (3%) of cases in the non- GCB/ABC subtype DLBCL (p=0.001).[31] International DLBCL Rituximab-CHOP Consortium Program evaluated 903 cases of de novo DLBCL. It was reported that approximately 14% of subjects with DLBCL express CD30. The subjects with CD30 expression DLBCL had superior Overall Survival (OS) and PFS regardless of the COO. In multivariate analysis, controlling other variables, including B symptoms, tumor size, IPI, COO classification and TP53 mutational status, absence of CD30 expression remained an independent inferior predictor of overall survival Hazard Ratio [HR] of 3.03; 95% Confidence Interval [CI], 1.33-6.89; P = .0082) and Progression Free Survival (PFS) (HR of 2.89; 95% CI, 1.35-6.20; P = .0064).The molecular elucidation in this group using gene expression profiling depicted up regulation of genes encoding negative regulators of NF κB activation and lymphocyte survival, and down regulation of genes encoding B-cell receptor signaling and proliferation, as well as prominent cytokine and stromal signatures in CD30 expressed DLBCL subjects, suggesting a distinct molecular basis for its favorable outcome.[32] Although the report is suggestive of favorable prognosis in de novo frontline R-CHOP treated subjects with CD30 expressed DLBCL, the prognostic implications of CD30 expressed DLBCL in relapsed setting remains unclear and some report suggest association with

CD30 expression as an adverse prognosticator.[33] Results from a phase II study in subjects with NHL has demonstrated efficacy of brentuximab vedotin in subjects with relapsed DLBCL.[23]

Based on these observations, it is postulated that combined immune modulation with antibody-mediated PD-1 immune-checkpoint blockade nivolumab and brentuximab vedotin may result in additive activity and synergistic activity translating into improved clinical outcomes in subjects with relapsed DLBCL.

1.1.3 Unmet medical need in Peripheral T Cell NHL (PTCL)

PTCL is a heterogeneous group of aggressive T cell NHL which carries a poor prognosis. The incidence of PTCL is < 1 case per 100, 000 people in the United States. Despite being a rare tumor PTCL accounts for substantial numbers of death worldwide.[34] PTCL encompasses several different types, among which the most frequent subtypes are PTCL- Not Otherwise Specified (NOS-25.9%) and Angioimmunoblastic T cell Lymphoma (AITL-18.5%). Historically the treatment of PTCL has comprised of integration of cytotoxic chemotherapy combination such as CHOP in the frontline treatment. The outcome for subjects with PTCL remains dismal with a reported 5 year overall survival of only 37%.[35,36] More intensive chemotherapeutic regimens such as ACVBP (dose-intensified doxorubicin, Cyclophosphamide, Vindesine, Bleomycin and Prednisone) have been employed for younger subjects with superior event free survival and overall survival albeit at the expense of increase in toxicities.[36] The majority of subjects with PTCL require many lines of therapies with ultimate dismal outcomes. Recently integration of novel agents in the management of PTCL has been employed with the aim to improve outcomes in this highly aggressive disease group. Pralatrexate is a novel folate antagonist which exerts its effects by binding to the reduced folate carrier. Pralatrexate has demonstrated activity in subjects with relapsed PTCL. The phase II PROPEL (Pralatrexate in Patients with Relapsed or Refractory T-cell Lymphoma) trial demonstrated activity of pralatrexate in subjects with relapsed refractory PTCL. The total number of subjects treated were 111 with a median of 3 prior therapies. Pralatrexate was administered at a dose of 30mg/m^2/week for 6 weeks in 7 weeks cycle. Approximately 63% of subjects were refractory to their last therapies. The reported ORR was 29%, CRR of 11% with a median duration of response of 10.1 months. The median PFS and OS were 3.5 and 14.1 months respectively.[37] Important toxicities include mucositis and thrombocytopenia. Pralatrexate was approved by the United States Food and Drug Administration as a single agent for the treatment of relapsed refractory PTCL. Romidepsin, one of the Histone Deacetylase Inhibitor (HDACi), has also demonstrated activity in the treatment of relapsed PTCL. In a phase II trial with 131 subjects with PTCL, romidepsin was administered at a dose of 14mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28 days cycle. The ORR was 25%, CRR 15% and the median duration of response was 17 months with the longest ongoing response at 34 months. The most common adverse events include cytopenias and infections along with nausea and fatigue.[38] Brentuximab vedotin has demonstrated promising activity in patient with relapsed ALCL. In a phase II trial 58 subjects with ALCL were treated with brentuximab vedotin at 1.8 mg/kg intravenously every 3 weeks. The ORR was 86%, CRR 57% and PRR 29%. The median duration of response was 12.6 months.[16] Horwitz

et al also demonstrated activity of brentuximab vedotin in subjects with relapsed CD30+ PTCL. In this phase II study the total number of subjects with PTCL NOS=22 and AITL n=13. The ORR was 41% (8CR, 6PR) in subjects with PTCL NOS and the ORR was 54% (5 Complete Response, 2 Partial Response) in subjects with AITL.[39] Nivolumab has also demonstrated activity in subjects with T NHL (n=23) the ORR has been reported as 17% with PRR for 4(17%), SD for 10(43%). In this phase I study the total number of subjects with PTCL was 5. Nivolumab was administered at 1mg/kg intravenously every 2 weeks and at 3 mg/kg intravenously every 2 weeks in the expansion cohort until unacceptable toxicities or disease progression. The ORR for the PTCL cohort was 40% and PRR (40%) Importantly, the duration of response appears durable in the responding group.[9]

The overall prognosis of PTCL remains poor, marked with multiple relapses and OS at 10 year of 10-15%, hence there remains a vital need to develop effective therapies. The availability of novel agents allows for exploring combination with scientific rationale to improve not only response rates but also durability of responses.

1.1.4 Rationale for nivolumab combination with brentuximab vedotin in PTCL

PTCL encompasses several subtypes originating from the post thymic T lymphocytes mature T cells.[40] The scarcity of cases of PTCL, diverse morphology and lack of diagnostic markers are some of the factors for impeding the progress in the molecular and genetic characterization in PTCL.[40,41] With the exception of ALCL which harbors the specific genetic abnormality t(2;5)(p23;q35), other subtypes of PTCL lack specific genetic abnormalities.[40,42] The cellular inception of several of the subtypes of PTCL remains obscure or appears to be heterogeneous. At the present time approximately 50% of PTCL cases are not classifiable.[41] Majority of PTCL NOS are related to the CD4 helper cells and a minority are analogous to CD8 cytotoxic cells. T follicular helper cells (TFH) have been identified as the cell of origin for a few subtypes of PTCL including AITL.[43,44] The AITL neoplastic cells are identified as clonal mature αβ CD4+ T cells which express numerous TFH markers such as; CXCL13, PD1, ICOS, CD200 and BCL6.[40] Studies incorporating gene expression profiling have began to delineate biological and prognostic subgroups to elucidate pathobiology in PTCL.[45] Iqbal et al recently examined gene expression profiling in 372 PTCL cases. The group demonstrated high expression of several signatures association with the tumor microenvironment in subjects with AITL. The genes in the signature depicted strong associated with angiogenesis and vascular endothelial function or cell migration. Furthermore, 2 major subgroups in PTCL NOS were recognized. The 2 subgroups include GATA3 with high expression of GATA3 and target genes (CCR4, IL18RA, CCL3, and IFNɣ) and the TBX21 with high expression of TBX2I, EOMES, and CXCR3, IL2RB, CCL3 and IFNɣ). The enrichment in these subgroups depicts gene signatures related to proliferation (MYC), mTOR (PI3K), IFNɣ induced genes and NFKB gene signatures. The presence of GATA3 profile was noted to be associated with inferior outcomes.[46] The role of immunosuppressive microenvironment in PTCL was further validated by a study by Wilcox et al. Tumor biopsies were evaluated for the expression of PD-L1 (B7-H1) from subjects with CTCL and PTCL.

Approximately 50% of T cell NHL cases examined depicted expression of PD-L1. The expression was noted in the cells within the microenvironment such as the monocyte derived cells, dendritic cells and the macrophages.[47] Collectively these observations suggest strong influence of pro inflammatory and immunosuppressive microenvironment in PTCL.[47]

In this context PD-1 modulation may provide a benefit by enhancing immune responses in subjects with PTCL. Results from a phase I trial are indicative of activity of nivolumab in PTCL. Additionally brentuximab vedotin appears active in PTCL, hence combination of these agents may provide a novel combination which will result in improving quality of responses.

1.1.5 Unmet medical need in CTCL Mycosis Fungoides (MF) and Sezary Syndrome (SS)

The incidence of CTCL in the United States is 6.4/million/year. MF and SS comprise 53 % of CTCL cases per year. Treatment for CTCL is stage dependent, with local therapies used for early stage and systemic therapies employed for extensive or relapsed diseases.[48] The response to systemic therapy for relapsed disease is often ephemeral and underscores the need for developing effective agents in this disease.[49] Numerous chemotherapeutic agents have shown activity in MF/SS. Gemcitabine has demonstrated CRR of 11-51% with duration of response of 10-15 months.[50] Pegylated liposomal doxorubicin has shown an ORR of 88% with disease free survival of 13 months.[51] Additionally combination chemotherapy CHOP has shown an ORR of 66% in subjects with CTCL.[52] Biological agents such as anti CD52 monoclonal antibody alemtuzumab and the fusion toxin denileukin diftitox targeting the interleukin 2 receptor and bexarotene have also demonstrated activity in CTCL (MF/SS).[53,54]Recently novel agents such as HDACi (romidepsin and vorinostat) have been approved for the treatment of MF/SS.[55,56] Romidepsin has demonstrated activity in subjects with CTCL. Results from a phase II trial in 96 subjects with CTCL demonstrated an ORR was reported as 34% & CRR 6%. The median duration of response was 15 months. Romidepsin was administered as an intravenous infusion at a dose of 14mg/m^2 on days 1, 8 and 15 every 28 days. The commonly reported adverse events reported were mild and mainly involving the gastrointestinal tract which included nausea, fatigue, infections, vomiting and decrease in white blood cells[57]. Vorinostat is another HDACi for the treatment of CTCL in subjects who have failed prior therapies. The pivotal study was a single agent vorinostat at an oral dose of 400 mg daily. The total number of subjects in this phase II trial was 74. The trial demonstrated an ORR of 30%, the estimated median duration of response was 168 days. The most common adverse events were diarrhea, fatigue, nausea and anorexia.[58] Nivolumab has demonstrated activity in subjects with CTCL. In the phase I trial with nivolumab the total number of subjects with CTCL (MF) was 13. Nivolumab was administered at 1 mg/kg intravenously followed by 3 mg kg intravenously every 2 weeks in the expansion cohort. The response for MF cohort was an ORR of 15% with PRR of (2, 15%) and SD in (9, 69%) subjects. Importantly, the duration of response appears durable in the responding group. Overall the therapy is well tolerated with majority of adverse events reported as grades 1-2.[9]

Brentuximab vedotin has also demonstrated activity in subjects with CD30+ CTCL. In a phase II trial of 32 subjects with relapsed CTCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 week up to 8 cycles with optional extension of additional 8 cycles for the responding subjects. The ORR was 70% (21/30), responses were observed in all clinical stages. Additionally 54% of subjects were progression free at 12 months. The median maximum CD30 expression by IHC of all subjects was 13 %(range 0-100%; 6 had < 5%), the median was noted to be higher in responders (CRR/PRR) 15%, versus non responders 3% (p = 0.037) It was also demonstrated that subjects with CD30 expression less than 5% had a lower likelihood of clinical response (17% versus 83%; p=0.0046). Overall the therapy was well tolerated with majority of adverse events reported as grades 1-2.[59]

There remains a significant need for new active agents in the therapy of CTCL as the outcomes continue to be poor for the majority of subjects with recurring disease and relapses due to limited duration of responses.

1.1.6 Rationale for nivolumab and brentuximab vedotin in CTCL (MF/SS)

With increased understanding of disease biology and the integration of novel agents in the treatment of NHL, the outcomes have improved. The progress is impeding in the management of T cell NHL, it is likely that elucidation of pathobiology will help to integrate novel agents in this disease to improve outcomes. Evidence is suggestive that the elements of microenvironment such as stromal cells, dermal fibroblasts, vascular endothelial cells, infiltrating T cells, macrophages, mast cells produce different types of growth factors, cytokines and chemokines which cause disease progression in subjects with CTCL.[60] Recent reports have shown increased expression of ICR and the associated ligands in subjects with T NHL. Wilcox et al demonstrated increased expression of B7-H1 (PD-L1, CD274) a member of the co stimulatory/co inhibitory ligands by the tumor cells, monocytes and the tumor infiltrating monocytes within the tumor microenvironment. The report also highlighted the role of PD-L1 in the suppression of host immunity by promoting induction of T regulatory FoxP3+ cells and inhibiting the effects of immune T cells in subjects with TNHL including CTCL and PTCL[47]. In another report from Kantekure et al the expression of PD-1 and PD-L1 in subjects with different stages of CTCL were examined. The study identified PD-1 as an important immunosuppressive protein, promoting immune inhibition in subjects with CTCL.[61] This suggests that PD-1 modulation by treatment with a PD-1 blocking antibody may result in clinical benefits by enhancing host immune response. Results from a Phase I trial in hematological malignancies are suggestive of activity of anti PD1 (Nivoulmab) in subjects with T NHL. Subjects with CTCL (MF/SS) have demonstrated variable expression of CD30. Brentuximab vedotin has demonstrated activity in CTCL (MF/SS).[59]

Given that nivolumab and brentuximab vedotin have demonstrated activity in subjects with CTCL (MF/SS), the combination has the potential of demonstrating increased activity which may translate into improving quality of responses in this patient population.

1.1.7 Unmet Need in Primary Mediastinal B Lymphoma (PMBL)

PMBL is a distinct type of Non Hodgkin Lymphoma NHL derived from the thymic B cells[62] PMBL is a rare NHL which compromises only 2-4 % of NHL and 10% of cases of DLBCL. PMBL affects subjects in the third and fourth decade of life with a female predominance[63]. The therapeutic approach to PMBL remains an active area of debate. Chemo immunotherapy is used in the frontline treatment with promising responses. However prognosis is poor for subjects who relapse following front line therapy[62]. The increased efficacy of dose dense regimens in this disease suggests that this requires a unique therapeutic approach[62]. During the pre- rituximab era, reports with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP-like) chemotherapy and radiation consolidation demonstrated suboptimal outcomes manifested by early progression and poor salvage options[64]. In the current chemo immunotherapy era, reports integrating rituximab with CHOP or third-generation regimens (eg, methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin [MACOP-B]) have resulted in favorable outcomes with cure rates generally in the range of 80% compared with approximately 50% in the past[62,65,66,67]. The Mab thera International (MinT) study, an important study in high grade B cell lymphomas. This study also included subjects with PMBL. In this study, subjects were treated with CHOP-like chemotherapy with or without rituximab. The number of subjects with PMBL was 87. The study demonstrated that rituximab treatment resulted in significantly improved rate of CR (90 versus 54 %) decrease in the rate of progression (3 versus 24 %) and increase in the rate of 3 years event free survival (78 versus 52%) and overall survival (89 versus 78)[68].

There has also been interest in intensifying chemotherapy with integration of dose dense regimen. In this context, results from a single center Phase II prospective study appear promising for the treatment of PMBL. In this study, total number of subjects with newly diagnosed PMBL was 51. Subjects were treated with six to eight cycles of dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab (da-EPOCH-R). All subjects were supported with growth factors and antimicrobial prophylaxis trimethoprim-sulfamethoxazole. After a median follow-up of 63 months, the reported rates of event-free and overall survival at five years were 93 percent and 97 percent (95% CI 81-99%), respectively. Approximately 10-30% of patients relapse after first line therapy. There is no standard therapy for relapsed or refractory PMBL. The general approach is to salvage subjects with chemo immunotherapy and if subjects demonstrate chemo sensitivity, consolidate with high dose therapy and hematopoietic stem cell transplant[64]. Prior to the immunotherapy era, the outcomes reported were inferior with salvage therapy in PMBL as compared to DLBCL; ORR 25% PMBL vs 48% in DLBCL, 2 year survival 15% PMBL vs 34% DLBCL[64]. Outcomes have improved in the rituximab era, 4 year PFS 69% have been reported[65,69]. In a retrospective study, a total of 44 subjects with relapsed/refractory PMBL were treated with high dose therapy and autologous stem cell transplant (ASCT). Approximately 41% of the subjects were refractory to front line treatment. The ORR after HDT/ASCT was 77% with CR of 63.6%. With a median follow-up of 53.5 months the OS and PFS at 4 years were 70 and 61% respectively. The OS at 4 years was 61% for subjects with primary

refractory disease[69]. It has been observed that the outcomes remain dismal for subjects with chemo refractory disease and for subjects who relapse after ASCT, underscoring the need for novel agents in this disease[62,64]. Pembrolizumab, a check point inhibitor, which has demonstrated activity in relapsed PMBL. In a phase IB study subjects with relapsed PMBL were treated with single agent pembrolizumab. The total number of subjects with relapsed PMBL was 16. The study reported ORR of 38%, with 6% CR, the median DOR was not reached, range (.03-17 months), additionally 6/16= 38% subjects progressed. The median follow up was 5 months[70]. The single agent activity of pembrolizumab appears less promising in PMBL as compared to its single agent activity in relapsed classical HL, where ORR were reported as 65%[70,71]. This suggests, perhaps efficacy can be improved by combining novel agents. Another novel agent, BV has also demonstrated activity in PMBL. In a phase II study of subjects with relapsed DLBCL, 6 subjects were enrolled with the diagnosis of relapsed PMBL. The subjects were treated with single agent BV. The median follow up was 6.6 months for all subjects participating in the study (range 2.2-22.7+). Preliminary evidence of activity of BV were reported in subjects with PMBL, out of 6 subjects, 1 subject demonstrated CR, 3 subjects demonstrated Stable Disease (SD) and 2 subjects progressed. Important to note that this is a small cohort of subjects treated with single agent BV[76]. BV has also been used in frontline treatment of PMBL in combination with chemo immunotherapy[72].

1.1.8 Rationale for nivolumab combination with brentuximab vedotin in PMBL

PMBL is derived from medullary thymic B cell. PMBL has a B cell phenotype and expresses CD20, CD79a, CD30, CD10, CD23, BCL6 where as CD15 is negative[62,63]. The CD30 expression is dim as compared to cHL. Gene expression profiling has demonstrated similarities among PMBL and nodular sclerosing Hodgkin Lymphoma (NSHL)[63]. Some of the common genetic aberrations reported include abnormalities on chromosomes 9p and 2p. The PD1 ligand genes, PD-L1 and PD-L2 are located on chromosome 9p24.1.[73] Chromosome 9p24.1 amplification and increased expression of the PD-1 ligands has been reported in Classical Hodgkin Lymphoma (cHL) and PMBCL cell lines.[74] Some studies have demonstrated and identified 9P24.1/CD274 (PD-L1)/PDCD1LG2(PD-L2), copy gain and increased expression of the PD-1 ligands in 65% of PMBLs[74]. In another molecular analysis of PMBL and DLBCL, twenty-three of 32 (72%) PMBLs but only 1 of 37 (3%) DLBCLs were noted to demonstrate expression of PD-L2 by Immunohistochemistry (IHC). These findings are highly suggestive of the presence of 9p24 genetic aberration in subjects with PMBL. This has critical implication for drug development, as these constitute important targets based on the inhibition of PD1 receptors and the PD1 ligand PDL1 and PDL2 for PMBL[73,75].

Given the variable expression of C30 that is observed in PMBL along with presence of 9p24 amplification, there is rationale to combine BV with nivolumab in PMBL.

1.1.9 Unmet Medical Need in Mediastinal Gray Zone Lymphoma (MGZL)

MGZL is an extremely rare form of NHL. MGZL affects, the majority of the time, the mediastinum of young subjects with a male propensity [62,76]. The World Health Organization recognizes MGZL a rare lymphoma with features analogous and intermediate between NSHL and PMBL[62]. The clinical characteristics and treatment have not been formulated and standardized due to the scarcity of the disease. Subjects with MGZL are treated with chemo immunotherapy similar to PMBL. The outcomes are inferior as compared to subjects with PMBL and NSHL [62,77]. In a prospective study where subjects were treated with infusional dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab (da-EPOCH-R), the event free survival and overall survival were 62% and 74% at 59 months median follow up[77]. Although the numbers are small, there is evidence of activity with BV in subjects with MGZL. In a phase II study of subjects with relapsed DLBCL, 6 subjects were enrolled with the diagnosis of relapsed MGZL. The subjects were treated with single agent BV. The median follow up was 6.6 months for all subjects participating in the study (range 2.2-22.7+). Preliminary evidence of activity of BV were reported in subjects with MGZL. For the 6 patients with MGZL enrolled on this study, responses reported were 1 CR and 2 PRs[76]. Due to low incidence of this lymphoma, there is scarcity of data on the treatment in the front line and relapsed setting. Most subjects are treated similar to relapsed PMBL[77].

1.1.10 Rationale for nivolumab combination with brentuximab vedotin in MGZL

Since the outcome remains dismal for relapsed refractory MGZL, incorporation of novel agents is needed to improve outcomes in therapy. MGZL similar to PMBL, expresses CD 20 and CD30. The expression of CD 30 is dim and variable and the expression of CD 20 is low. The molecular characterization of mediastinal grey zone lymphoma is an area of research. Molecular analysis has demonstrated amplifications in 2p16.1 (REL/BCL11A locus) as well as alteration of the JAK2/PDL2 locus. Alterations affecting the JAK2/PDL2 locus in 9p24 have been reported in 55% of subjects with MGZL[78]. Additionally studies suggest similarities in the epigenetic characteristics in PMBL, NSHL and MGZL.

Given the variable expression of C30 that is observed in MGZL along with presence of 9p24 amplification, there is rationale to combine BV with nivolumab in MGZL.

1.1.11 Rationale for permitting continued treatment in select cases of PD

Immune therapies have been noted to be associated with atypical responses known as tumor flare or immune related response.[79,80] There is increasing evidence that subjects treated with immune therapies including checkpoint inhibitors may manifest disease progression (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. Ongoing clinical trials with nivolumab have reported this phenomenon in approximately 10% of subjects.[81] Similar response has also been observed with other immune therapies. Treatment with antiviral agent in combination with interleukin-12 demonstrated evidence of objective responses after an

initial Progressive Disease (PD) in a patient with human immunodeficiency virus related kaposi sarcoma.[82] The exact etiology for this phenomenon remains unknown. There is suggestion that enhanced inflammation within tumors results in increase in tumor size which may manifest as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti tumor activity will dominate and become clinically apparent. Given the observation of this phenomenon, subjects will be allowed to continue study therapy (nivolumab and brentuximab vedotin) after initial investigator-assessed Response Evaluation Criteria (Lugano Lymphoma 2014, Response Criteria in MF/SS; consensus Global Response Score) defined progression.[83,84] If the subjects are assessed to be deriving clinical benefit and if they continue to meet the following criteria;

1. Investigator-assessed clinical benefit
2. Stable performance status
3. Treatment beyond disease progression will not delay an imminent intervention to prevent serious complications of disease progression
4. Subject will be re-consented for treatment beyond progressive disease
5. Tolerance of study drug

1.1.12 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. Additionally, in the lymphoid malignancies, PD-1 blockade in the tumor microenvironment appears a biologically important parameter to correlate with response. Brentuximab vedotin has shown to execute anti tumor effects by inducing cell death and apoptosis, along with immune modulation through induction of ICD. Understanding the biology of tumor microenvironment both pre and post treatment will be crucial for evaluating the role of combination in modulation of the immune system and its response to PD-1 blockade. In this context, relevant biomarker panels will be obtained in this trial, see Section 5.6.

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. The 9p24 amplicon induces JAK2, and gene dose dependent JAK-STAT induces PD-1ligand transcription. Effects of nivolumab on JAK/STAT pathway (pJAK2, pSTAT1 and pSTAT3), will be evaluated in DLBCL and T NHL.

Therefore, the major questions that will be addressed are:

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

- Can we define distinct pharmacodynamic markers of combination therapy in the peripheral compartment?
- How does nivolumab in combination with brentuximab vedotin alter the activating and negative costimulatory molecules on immune cells in the periphery and at the tumor site? Are there any distinct mechanisms of resistance to nivolumab?
- Does the composition and phenotype of the tumor microenvironment correlate with clinical efficacy?
- Does the treatment with brentuximab vedotin enhance effects of nivolumab?
- Is there a correlation between the effects of combination therapy and immune related genes, cytokines and signaling pathways?

1.1.13 Rationale for Study Design

CA209436 is a Phase I/II open-label study of nivolumab combined with brentuximab vedotin to evaluate the safety and efficacy in subjects with relapsed and/or refractory DLBCL, PTCL (excluding ALCL) and CTCL (MF/SS). CD30 expression ≥ 1% by IHC is a prerequisite for all subjects participating in this study. A dose limiting toxicity (DLT) evaluation period will be conducted for the first 6 subjects during cohort A (Dose Evaluation Phase). In this cohort the first dose of brentuximab vedotin 1.8 mg/kg will be given on Cycle 1 Day 1. The first dose of nivolumab 240 mg flat dose will be given on Cycle 1 Day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30-minute rest. Nivolumab will then be administered as a 30-minute infusion. By administering brentuximab vedotin, a directly cytotoxic agent which also induces ICD, it is anticipated that the tumor associated antigens will be released and available for presentation to cytotoxic T cells, which may enhance effects of nivolumab. Given the long half-life of nivolumab, there is no rationale to continue staggered dosing beyond Cycle 1.

In Cohort A, the safety of the combination treatment will be evaluated by the BMS study team along with the Seattle Genetics study team and the investigators participating in the trial prior to expansion of enrollment to evaluate treatment effect in Cohort B, as detailed in Section 4.5.1

After 6 DLT-evaluable subjects have been followed throughout the first 6 weeks of treatment, or at the point that 2 or more subjects experience a DLT, whichever comes first, the study team will review the available data and provide any of the following recommendations, that may include but are not limited to:

1. If one or none (≤ 1) of the 6 subjects experience a DLT, the expansion cohort will begin with brentuximab vedotin 1.8 mg/kg Cycle 1 Day 1 and nivolumab 240 mg flat dose on Cycle 1 Day 8.
2. If two or more (≥ 2) of the 6 subjects are determined to have had a DLT based on the protocol definition (refer to section 4.5.1), the following options will be considered
   a. To repeat Cohort A of the study and treat up to 6 additional subjects at the same drug doses and schedule previously tested

b. To repeat Cohort A of the study and treat up to 6 additional subjects at a reduced dose of brentuximab vedotin 1.2 mg/kg;
c. Administration of the combination treatment on Day 1 of every cycle, including cycle 1
d. To close the study to additional enrollment.

Cohort B of the study will further characterize safety and evaluate the antitumor activity of brentuximab vedotin combined with nivolumab in subjects with relapsed and/or refractory DLBCL, PTCL (excluding ALCL), PMBL, MGZL and CTCL (MF/SS) who have failed prior chemotherapy or autologous transplant or are ineligible for autologous transplant. The Expansion Phase (Cohort B) plans to treat approximately 130 subjects.

If the combination of nivolumab and brentuximab vedotin is considered safe based on the DLT evaluation, nivolumab will be a 240 mg flat dose for the expansion cohort q 3 weeks administered as a 30-minute infusion.

1.1.13.1 Rationale for Dose Selection

Brentuximab Vedotin

The recommended dose for brentuximab vedotin per its prescribing information is 1.8 mg/kg via intravenous (IV) infusion administered every 3 weeks (first day of every treatment cycle). This dose and schedule was evaluated in two pivotal phase 2 studies in subjects with CD30-positive hematologic malignancies.

Nivolumab

In both Cohorts A and B, the first dose of nivolumab 240 mg flat via 30 minute IV infusion will be given on Cycle 1 Day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle (every 3 weeks). The rationales for using the flat dose, every 3 week dosing intervals, and 30-minute infusion times are provided in section 1.1.13.2, section 1.1.13.3, and section 1.1.13.4.

1.1.13.2 Flat Dose Rationale

The flat dose of 240 mg 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 flat dose was selected for future investigation. To predict relevant summary exposures of nivolumab 240 mg flat, the PPK model was used to simulate 100 virtual trials, with 1000 subjects per treatment arm (240 mg flat dose or 3 mg/kg) randomly sampled from aforementioned pooled database of cancer subjects. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data are applicable to subjects with other tumor types. The simulated geometric mean Cavgss predicted for 240 mg flat dose every 2 week are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg every 2 week.

Nivolumab is safe and well tolerated up to 10 mg/kg every 2 week 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 every 2 week 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 every 2 week) 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 flat dose every 2 week are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC.

1.1.13.3 Every 3 Week Dosing Interval Rationale

For previously approved indications of melanoma and NSCLC and for other indications currently being investigated using the flat dose, the dosing frequency for nivolumab monotherapy is 3 mg/kg and 240 mg flat dose, respectively, every 2 weeks. Nivolumab over a dose range of 0.3 mg/kg to 10 mg/kg has been studied as monotherapy and in combination in several tumor types using an every 3 weeks dosing regimen. It has been demonstrated that following administration of nivolumab 0.3 mg/kg, 2 mg/kg, and 10 mg/kg every 3 weeks, > 90% receptor occupancy (RO) is achieved beginning with the first cycle. Because nivolumab will be administered in combination with brentuximab vedotin, which has every 3 week dosing and the supporting RO data, the nivolumab dosing regimen in this study will be 240 mg flat dose administered every 3 weeks with brentuximab vedotin.

1.1.13.4 Thirty Minute Infusion Time Rationale

Long infusion times place a burden on subjects 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 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. An infusion duration of 30 minutes for 240 mg flat dose of nivolumab (~ 30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration.

1.2 Research Hypothesis

The study will investigate the hypothesis that brentuximab vedotin can be safely combined with nivolumab. Additionally the study will investigate that the combination can result in a clinical meaningful ORR in subjects with relapsed/refractory DLBCL, relapsed/refractory PTCL (all subtypes excluding ALCL), relapsed/refractory PMBL, relapsed/refractory MGZL and relapsed/refractory CTCL (MF/SS).

1.3 Objectives(s)

The purpose of this study is to evaluate the safety profile, tolerability and antitumor activity following administration of nivolumab in combination with brentuximab vedotin in subjects with the diagnosis of relapsed/refractory DLBCL, PTCL (all subtypes excluding ALCL), PMBL. MGZL and CTCL (MF/SS).

1.3.1 Primary Objectives

- To evaluate the safety and tolerability of the combination of nivolumab and brentuximab vedotin in subjects with the diagnosis of relapsed, refractory DLBCL, PTCL (all subtypes excluding ALCL), PMBL, MGZL and CTCL (MF/SS).
- To assess the clinical benefit of nivolumab and brentuximab vedotin combination regimen in subjects with the diagnosis of relapsed/refractory DLBCL, relapsed/refractory PTCL (excluding ALCL), relapsed/refractory PMBL, relapsed/refractory MGZL and relapsed/refractory CTCL (MF/SS) (CD30 expression ≥ 1% by IHC is a prerequisite for all subjects participating in this study), as measured by ORR, defined as the proportion of subjects achieving either a PR or CR. In subjects with relapsed/refractory DLBCL, relapsed/refractory PTCL, relapsed/refractory PMBL, relapsed/refractory MGZL the response will be assessed according to Lugano Classification 2014. For subjects with relapsed/refractory CTCL, response will be assessed according to consensus Global Response Score as per the consensus statement of the International Society for Cutaneous Lymphoma.

1.3.2 Secondary Objectives

- To assess overall duration of response (DOR) of the brentuximab vedotin and nivolumab combination regimen based on investigators assessments.
- To assess the CRR with the nivolumab and brentuximab vedotin combination regimen and the duration of CR based on investigators assessments.

- To assess PFS based on investigators assessments and OS of the brentuximab vedotin and nivolumab combination regimen.

1.3.3 Exploratory Objectives

- To assess the Indeterminate response (IR) per Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) [85] in subjects with DLBCL, PTCL, PMBL, MGZL and CTCL (if applicable).
- To assess CD30 expression and correlate with response, and to assess PD-L1/L2 status and correlate it with response.
- To characterize the molecular effects of the brentuximab vedotin and nivolumab combination regimen on tumor cells and the immune response; and identify biomarkers of response or resistance to the combination.
- To assess tumor microenvironment and peripheral immune status
- To characterize pharmacokinetics of nivolumab and brentuximab vedotin and explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab and brentuximab vedotin following combination therapy.
- To evaluate changes in general health status assessed by the EQ-5D 3L (Cohort B only).

1.4 Product Development Background

1.4.1 Clinical Pharmacology Summary (Nivolumab)

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure.

1.4.2 Clinical Pharmacology Summary (Brentuximab Vedotin)

The PK of brentuximab vedotin was assessed in phase 1 and 2 trials in oncology patients. Maximum serum concentrations of brentuximab vedotin antibody-drug conjugate (ADC) were generally observed close to the end of the 30 minute IV infusion. ADC exposures increased approximately dose proportionally from 1.2 to 2.7 mg/kg, and there was minimal to no accumulation upon multiple-dosing on a Q3W schedule. Serum ADC concentrations declined in a multi-phasic manner, with a terminal half-life of approximately 4 to 6 days. The mean Vss of the ADC was approximately 6 – 10 L, suggesting limited or modest extravascular distribution. Following administration of brentuximab vedotin, free or unconjugated MMAE levels were quantifiable in plasma, though at concentrations that were markedly (roughly 1/10th to 1/40th on a molar basis) lower than those of the ADC. Maximum plasma MMAE concentrations were attained approximately 1 to 3 days after the infusion. MMAE exposures decreased by approximately 20% to 50% with continued administration of brentuximab vedotin (relative to the first dose). Based on a population PK analysis, gender, age and race do not have a meaningful effect on the PK of brentuximab vedotin. Patients with hepatic impairment (Child-Pugh class A to C) exhibited a trend toward moderate decreases in ADC exposures, but increases in MMAE exposures of approximately 2.3 - fold. ADC and MMAE exposures were not meaningfully altered by mild or moderate renal impairment; however, severe renal impairment (CrCl < 30 mL/min) was associated with a trend toward moderate decreases in ADC exposures, but increases in MMAE exposures of approximately 1.9 - fold.

Further details on the clinical pharmacology of brentuximab vedotin can be found in the Investigator Brochure.

1.4.3 Safety Summary (Nivolumab)

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date. Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management algorithms provided in Appendix 6 and nivolumab investigator brochure. The spectrum, frequency, and severity of drug-related AEs were generally similar across the dose levels tested. A review of the safety data by tumor type (RCC, NSCLC, mCRPC, CRC, and melanoma) also did not show any clinically meaningful differences in the proportion of subjects with AEs noted across tumor type. Although tumor progression was the most common cause of mortality, there were 3 drug-related deaths associated with grade 3-4 pneumonitis. Pneumonitis (any grade) occurred in 12 of 306 subjects (4%), and grade 3-4 pneumonitis occurred in 4 subjects (1%), with clinical presentations ranging from asymptomatic radiographic abnormalities to progressive, diffuse pulmonary infiltrates associated with cough, fever, and/or dyspnea. No clear relationship between the

occurrence of pneumonitis and tumor type, dose level, or treatment duration was noted. In 9 of 12 subjects, pneumonitis was reversible with treatment discontinuation and/or immunosuppression (glucocorticoids, infliximab, mycophenolate).

Nivolumab, at 1 or 3 mg/kg, has an acceptable safety profile in subjects with relapsed or refractory hematologic malignancy. The following were the key safety findings for 105 subjects treated with nivolumab monotherapy in CA209039 as of 15-Apr-2015:

1. The most frequently reported drug-related AEs (> 10% of subjects) were fatigue (16.2%) and rash (10.5%). The majority were Grade 1-2 in severity.
2. The most frequently reported drug-related SAE was pneumonitis (4.8%).
3. Drug-related AEs leading to discontinuation were reported for 14.3% of subjects. The most frequently reported AE leading to discontinuation were pneumonitis (2.9%).
4. The most frequently reported drug-related select AE categories were skin (19.0%), GI (9.5%), and pulmonary (9.5%). The most frequently reported (≥ 5% of total treated subjects) drug-related select AEs were rash (10.5%), pneumonitis (9.5%), pruritus (9.5%), and diarrhea (8.6%). Drug-related select AEs were mostly Grade 1-2 in all categories.
5. Most deaths were due to disease progression. One death was reported due to study drug toxicity (The subject with non Hodgkin's lymphoma [small lymphocytic lymphoma] in the 3 mg/kg treatment group died due to Grade 5 pneumonitis with onset 10 days after the subject received the only dose of nivolumab).

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the Investigator Brochure (IB).

1.4.4 Safety Summary (Brentuximab Vedotin)

Two pivotal phase 2 studies evaluating the efficacy and safety of brentuximab vedotin as a single agent were performed in patients with relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL) (Studies SG035-0003 and SG035-0004, respectively). Treatment-emergent adverse events (AEs) occurring in ≥ 20% of HL and systemic ALCL patients in the phase 2 studies were peripheral sensory neuropathy (45%), fatigue (43%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (31%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and Grade 4 events were reported for 13% and 7% of patients, respectively. Similar patterns and incidences of AEs were generally observed for HL and ALCL patients.

A phase 3, randomized, placebo-controlled study evaluating efficacy and safety of brentuximab vedotin in the treatment of patients with HL who are at risk of disease progression following autologous stem cell transplant (ASCT) has been completed (SGN35-005). A total of 329 patients were randomized (164 patients to brentuximab vedotin and 165 to placebo) and there were 327 patients who received study treatment (167 patients received at least 1 dose of brentuximab vedotin and 160 patients received placebo). AEs that had a higher relative risk of occurring in patients in the brentuximab vedotin arm of Study SGN35-005 compared with patients in the

placebo arm (as indicated by a relative risk >1 and confidence intervals that do not include 1) were peripheral motor neuropathy, paresthesia, abdominal pain, constipation, peripheral sensory neuropathy, weight decreased, neutropenia, nausea, myalgia, vomiting, diarrhea, and arthralgia.

Additional oncology clinical studies, compassionate-use programs, and postmarketing use have contributed further brentuximab vedotin safety data. Notable adverse events observed with brentuximab vedotin treatment of various cancers to date include peripheral neuropathy, infusion-related reactions, and cytopenias; and, less commonly, progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), tumor lysis syndrome (TLS), acute pancreatitis, pulmonary toxicity, and hepatotoxicity. In addition, concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity that occurred in some patients receiving this combination of treatments.

1.5 Overall Risk/Benefit Assessment

Subjects with relapsed/refractory Non Hodgkin Lymphoma (DLBCL, PTCL, CTCL, PMBL and MGZL) after progression on systemic therapy represent an area of substantial unmet medical need. Allogeneic Stem Cell Transplant has the potential to offer cure in this patient population, majority of subjects are ineligible for this treatment due to age, refractory disease status or lack of suitable stem cell donor. Additionally allogeneic stem cell transplant has significant risk of associated morbidity and mortality. Although a significant numbers of novel agents are emerging in the treatment of relapsed NHL, the duration of response remains short with the majority as single agents. Therefore the development of new approaches is needed in relapsed NHL. The clinical activity of nivolumab observed to date in heavily pretreated subjects with solid tumors as well as early results in NHL and HL suggests the potential for improved clinical outcomes for these subjects. Additionally brentuximab vedotin has demonstrated promising activity in HL and NHL. Nivolumab and brentuximab vedotin also have the potential for clinically relevant adverse events including pulmonary toxicity, hepatotoxicity, diarrhea/colitis, endocrinopathies, nephrotoxicity, peripheral neuropathy and cytopenias. To date, serious AEs have been manageable with prompt diagnosis and initiation of corticosteroids, dose interruption, and adequate supportive care with both agents. Together the data suggest a positive benefit-risk potential, supporting a Phase I/II study to further assess the safety and efficacy of nivolumab and brentuximab vedotin combination in subjects with relapsed, refractory DLBC, PTCL (excluding ALCL), CTCL (MF/SS), PMBL & MGZL.

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 Investigator Brochure 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

This is an open-label, multicenter phase I/II study of nivolumab in combination with brentuximab vedotin designed to evaluate the safety and efficacy in subjects with the diagnosis of relapsed/refractory DLBCL, PTCL (excluding ALCL), CTCL (MF/SS), PMBL, and MGZL.

The study will consist of three phases: Screening, Treatment and Follow-up. The treatment phase is divided in two parts: Cohort A consists of the Dose Evaluation Phase and Cohort B is the Expansion Phase.

It is anticipated that 170 subjects will be enrolled in the United States, Canada and Europe for the entire study (Cohort A and Cohort B combined). All subjects will undergo a screening period to determine eligibility within 28 days prior to initial dosing.

Dose Evaluation Phase (Cohort A)

The Dose Evaluation Phase (Cohort A) will include a dose limiting toxicity (DLT) evaluation for the dose level of brentuximab vedotin 1.8 mg/kg intravenously in combination with nivolumab 240 mg flat dose intravenously in a q 3 week cycle. Refer to section 4.5.1 for further details.

In cycle 1, brentuximab vedotin 1.8mg/kg will be administered on day 1 where as nivolumab 240 mg flat dose will be administered on day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30-minute rest. Nivolumab will then be administered also as a 30-minute infusion.

The DLT evaluation period, which consists of the first dose of study drug through the first 6 weeks of treatment, will be conducted in the first 6 treated subjects (all comers). Decisions to enroll up to 6 additional subjects onto the same dose of brentuximab vedotin 1.8 mg/kg in combination with nivolumab 240 mg flat dose intravenously every 3 weeks or at a reduced dose of brentuximab vedotin at 1.2 mg/kg will be based on the safety data reviewed throughout the DLT evaluation period.

If any of the first 6 treated subjects discontinue treatment for reasons other than a DLT but prior to completing the DLT evaluation period, then they will be replaced. Subjects enrolled to Cohort A will be monitored for DLT throughout the DLT evaluation period. Refer to section 4.5.1 for DLT definition.

After 6 DLT-evaluable subjects have been followed throughout the first 6 weeks of treatment, or at the point that 2 or more subjects experience a DLT, whichever comes first, the study team will review the available data and provide any of the following recommendations that may include but are not limited to:

1) If one or none (≤ 1) of the 6 subjects experience a DLT, the expansion cohort will begin with brentuximab vedotin 1.8 mg/kg Cycle 1 Day 1 and nivolumab 240 mg flat dose on Cycle 1 Day 8.
2) If two or more (≥ 2) of the 6 subjects are determined to have had a DLT based on the protocol definition (refer to section 4.5.1), the following options will be considered
   a) To repeat Cohort A of the study and treat up to 6 additional subjects at the same drug doses and schedule previously tested
   b) To repeat Cohort A of the study and treat up to 6 additional subjects at a reduced dose of brentuximab vedotin 1.2 mg/kg;
   c) Administration of the combination treatment on Day 1 of every cycle, including cycle 1
   d) To close the study to additional enrollment.

   NOTE: Doses may not be increased to above 1.8 mg/kg brentuximab vedotin or nivolumab 240 mg flat dose.

On review of all available data, the study team may determine that the classification of DLT was not appropriate for one or more of the subjects, in which case enrollment may resume if the target of 6 DLT-evaluable subjects has not yet been reached. However, if 2 or more subjects were determined to have experienced DLTs, then expansion will not occur as the next step. Based on the study team's recommendations, up to 6 additional subjects may be enrolled in Cohort A at the same drug dose levels and schedule or at a modified treatment (described above in this section). These additional subjects will then be assessed for DLT in the same manner described above to determine if it is appropriate to move to the Expansion Phase (Cohort B). If it is determined by the study team that due to safety concerns no additional dose levels or schedules should be enrolled, then the study will be closed to enrollment.

There is no planned interim analysis (IA). However, all available efficacy and safety data will be used to select the recommended brentuximab vedotin dose and treatment schedule that will be further evaluated in the Expansion Phase (Cohort B).

Expansion Phase (Cohort B)

The Expansion Phase will consist of a single-arm phase II study which will expand enrollment at the recommended dose level and treatment schedule as deemed safe by the study team in Cohort A. An additional 40 subjects in DLBCL (cohort B1), 30 subjects in PTCL (cohort B2) 20 subjects in CTCL (cohort B3), 30 subjects in PMBL (cohort B4) and 10 subjects in MGZL (cohort B5) will be enrolled to complete this evaluation.

If one or none (≤ 1) of the 6 subjects in cohort A experience a DLT, the expansion cohort will begin with brentuximab vedotin 1.8 mg/kg Cycle 1 Day 1 and nivolumab 240 mg flat dose on Cycle 1 Day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30-minute rest. Nivolumab will be then be administered as a 30-minute infusion. If two or more (≥ 2) of the 6 subjects are determined to have had a DLT based on the protocol definition (refer to section 4.5.1) treatment modification or enrollment closure will be considered, as described above.

All subjects in the study (Cohort A and Cohort B) will be allowed to be treated until disease progression or unacceptable toxicity as described in Section 4.5.3 and Section 4.5.5. If during therapy it appears that a subject is benefiting from the combination but experiencing toxicities related to one agent that would require permanent treatment discontinuation, then they have the option to continue therapy with the single agent not attributing to toxicities.

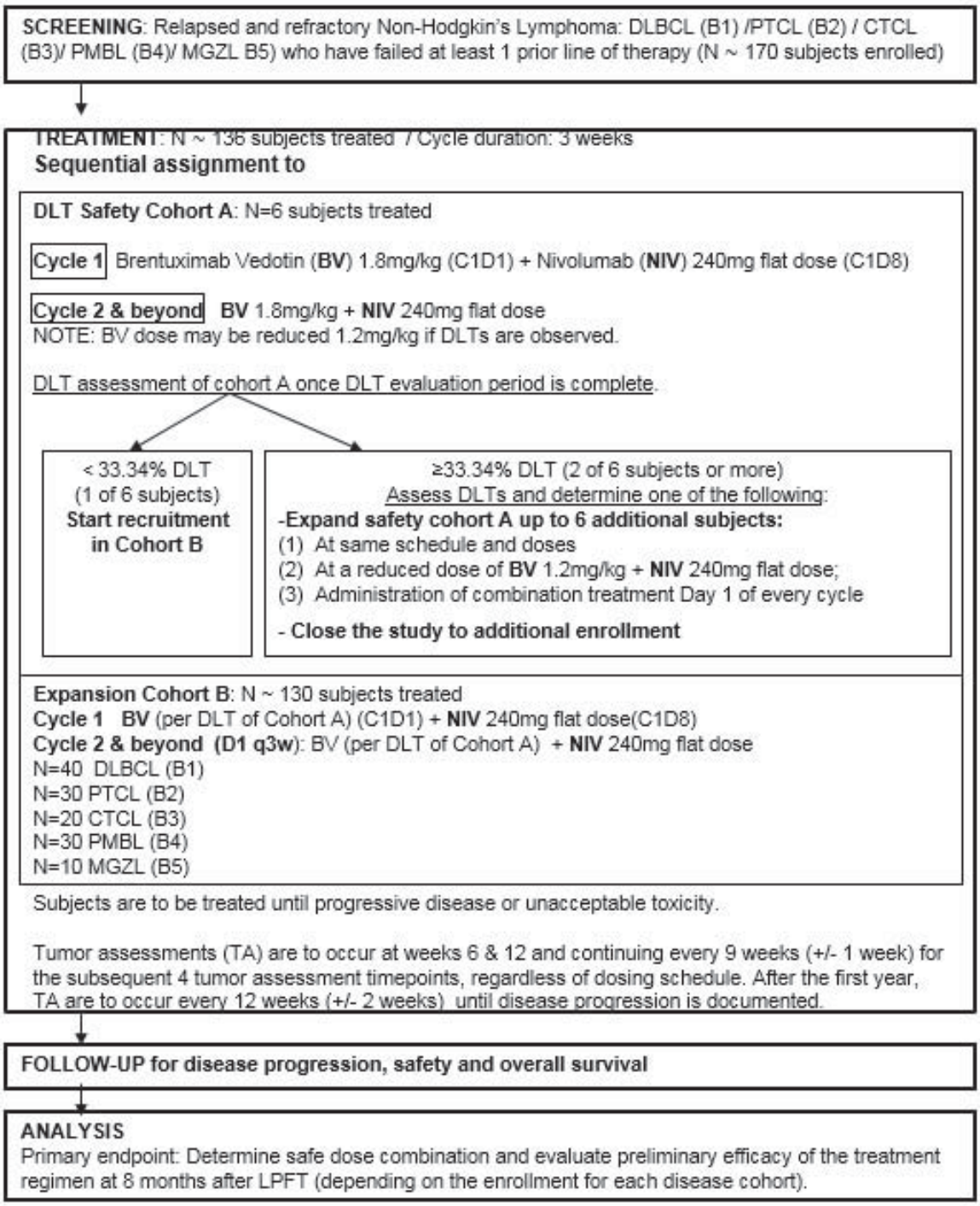
Subjects that present progressive disease during treatment may be allowed to be treated beyond progression until further progression is observed. Refer to Section 4.5.9 for further details.

Once subjects discontinue from study treatment for any reason, subjects will enter the follow-up phase of the study. During follow-up long-term safety, survival status, disease progression, subsequent anticancer therapy and occurrence of other primary malignancy data will be collected. Follow-up visit 1 (X01) and follow-up visit 2 (X02) will be in person visits and all subsequent

follow-up visits may be done in person or by phone. All treated subjects will be followed for survival at least every 3 months until death or lost to follow-up. Subjects with residual toxicity G ≥ 2 at the time of discontinuation must follow these until resolved to at least G1, end of study or deemed irreversible, whichever occurs first. Subjects who discontinue for reasons different than progressive disease must continue to perform tumor assessments as described in Section 5.4 until disease progression is documented.

The primary endpoint for Cohort B will be investigator-assessed ORR for all five tumor types. Primary endpoint analysis will occur 8 months after the last patient receives their first treatment (LPFT). Depending on the enrollment for each disease cohort, the analysis may be done at different times for each cohort, or at the same time for the five cohorts. The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



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 (brentuximab vedotin and nivolumab). 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.

c) Each participant must be informed about the nature of the study to the extent compatible with his or her understanding. Should a participant become capable or reach the age of majority, his or her consent should be obtained as soon as possible. The explicit wish of a participant who is a minor or 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

d) Minors who are judged to be of an age of reason as determined by local requirements should also give their assent. The assent should be documented based on local requirements. Continued assent should be documented when important new information becomes available that is relevant to the participant's assent.

2. Target Population

a) Subject must be 18 years of age or older (for PMBL ≥ 15 years or older)

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

c) All subjects in this study are required to have expression of CD30 ≥ 1% in the tumor or tumor infiltrating lymphocytes (TILs) by local immunohistochemistry prior to the first dose.

d) Histological confirmation of the following NHL subtypes is permitted:

i) DLBCL by standard immunopathology, relapsed/refractory disease as follows:

(1) Subjects with relapsed and/or refractory DLBCL or Transformed Lymphoma (TL) after high-dose conditioning chemotherapy and ASCT, or subjects with relapsed

and/or refractory DLBCL or TL after at least 2 prior multi-agent chemotherapy regimens if ASCT ineligible.

(2) Subjects with Richter' s transformation (TL) (transformed chronic lymphoid leukemia into DLBCL) are allowed to participate in this study

ii) PTCL with immunopathological and molecular biological diagnosis, all subtypes with the exception of ALCL

(1) PTCL must be relapsed and/or refractory disease after 1 or more lines of standard systemic therapy

iii) CTCL (MF/SS subtypes only) with diagnosis of MF/SS by immunopathological and molecular, biological criteria

(1) CTCL must be relapsed and/or refractory disease after 1 or more lines of standard systemic therapy

(2) Stage IB-IV per TNMB modified International Society of Cutaneous Lymphoma (ISCL) and WHO-EORTC staging criteria (Appendix 3).

iv) PMBL must be relapsed/refractory disease after high-dose conditioning chemotherapy and ASCT, or subjects with relapsed and/or refractory PMBL after at least 2 prior multi-agent chemotherapy regimens if ASCT ineligible

v) MGZL must be relapsed/refractory disease after high-dose conditioning chemotherapy and ASCT, or subjects with relapsed and/or refractory MGZL after at least 2 prior multi-agent chemotherapy regimens if ASCT ineligible

e) Evaluable tumor tissue (archived or new biopsy) must be provided for biomarker analysis as FFPE tumor block or a minimum of 20 slides. Bone marrow aspirate and biopsy and peripheral blood are not to be submitted for evaluable tumor tissue. In order to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period.

f) All subjects with PTCL, DLBCL, PMBL and MGZL must have measurable disease defined as:

i) At least 1 measurable site of disease according to the Lugano Classification 2014 (Appendix 2). (Criteria does not apply for CTCL).

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

3. Physical and Laboratory Test Findings

a) Screening laboratory values must meet these following criteria:

i) Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$cells/L (ie, $\geq$ 1000/ µL)

ii) Platelets $\geq 50 \times 10^9$cells/L (ie, $\geq$ 50,000/µL) without transfusion support within 14 days prior to test

iii) Hemoglobin $\geq$ 8.5 g/dL without transfusion support within 7 days prior to test

iv) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal (ULN)

v) Serum bilirubin ≤ 1.5 X ULN (unless due to Gilbert's syndrome, in which case the cut off is < 3.0 x ULN)

vi) Calculated creatinine clearance of ≥ 30 mL/min/1.73m^2 measured using the Cockcroft-Gault formula below:

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

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

4. Age and Reproductive Status

a) Males and Females, ≥ 18 years of age, inclusive (for PMBL ≥ 15 years or older)

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) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus approximately 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post-treatment completion. .(Note: half-life of nivolumab is greater than brentuximab vedotin)

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus approximately 5 half-lives of the study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.

f) Azoospermic 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. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Location of the NHL in the central nervous system (CNS)

2. Medical History and Concurrent Diseases

a) Subjects with history of progressive multifocal leukoencephalopathy (PML)

b) Any positive test for hepatitis B virus, including HBs Ag+ or anti-HBc+, or positive test for hepatitis C virus indicating acute or chronic infection (including anti-HCV+ or presence of HCV-RNA)

c) Positive test for human immunodeficiency virus (HIV)

d) Pre-existing neuropathy of ≥ grade 2

e) Any active grade 3 or higher (per the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE], version 4.03) viral, bacterial or fungal infection within 2 weeks prior to the first dose of brentuximab vedotin; routine antimicrobial prophylaxis is permitted.

f) Documented history of cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction or cardiac symptoms with New York Heart Association Class III-IV within 6 months prior to the first dose of the study drugs

g) Subjects with an active, known or suspected autoimmune disease.

NOTE: Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

h) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose

NOTE: Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

i) Known history of pancreatitis

j) Other serious underlying medical condition that, in the opinion of the investigator, would impair the ability to receive or tolerate the planned treatment and follow-up

k) History of another primary invasive malignancy that has not been in remission and is requiring therapy in the last 3 years

3. Prohibited Treatments and/or Therapies

a) Prior exposure to brentuximab vedotin

b) Prior exposure to anti-PD1, anti-PDL1, anti-PD-L2, anti-CD137 or anti- CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

c) Concurrent enrollment in another therapeutic investigational clinical study

d) History of hypersensitivity reactions to monoclonal antibody therapy

e) Prior exposure to anti-CD30 directed treatment

f) Nitrosoureas within 6 weeks of first dose

g) Chemotherapy within 4 weeks of first dose

h) Therapeutic antibodies within 4 weeks of first dose

i) Radio- or toxin-immunoconjugates within 10 weeks of first dose

j) Radiation therapy within 3 weeks of first dose, or chest radiation ≤ 12 weeks prior to first dose

k) Investigational agents within 3 weeks of first dose

l) Carmustine (BCNU) > 1000 mg received as part of pre-transplant conditioning regimen

m) Received an allogeneic hematopoietic Stem Cell Transplant

n) Topical and targeted therapies; such as histone deacetylase inhibitors (HDAC inhibitors), anti-folate antagonist, nucleoside analogs or retinoids such as bexarotene, topical nitrogen mustard

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

c) Women who are pregnant or breastfeeding

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

A 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, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females 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

judgement 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 (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.2.1)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents)

3.4.2 Other Restrictions and Precautions

Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.4.2.1 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg

daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy. Palliative radiotherapy must have been completed at least 3 weeks prior to first dose. Palliative radiation therapy is allowed on study, study treatment must be held 2 weeks prior to and 2 weeks post treatment.

The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed. The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

Routine premedication for infusion reactions should not be administered prior to the first dose of study drug(s). However, subjects who experience an infusion-related reaction may receive subsequent treatment with premedication as described in Section 4.5.6.

Subjects who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

Routine prophylaxis with vaccines is permitted prior to study entry; it is recommended that vaccines used do not contain live micro-organisms.

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:

- 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 Section 4.5.5 and Section 4.5.3

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug and it is allowed by local regulations, 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 Table 5.1-3. 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 Study Follow up

In this study, overall survival is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving 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 Table 5.1-3 until death, withdrawal of consent, lost to follow-up or the conclusion of the study.

In addition, 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 Lugano Classification 2014 (DLBCL/PTCL) and consensus Global Response Score (CTCL) 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. For the subjects who discontinue study therapy by proceeding to allogeneic SCT, documentation of acute and chronic GVHD will be simultaneously collected see Appendix 5 for more details.

Subjects who discontinue study drug may continue to be followed. BMS may request that survival data be collected on all *treated* subjects outside of the 3 month specified visit schedule. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

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 both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for CA209436

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection*	100 mg (10 mg/mL)	IP	OPEN LABEL	Clear to opalescent colorless to pale yellow liquid. May contain particles.	2-8°C. Protect from light and freezing.
Brentuximab Vedotin Powder for Injection	50mg	IP	OPEN LABEL	White to off-white lyophilized preservative-free cake or powder in a single-use vial for reconstitution.	2-8°C. Protect from light.

*May be labeled as either "BMS-936558-01" or "Nivolumab".

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 products are:

- Nivolumab (BMS-936558)
- Brentuximab Vedotin

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).

4.3.1 Brentuximab Vedotin

Brentuximab vedotin will be administered every 21 (q 3 weeks) days by IV infusion given over approximately 30 minutes. In the absence of infusion-related reactions, the infusion rate for all subjects should be calculated in order to achieve a 30 minute infusion period. Brentuximab vedotin must not be administered as an IV push or bolus nor mixed with other medications. Brentuximab vedotin will be administered first as a 30 minute infusion followed by a minimum 30 minute rest prior to the nivolumab infusion.

Dosing is based on subject's actual body weight. Doses must be adjusted for subjects who experience a ≥ 10% change in weight from baseline. Other dose adjustments for changes in body weight are permitted per institutional standard. An exception to weight-based dosing is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

Refrigeration should be set at 2–8°C for storage of vials and solutions containing brentuximab vedotin. The controlled location must be accessible only to the pharmacist, the investigator, or a designated person. Brentuximab vedotin does not contain preservatives; therefore, opened and reconstituted vials of brentuximab vedotin should be used as soon as possible. If not used immediately, the in-use storage should not be longer than 24 hours. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use. Reconstituted vials and solutions must not be shaken.

Drug product vials may be labeled as brentuximab vedotin, the United States adopted name (USAN) and the International Nonproprietary Name (INN), or as SGN 35, the compound code; the 2 names can be used interchangeably.

Brentuximab vedotin vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

Brentuximab vedotin should be reconstituted with 10.5mL of Sterile Water for Injection, United States Pharmacopeia (USP) or equivalent (see Pharmacy Binder for details) for a final concentration of 5mg/mL. The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

The required volume of reconstituted drug product should be diluted into an infusion bag. The bag should be gently inverted to mix the solution. The bag must not be shaken. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

Detailed drug preparation and drug accountability instructions for brentuximab vedotin are provided in the Pharmacy Binder.

4.3.2 Nivolumab

Nivolumab will be administered every 21 days (q 3weeks) by IV infusion given over approximately 30 minutes. Nivolumab (BMS-936558) vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

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**.**

At the end of the infusion, flush the line.

For both study drugs, 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 for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab).

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
- Lymphoma Disease Diagnosis (DLBCL, PTCL, CTCL, PMBL, MGZL)

A separate call will need to be placed to assign eligible subjects their first treatment once the tumor tissue submitted to the central laboratory has gone through the quality assessment and the information is available in the IVRS.

4.5 Selection and Timing of Dose for Each Subject

There will be 2 parts to this study. During the Dose Evaluation Phase (Cohort A) six eligible subjects will be enrolled and treated with brentuximab vedotin (IV) 1.8 mg/kg as the starting dose and may be reduced to 1.2 mg/kg if toxicities described in Table 4.5.3-1 are observed. Subjects enrolled to Cohort A will be treated with a combination of brentuximab vedotin and nivolumab 240 mg flat dose (IV) of every 3 week cycle. In cycle 1, brentuximab vedotin will be administered on day 1 where as nivolumab will be administered on day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30-minute rest. Nivolumab will be then be administered as a 30-minute infusion

The starting dose of brentuximab vedotin 1.8 mg/kg is to be given over approximately 30 minutes intravenously. In the absence of infusion related reaction, the infusion rate for all subjects should be calculated in order to achieve a 30-minute infusion period. Dosing calculations should be based on the subject's actual body weight. If the subject's weight on the day of dosing differs by > 10% from the previous weight used to calculate the required dose, a corrected dose must be recalculated. Other dose adjustments for changes in body weight are permitted per institutional standard. All

doses should be rounded to the nearest milligram. Brentuximab vedotin may be reduced to 1.2mg/kg if toxicities described in Table 4.5.3-1 are observed. The Cohort B will open with a proposed dosing regimen with cycle duration of 21 days (3 weeks). Brentuximab vedotin will be administered based on the dose identified in Cohort A (1.8 mg/kg or 1.2 mg/kg) and nivolumab will be given over 30 min intravenously at a 240 mg flat dose.

An exception to weight-based brentuximab vedotin dosing is made for subjects weighing greater than 100 kg; doses will be based on 100kg for these individuals. Rounding is permissible within 5% for the nominal dose.

There will be no dose escalations or reductions of nivolumab allowed. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

First dose of nivolumab will be administered on Cycle 1 Day 8, which is only 2 weeks away from Cycle 2 Day 1. For safety reasons, subjects may be dosed no less than 12 days between doses. For all other cycles, treatment is to occur within 3 days of the scheduled dosing date. Dose given after the 3 day window is considered a dose delay. Treatment may be delayed for up to a maximum of 6 weeks from the previous dose. Refer to Section 4.5.4 for further details**.**

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay, interruption or discontinuation) will be based on specific laboratory and AE criteria (further details described in Section 4.5.3 and Section 4.5.4).

4.5.1 Dose Evaluation Phase: (Cohort A)

The Dose Evaluation Phase (Cohort A) will include a dose limiting toxicity (DLT) evaluation for the dose level of brentuximab vedotin 1.8 mg/kg intravenously in combination with nivolumab 240 mg flat dose intravenously in a q 3 week cycle. In cycle 1, brentuximab vedotin 1.8 mg/kg will be administered on day 1 where as nivolumab 240 mg flat dose will be administered on day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30-minute rest. Nivolumab will be then be administered as a 30-minute infusion.

The DLT evaluation will be conducted in the first 6 treated subjects (all comers). Decisions to enroll up to 6 additional subjects onto the same dose of brentuximab vedotin 1.8 mg/kg in combination with nivolumab 240 mg flat dose intravenously every 3 weeks or at a reduced dose of brentuximab vedotin at 1.2 mg/kg will be based on the safety data reviewed throughout the DLT evaluation period. The DLT evaluation period consists of the first dose of study drug through the first 6 weeks of treatment.

If any of the first 6 treated subjects discontinue treatment for reasons other than a DLT, prior to completing the DLT evaluation period, then they will be replaced. These subjects will be monitored for DLT throughout the DLT evaluation period (DLT definition is provided further below in this section). After 6 DLT-evaluable subjects have been followed through the end of the DLT evaluation period, or at the point that 2 or more subjects experience a DLT, whichever comes first, the study team will review the available data. The BMS study team along with Seattle

Genetics study team and the investigators participating in the trial, will review all of the available safety data and provide any of the following recommendations that may include, but are not limited to:

1. One or none (≤ 1) of the 6 subjects experience a DLT, the expansion cohort will begin with brentuximab vedotin 1.8 mg/kg Cycle 1 Day 1 and nivolumab 240 mg flat dose on Cycle 1 Day 8. Subsequent to cycle 1, both drugs will be administered on the first day of the new cycle. Brentuximab vedotin will be administered first as a 30-minute infusion followed by a minimum 30 minute rest. Nivolumab will be then be administered as a 30 min infusion.
2. If two or more (≥ 2) of the 6 subjects are determined to have had a DLT based on the protocol definition, the following options will be considered
    a. To repeat Cohort A of the study and treat up to 6 additional subjects at the same drug doses and schedule previously tested
    b. To repeat Cohort A of the study and treat up to 6 additional subjects at a reduced dose of brentuximab vedotin 1.2 mg/kg;
    c. Administration of the combination treatment on Day 1 of every cycle, including cycle 1
    d. To close the study to additional enrollment.

    NOTE: Doses may not be increased to above 1.8 mg/kg brentuximab vedotin or nivolumab 240 mg flat dose

On review of all available data, the study team may determine that the classification of DLT was not appropriate for one or more of the subjects, in which case enrollment may resume if the target of 6 DLT-evaluable subjects has not yet been reached. However, if 2 or more subjects were determined to have experienced DLTs, then expansion will not occur as the next step. Based on the study team's recommendations, up to 6 additional subjects may be enrolled in Cohort A at the same drug doses and schedule or at a modified treatment (described above in this section). These additional subjects will then be assessed for DLT in the same manner described above to determine if it is appropriate to move to the Expansion Phase (Cohort B). If it is determined by the study team that due to safety concerns no additional dose levels or schedules should be enrolled, then the study will be closed to enrollment.

Dose Limiting Toxicity

The incidence of dose limiting toxicities assessed in the first 6 DLT-evaluable subjects beginning Cycle 1 Day 1 through the first 6 weeks of treatment will determine whether the combination, nivolumab with brentuximab vedotin is tolerable. A subject will be considered evaluable for DLT if they have received at least one dose of either drug in the first 6 weeks of treatment. However, if the subject discontinues treatment for reasons other than a DLT prior to completing the DLT evaluation period, then they are **not** considered DLT evaluable and will be replaced. DLT should not be AEs considered by the investigator to be disease related. For the purpose of this study, DLTs are defined as any study drug-related toxicity (brentuximab vedotin or nivolumab) that requires either a dose reduction or delay of more than 7 days of either study drug in Cycle 2 or delays the Cycle 3 Day 1 administration of combined treatment by more than 7 days. The DLT evaluation period consists of the first dose of study drug through the first 6 weeks of treatment. The IBs for

brentuximab vedotin and nivolumab individually describe adverse events commonly observed relative to either agent (ie, neutropenia or peripheral neuropathy with brentuximab vedotin; immune-mediated adverse events with nivolumab), as well as less common serious findings. However, the final decision regarding causality is at the discretion of the Investigator.

There is no planned interim analysis (IA). However, all available efficacy and safety data will be used to select the recommended dose that will be further evaluated in the Expansion Phase (Cohort B).

4.5.2 Premedication

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of study drug(s). However, subjects should be carefully monitored for infusion reactions during administration of study drug(s). If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

Subjects should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of brentuximab vedotin. Subjects should receive prophylaxis as appropriate per the institutional standards.

4.5.3 Dose Modifications for Brentuximab Vedotin

Table 4.5.3-1 describes the recommended dose modifications for brentuximab vedotin treatment associated toxicity. Doses reduced for brentuximab vedotin-related toxicity should not be re-escalated without discussion with the sponsor. Dose escalation of brentuximab vedotin beyond 1.8 mg/kg is not permitted.

Dose reductions below 1.2mg/kg are not allowed, and toxicities should be managed with dose delays.

If brentuximab vedotin treatment is delayed for any reason, nivolumab must also be delayed until the subject has appropriately recovered and is able to resume the combination treatment on the first day of the subsequent cycle. Nivolumab should only be given alone in case a decision has been made to permanently discontinue brentuximab vedotin.

Table 4.5.3-1: Dose Modifications for Brentuximab Vedotin

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral Neuropathy	Continue at same dose level	Reduce dose to 1.2 mg/kg and resume treatment[a]	Withhold (delay) until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at 1.2 mg/kg or discontinue if reduction has already occurred.	Discontinue treatment

Table 4.5.3-1: Dose Modifications for Brentuximab Vedotin				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Non-hematologic (except peripheral neuropathy)	Continue at same dose level	Continue at same dose level	Withhold (delay) dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at the same dose level[b]	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator[a,b, c]
Hematologic[d]	Continue at same dose level	Continue at same dose level	Withhold (delay) until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at the same dose level[e]. Growth factor support (G-CSF or GM-CSF) should be considered for subsequent cycles. If Grade 4 neutropenia recurs despite growth factor support, consider discontinuation or dose reduction to 1.2 mg/kg.	

[a] Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays.

[b] Subjects who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without dose delay.

[c] Treatment should be discontinued for subjects who experience Grade 4 infusion-related reactions.

[d] Support with blood product transfusions allowed per institutional standard of care.

[e] Subjects who develop Grade 3 or 4 lymphopenia may continue study treatment without dose delay.

Subjects who discontinue nivolumab due to a related AE may continue treatment with brentuximab vedotin monotherapy until disease progression or unacceptable toxicity. Similarly, subjects who discontinue brentuximab vedotin due to related AE may choose to continue on nivolumab monotherapy. In the Cohort A, if toxicity is observed during the DLT evaluation period that requires discontinuation of study treatment, both compounds must be discontinued.

4.5.4 Dose Modifications for Nivolumab

4.5.4.1 Nivolumab Dose Delays

Dose delay criteria apply for all drug-related AEs. Nivolumab must be delayed until treatment can resume (see Section 4.5.4.2)

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.

4.5.4.2 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 nivolumab treatment is delayed for any reason, brentuximab vedotin must also be delayed until the subject has appropriately recovered and is able to resume the combination treatment on the first day of the subsequent cycle. Brentuximab vedotin should only be given alone in case a decision has been made to permanently discontinue nivolumab.

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

4.5.4.3 Nivolumab Dose Reductions and Escalations

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

4.5.5 Nivolumab Treatment Discontinuation

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 > 8 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.
- 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 Appendix 2 and Appendix 4 with the exception described in Section 4.5.9.
- Subject who initiated the preparative regimen for allogeneic SCT or ASCT any time 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)

Subjects who discontinue nivolumab due to a related AE may continue treatment with brentuximab vedotin monotherapy until disease progression or unacceptable toxicity. The same applies in case subjects discontinue brentuximab vedotin due to related AE and chose to continue on nivolumab monotherapy. During Cohort A, however, if subject meets discontinuation criteria within the DLT evaluation period, both drugs must be discontinued.

4.5.5.1 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 Appendix 6 and the Nivolumab IB. 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.

4.5.6 Treatment of Infusion Related Reactions (nivolumab/brentuximab vedotin)

Infusion-related reactions may occur during the infusion of study treatment(s). The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for infusion-related reactions.

Infusion or hypersensitivity reactions may occur to either brentuximab vedotin or nivolumab. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

Subjects who experience a Grade 1 or Grade 2 infusion-related reaction should be premedicated for subsequent infusions. Premedication should be given at least 30 minutes prior to dosing study drug(s) and should include an antihistamine and corticosteroid. Recommended doses are: diphenhydramine 25-50 mg IV (or equivalent) and methylprednisolone 40 mg IV (or equivalent). In addition, acetaminophen/paracetamol 325 to 1000 mg and ranitidine 50 mg IV may be given. If the onset of a reaction occurs during an infusion, the infusion may be interrupted for treatment of the infusion-related reaction, including treatment with antihistamines, corticosteroids, and/or bronchodilator therapy, as appropriate. Subjects who experience a Grade 3 infusion-related reaction to brentuximab vedotin or nivolumab may potentially receive additional treatment with the study drug(s) at the discretion of the investigator after discussion with the sponsor.

If anaphylaxis or a Grade 4 infusion-related reaction occurs, administration of the implicated agent(s) (brentuximab vedotin and/or nivolumab) should be immediately and permanently discontinued.

In case of late-occurring hypersensitivity symptoms to nivolumab (eg, appearance of a localized or generalized pruritus within 1 week after nivolumab treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.5.7 Management of Suspected PML

Signs and symptoms of PML may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. See the brentuximab vedotin (IB) for further details.

If PML is suspected, hold further dosing of brentuximab vedotin and nivolumab and undertake a diagnostic work-up including (but not limited to):

- Neurologic examinations, as warranted
- Brain radiologic features by magnetic resonance imaging (MRI)
- PCR analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin and nivolumab.

4.5.8 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.

4.5.9 Treatment Beyond Disease Progression

4.5.9.1 Circumstances in which post-progression treatment is permitted

Subjects meeting progression defined by relapsed disease (after CR) or progressive disease (after PR, SD) per 2014 Lugano Classification & the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) [85]for DLBCL/PTCL/PMBL/MGZL (Appendix 2) or modified Severity Weighted Assessment Tool (mSWAT) and Global Response Score in CTCL criteria (Appendix 4) may continue receiving study medication beyond investigator-assessed progression as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Subjects will be re-consented for treatment beyond progressive disease
- 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. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

4.5.9.2 Assessment Schedule for the Subjects with Post-progression Treatment

The subject should continue to receive monitoring according to the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) a minimum of 12 weeks On-Treatment Assessments on Table 5.1-2. Radiographic assessment described in section 5.4.1 should be performed when subjects continue post progression treatment as outlined in appendix 2.

4.5.9.3 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, increase in tumor burden without a 5mm absolute increase does not require discontinuation) from previous PET-CT, CT and/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. Increase in tumor burden without a 5mm absolute increase does not require discontinuation.
- 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.

4.5.9.4 Efficacy Assessment for 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 (Table 5.1-3). The subjects who proceed to allogeneic SCT or ASCT will be followed with specific tumor assessment 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.

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.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not Applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209436)

Procedure	Screening Visit	Notes (Screening procedures are to occur within 28 days from first dose unless otherwise specified)
Eligibility Assessment		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening
Medical History	X	
Prior Systemic Therapy	X	
Safety Assessments		
Complete Physical Examination	X	Include assessment of lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen) and neurological examination Skin evaluations using m SWAT for CTCL
Physical Measurements	X	Include height, weight and ECOG Performance Status
Vital Signs and oxygen saturation	X	Temperature, BP, HR, and O_2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable).
Assessment of Signs and Symptoms	X	Required for the 14 days prior to first dose
Concomitant Medication Collection	X	Required for the 14 days prior to first dose,
Laboratory Tests	X	CBC with differential, Chemistry panel including LDH, AST, ALT, ALP, albumin, total bilirubin, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, Free T3, Free T4 within 14 days prior to first dose. Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA) within 28 days prior to first dose. HIV test within 28 days prior to first dose

Table 5.1-1: Screening Assessments (CA209436)		
Procedure	**Screening Visit**	**Notes (Screening procedures are to occur within 28 days from first dose unless otherwise specified)**
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 and must be done within 24 hours of first dose.
Efficacy/Biomarker Assessment		
Radiographic Tumor Assessment CT chest, CT/MRI abdomen, pelvis and other known sites of disease (also required for CTCL) FDG PET-CT (DLBCL, PTCL, PMBL & MGZL only)	X	To be performed within 28days prior to first dose. Contrast enhanced CT chest, CT/MRI abdomen, pelvis and other known sites of disease. Brain MRI for CNS assessment (only if clinically indicated). Non-contrast CT chest and MRI abdomen/pelvis acceptable if CT with contrast is contra-indicated. Modality should remain the same for each subject throughout the study FDG PET-CT will be used for response assessment for DLBCL, PTCL, PMBL and MGZL only. Refer to section 5.4.3.3
Blood tumor burden assessment (SS-CTCL only)	X	Required only for CTCL Sezary Syndrome for assessment of tumor burden and baseline staging. Refer to section 5.4.3.6 and Appendix 3 for further details
Modified Severity Weighted Assessment Tool	X	Required for subjects with Cutaneous T Cell Lymphoma. Refer to Appendix 4.
Medical Photography	X	Suggested for subjects with Cutaneous T Cell Lymphoma only. Refer to Section 5.4.3.5
CD30 Expression	X	CD30 expression ≥ 1% in tumor or TILs must be confirmed by local IHC testing prior to first dose. It will also be done centrally and assessed retrospectively.
Bone Marrow Biopsy & Aspirate	See Note	Bone Marrow assessment is **not** required for DLBCL/CTCL/PMBL/MGZL subjects unless clinically indicated. It is recommended for PTCL subjects if there is clinical suspicion for disease involvement in the bone marrow. Refer to section 5.4.4 for further details. Only if clinically indicated, bone biopsy & aspirate collected during screening are acceptable. If a biopsy and/or aspirate is performed during treatment, submission for biomarker analyses is optional. Refer to Table 5.6-1 for further details.

Table 5.1-1: Screening Assessments (CA209436)		
Procedure	**Screening Visit**	**Notes (Screening procedures are to occur within 28 days from first dose unless otherwise specified)**
Tumor tissue submission	X	Submission of tumor tissue (FFPE tumor tissue block or a minimum of 20 unstained slides, obtained during the screening phase or collected as a standard of care procedure prior to obtaining informed consent) is mandatory. Tumor tissue must have been collected within 20 months from screening, while slides must have been cut within 6 months from screening. In order to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period. Biopsy samples should be excisional, incisional or core needle. Refer to Section 5.6.1 and also to Table 5.6-1 for further details.
Serum/plasma	X	Specification of test performed is described in Table 5.6-1
IVRS/Clinical Drug Supplies		
Phone calls to IVRS	X	Phone calls must be made to IVRS as follows: For subject number assignment at the time informed consent is obtained and trigger 1st shipment of drug. Refer to section 4.4 for further details.

Table 5.1-2: On Treatment Procedures (CA209436)				
	On treatment procedures			
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified.**
Safety Assessments				
Targeted Physical Examination	X		X	Include assessment of lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen) and neurological examination Skin evaluation using mSWAT scoring for CTCL Refer to section 5.3 for further details.
Vital Signs and Oxygen Saturation	X	X	X	Temperature, BP, HR, O_2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms. Refer to section 5.3 for further details.
Adverse Events Assessment	----------Continuously----------			Assessed using NCI CTCAE v. 4.03
Review of Concomitant Medications	X	X	X	
Physical Measurements	X	X	X	Includes weight and ECOG status
Laboratory Tests		X	X	To be done within 72 hours prior to dosing and include: CBC with differential, uric acid, BUN or serum urea level, creatinine, Ca, Mg, K, Cl, Na, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH.
Thyroid Function Testing			See Note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed at every other cycle (C3, C5, etc). Refer to section 5.3 for further details.
Pregnancy Test (WOCBP only)	X		See Note	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule.

Table 5.1-2: On Treatment Procedures (CA209436)

	On treatment procedures			
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified.**
Efficacy/Biomarker Assessments				
Radiographic Tumor Assessment • CT chest, CT/MRI of abdomen, pelvis and any other known sites of disease (required for CTCL) FDG PET-CT (DLBCL, PTCL, PMBL & MGZL only)			See Note	Tumor assessments will occur at Week 6 and Week 12 continuing every 9 weeks (+/- 1 week) for the subsequent 4 tumor assessment timepoints, regardless of dosing schedule. After the first year, tumor assessments are to occur every 12 weeks (+/- 2 weeks) until disease progression is documented. Patients with treatment beyond progression should be evaluated at minimum every 12 weeks (see appendix 2). Radiographic evaluations in subjects with CTCL will be performed as clinically indicated by the disease stage. FDG PET-CT is the method of assessment for DLBCL, PTCL, PBML & MGZL subjects. Subjects with PET-Avid lesions at baseline should be followed with PET, subjects with non-Pet avid lesions and lesions on CT scans at baseline should be followed with CT Scans. Refer to section 5.4 for further details.
Blood tumor burden assessment (SS-CTCL only)			See Note	Only required to confirm CR in CTCL SS subjects in case blood was positive for tumor cells at screening. Refer to section 5.4.3.6.
Modified Severity Weighted Assessment Tool			See Note	Required for subjects with Cutaneous T Cell Lymphoma as part of disease assessment. To be completed at each visit. Refer to Appendix 4 for further details.
Medical Photography			See Note	Suggested for subjects with Cutaneous T Cell Lymphomas as part of disease assessment. To be done along with the radiographic assessment timepoints. Refer to section 5.4.3.5 for further details.

Table 5.1-2: On Treatment Procedures (CA209436)				
	On treatment procedures			
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified.**
Bone Marrow Aspirate and Biopsy			See Note	Bone Marrow assessment is **not** required for DLBCL/CTCL/PMBL/MGZL subjects unless clinically indicated. It is recommended for PTCL subjects if there is clinical suspicion for disease involvement in the bone marrow. If a biopsy and/or aspirate is performed during treatment, submission for biomarker analyses is optional. Refer toTable 5.6-1 for further details. Required to confirm complete response (CR) in subjects with bone marrow disease at screening.
Additional Biomarker Samples • Tumor biopsy • Blood	See Note	See Note	See Note	See Table 5.6-1 for collection of samples for biomarker studies
Outcomes Research Questionnaire				
EQ-5D 3L Questionnaire	X		X	Subjects will be asked to complete the EQ-5D 3L prior to study drug administration and before any clinical activities. Refer to section 5.7 for more information. To be completed only for subjects enrolled in the Expansion Phase (Cohort B).
PK and Immunogenicity Assessments				
PK and Immunogenicity Samples				See Table 5.6-1 for sampling details.

Table 5.1-2: On Treatment Procedures (CA209436)				
	On treatment procedures			
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified.**
Clinical Drug Supplies				
Administer Study Drug	Brentuximab vedotin	Nivolumab	X	Brentuximab vedotin will be administered at C1D1 and Nivolumab will be administered on C1D8. At all subsequent cycles, both study drugs will be administered on the same day. Brentuximab vedotin will be administered first followed by a minimum 30 minute rest. Nivolumab will be administered second. Refer to Section 4.5 for further details. IVRS should be called within 3 days prior to study drug administration to receive vial assignment.

Table 5.1-3: Follow-up Assessments (CA209436)			
Follow-up Assessments (CA209436)			
Procedure	**Follow Up, Visits 1 and 2[a] (X01 & X02)**	**Survival Follow-Up Visits[b]**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg,spleen) and neurological examination Skin evaluation with mSWAT scoring in CTCL
Adverse Events Assessment	X		
Laboratory Tests	X		Required for X01: CBC with differential, uric acid, serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, TSH (reflex to free T3, free T4 for abnormal TSH result). Panel should also be performed at X02 if X01 results were abnormal.
Pregnancy Test (WOCBP only)	X		Serum or urine

Table 5.1-3: Follow-up Assessments (CA209436)

Follow-up Assessments (CA209436)			
Procedure	**Follow Up, Visits 1 and 2[a] (X01 & X02)**	**Survival Follow-Up Visits[b]**	**Notes**
Efficacy Assessments			
Radiographic Tumor Assessment CT chest, CT/MRI abdomen, pelvis, and any other known sites of disease FDG PET-CT (DLBCL,CTCL, PMBL &MGZL only)	X	X	Only for subjects without documented progression since first dose of study therapy Tumor assessments will occur at Week 6 and Week 12 continuing every 9 weeks (+/- 1 week) for the subsequent 4 tumor assessment timepoints, regardless of dosing schedule. After the first year, tumor assessments are to occur every 12 weeks (+/- 2 weeks) until disease progression is documented. FDG PET-CT is required for assessment of DLBCL/PTCL/PMBL/MGZL subjects NOTE: Subjects proceeding to allogeneic SCT or ASCT will be assessed 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. Refer to section 5.4for further details.
Blood tumor burden assessment (SS-CTCL only	See note	See note	Only required to confirm CR in CTCL SS subjects in case blood was positive for tumor cells at screening. Refer to section 5.4.3.6 for details.
Modified Severy Weighted Assessment Tool for subjects with Cutaneous T Cell Lymphoma	See note	See note	Required for subjects with Cutaneous T Cell Lymphoma as part of disease assessment. Refer to Appendix 4 for details.
Medical Photography	See note	See note	Suggested for subjects with Cutaneous T Cell Lymphomas as part of disease assessment. To be done along with the radiographic assessment for all of those respective timepoints. Refer to section 5.4.3.5 for details.

Table 5.1-3: Follow-up Assessments (CA209436)

Follow-up Assessments (CA209436)			
Procedure	**Follow Up, Visits 1 and 2[a] (X01 & X02)**	**Survival Follow-Up Visits[b]**	**Notes**
GVHD Assessments			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. Refer to Appendix 5 for further details.
Subsequent Anticancer Therapy	X	X	
Other Primary Malignancies	X	X	
Biomarker Assessments			
Serum, Tumor Biopsy, Bone Marrow Aspirate/biopsy	See Note		Optional biomarker samples collected at time of progression. See Table 5.6-1 for biomarker sampling details
Pharmacokinetic/Immunogenicity Assessments			
PK and Immunogenicity samples	X		See Table 5.5.1-1 for PK and immunogenicity sampling details
Outcomes Research Assessments			
EQ-5D 3L Questionnaire	X	X	EQ-5D-3L questionnaires administered during survival follow-up will be completed in clinic or via phone contact. Refer to section 5.7 for more information. To be completed only for subjects enrolled in the Expansion Phase (Cohort B).

Table 5.1-3: Follow-up Assessments (CA209436)

Follow-up Assessments (CA209436)			
Procedure	**Follow Up, Visits 1 and 2[a] (X01 & X02)**	**Survival Follow-Up Visits[b]**	**Notes**
Subject Status			
Survival Status	X	X	Survival follow-up visits are expected to occur every 3 months after X02; may be accomplished by visit, phone contact or email, to update survival information and assess subsequent anti-cancer therapy. BMS may request that survival data be collected on all treated subjects outside of the 3 month specified window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

[a] Follow-up visit 1 (X01) = 35 days from the last dose +/- 7 days. Follow-up visit 2 (X02) = 80 days (+/- 7 days) from follow-up visit X01.

[b] Survival Follow-up visits to occur every 3 months from X02. BMS may request that survival data be collected on all treated subjects outside of the 3 month specified window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

5.1.1 Retesting During Screening or Lead-in Period

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

Any new result will override the previous result 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, 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

- NCI CTCAE version 4.03
- Nivolumab IB
- Brentuximab Vedotin 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 submission of local laboratory data
- Serious Adverse Events (or eSAE) case report forms
- EQ-5D 3L questionnaires
- Pregnancy Surveillance Forms

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) and should be performed within 28 days prior to first dose.

Physical examination will be performed as clinically indicated and clinical signs and symptoms are to be collected within 14 days of first dose. For subjects with CTCL, a skin examination following the mSWAT should be included. During the on-treatment visits, a target physical examination is acceptable and it should include the assessment of the lymph node areas, abdominal organs (eg, spleen), neurological assessment and skin lesions if applicable. 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.

Pregnancy testing (urine or serum) must be done in WOCBP only and within 24 hours of first dose and at least every 4 weeks (+/- 3days) thereafter regardless of dosing schedule.

Baseline local laboratory assessments must be done within 14 days prior to first dose to include CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, uric acid, Ca, Mg, Na, K, Cl, LDH, glucose, albumin, amylase, lipase and urinalysis (total protein, glucose blood, leukocyte esterase, specific gravity and pH).

Baseline local laboratory assessments for Hep B and C testing (HBV sAg, HCV Ab or HCV RNA) must be done within 28 days prior to first dose.

On treatment oxygen saturation by pulse oximetry should be obtained within 72 hours prior to dosing and at any time a subject has any new or worsening respiratory symptoms. A reading at rest should be obtained at each time point. 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 Appendix 6 and the nivolumab IB.

Thyroid function testing is to be done at every other cycle (approximately every 6 weeks, unless treatment delays are observed) for subjects receiving study drug. At baseline TSH, Free T3 and Free T4 will be performed within 14 days of first dose. During treatment TSH will be done (with reflexive Free T4 and Free T3 if TSH results are abnormal) within 72 hours prior to dosing.

On treatment local laboratory assessments should be done within 72 hours prior to dosing; and will 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 and LDH.

Local laboratory assessments are to be performed for the Follow-up X01 visit and include CBC with differential, uric acid, serum urea level, uric acid, albumin, creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, TSH (reflex to free T3, free T4 for abnormal TSH result). This panel should be repeated at Follow-up visit X02 if Follow-up visit X01 results were abnormal.

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.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the Follow-Up Phase at Visits X01 and X02, toxicity assessments should be done in person. Follow-up visit 1 (X01) is to occur 35 days from the last dose +/- 7 days. Follow-up visit 2 (X02) is to occur 80 days (+/- 7 days) from follow-up visit X01. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls/email correspondence to assess the subject's status are acceptable. Survival visits should occur every 3 months. BMS may request that survival data be collected on all treated

subjects outside of the 3 month specified window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.03.

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 evaluations) 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.

Some of the assessments referred to in this section 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.

5.3.1 Imaging Assessment for the Study

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.

At the sponsor's discretion, scans may be collected centrally to be reviewed by independent radiologists.

5.4 Efficacy Assessments

DLBCL, PTCL, PMBL and MGZL Efficacy Assessment:

The primary efficacy assessment is Objective Response (OR). Objective Response is defined as a subject achieving either a PR or CR according to the Lugano Classification 2014 and Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) (Appendix 2) and will be based on investigator assessed response. Efficacy assessment for DLBCL, PTCL, PMBL and MGZL will be primarily derived from the FDG PET-CT performed according to the timepoints described in Table 5.1-1 Table 5.1-2 and Table 5.1-3. Subjects with PET-Avid lesions at baseline should be followed with PET, subjects with non-Pet avid lesions and lesions on CT scans at baseline should be followed with CT Scans. Tumor assessment (CR or non-CR) will be assessed by the investigator according to the Lugano Classification 2014.

CTCL Efficacy Assessment:

Efficacy assessment for Cutaneous T Cell lymphomas will include CT/MRI for visceral disease assessment and peripheral lymph nodes at the pre-determined timepoints described in Table 5.1-1 Table 5.1-2 and Table 5.1-3. The consensus Global Response Score assessment to evaluate disease activity will also be completed at every tumor assessment time point to assess extent of disease. Medical photographies are recommended to document the appearance of skin lesions throughout the study. The mSWAT will be used to assess skin involvement, it is preferable that the mSWAT assessments should be performed by the same investigator at all time points to eliminate inter-

observer variability for a given patient. Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) will be used where clinically indicated (Appendix 2).

Whole blood must be included for assessment of SS-CTCL at baseline to evaluate blood tumor burden. In the case the blood is confirmed to be positive for tumor cells, it must be reassessed at the time of response documentation, prior to its confirmation.

All subjects treated are expected to be followed for disease progression. Subjects that discontinue treatment for other reasons different from disease progression must continue to perform tumor assessments as described in Table 5.1-3 until disease progression is documented.

The primary analysis of the study will be performed 8 months after the last subject has received the first dose of study medication, or earlier if that subject discontinues study therapy. After the cut off for the primary analysis, subjects who are receiving study treatment can continue treatment per protocol until progression, unacceptable toxicity, withdrawal of consent, or other reasons as listed in Section 3.5.

Once subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo radiographic assessments at the predetermined timepoints described in Table 5.1-3. Instead, they will be evaluated 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.

Sites are required to have available on site all of the on-study tumor scans.

5.4.1 Radiographic Assessments

Baseline assessments should be performed within 28 days prior to the first dose, utilizing FDG PET-CT, CT or MRI. CT scans are preferred for CTCL. In addition to chest, abdomen, pelvis, all known sites of disease should be assessed at baseline. FDG PET-CT will be performed for assessment throughout the study for subjects with DLBCL, PTCL, PMBL and MGZL. Low dose or attenuation correction CT portions of a combined FDG 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 FDG PET-CT is of identical diagnostic quality to a diagnostic CT with oral contrast, (+/- IV contrast) then the adequate dose CT of the FDG PET-CT can be used for tumor measurements. Subjects with CTCL are to perform the CT scans described above in addition to medical photographies if appropriate for disease assessment.

Subjects will be evaluated for tumor response by FDG PET-CT, or CT/MRI at week 6 and week 12 continuing every 9 weeks (+/- 1 week) for the subsequent 4 tumor assessment timepoints, regardless of dosing schedule. After the first year, tumor assessments are to occur every 12 weeks (+/- 2 weeks) until disease progression is documented.

Tumor assessments for ongoing study treatment decisions will be completed by the investigator using the Lugano Classification 2014 for Diffuse Large B Cell Lymphomas and Peripheral T Cell Lymphomas. Refer to Appendix 2 for further details. For Cutaneous T Cell Lymphomas, response

should be assessed by the consensus Global Response Score. Refer to Appendix 4 for further details.

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.

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

5.4.2.1 Measurable Lesions

Measurable lesions must be accurately measured in at least two perpendicular dimensions. For subjects staged with PET-CT (DLBCL, PTCL, PMBL and MGZL), focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. For subjects staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have a LDi greater than 15 mm. Measurable extranodal disease (eg, hepatic nodules) may be included in the six representative, measured lesions. For extranodal measurable lesion the LDi must be greater than 10 mm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non measurable disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites). In subjects in whom a discordant histology or malignant transformation is suspected, a PET-CT may identify the optimal site to biopsy for confirmation.

For subjects with CTCL measurable, skin lesions are defined as papules, plaques and patches covering ≥ 10% of the skin surface (T2). Lymph nodes are qualified as abnormal if > 15 mm in diameter.

5.4.2.2 Non-Measurable Lesions

Non-measurable lesions will be all other lesions, including small lymph nodes (longest diameter ≤ 15 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, abdominal masses/abdominal organomegaly identified by physical exam and 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 the eCRF in metric notation (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 exam.

5.4.3.3 FDG PET-CT, CT Scan and MRI

Contrast-enhanced Computed Tomography (CT) scans acquired on dedicated CT equipment are preferred for response assessment of subjects with CTCL or DLBCL/PTCL/PMBL/MGZL subjects without FDG avid tumors in this study. CT with contrast of the chest, abdomen and pelvis (as clinically indicated) are to be performed for tumor assessments at week 6 and week 12 continuing every 9 weeks (+/- 1 week) for the subsequent 4 tumor assessment timepoints, regardless of dosing schedule. After the first year, tumor assessments are to occur every 12 weeks (+/- 2 weeks) until disease progression is documented. CT scans should be acquired with 5mm slices with no intervening gap (contiguous). When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of 5 mm with no gap (contiguous).

Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

FDG PET-CT with oral contrast and intravenous contrast will be performed for assessment throughout the study for patients with DLBCL, PTCL, PMBL and MGZL. If however CT is low dose and intravenous contrast is not available, then sites may obtain additional CT with oral and intravenous contrast.

Note on CT component of a PET-CT scanner: 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 used. Site should 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). In certain cases where the CT portion of the PET-CT scan is low dose, then a diagnostic CT scan with oral and intravenous contrast should be performed.

MRI of the brain should be done at baseline if CNS involvement is suspected to rule out active disease. Scans during on-study treatment and follow up periods are required only as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.

5.4.3.4 Clinical Lesions

Clinical lesions (nodal, extranodal) will only be considered measurable when they are superficial and ≥ 15 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.

In regards to CTCL, skin evaluation will be performed using the m SWAT scoring system. It is recommended that the mSWAT at the bedside should be performed by the same investigator at all time points. If the same investigator cannot perform all the assessments, then all personnel grading the same patient must have completed prior training, ideally before study initiation.

5.4.3.5 Medical Photography (Skin lesions only)

Medical photography with ruler measurements for documentation of skin lesions are recommended in subjects with CTCL.

5.4.3.6 Whole Blood (SS-CTCL only)

Peripheral blood flow cytometry to evaluate for SS cell at screening and at response confirmation is required in subjects with CTCL(SS).

5.4.3.7 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 should be identified as target lesions and their measurements recorded. 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.

5.4.3.8 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’).

5.4.4 Bone Marrow Assessments

Bone marrow assessments are not mandatory in the study, unless clinical suspicion is high. In subjects with PTCL, if there is clinical suspicion for bone marrow involvement, it is recommended

to obtain a bone marrow aspirate and biopsy at the time of screening. All subjects may volunteer to undergo bone marrow biopsy and aspirate at any time during therapy if clinically indicated for DLBCL, CTCL, PMBL and MGZL.

Only if clinically indicated, bone marrow biopsy and aspirate performed within 90 days prior to obtaining consent or fresh sample collected during screening are acceptable options. If a bone marrow biopsy/aspirate is performed during the screening period, consider submitting a bone marrow aspirate sample for biomarker analyses. For subjects that perform bone marrow assessment at screening and there is marrow involvement confirmed, a bone marrow biopsy and aspirate will be required to confirm a CR, and submission of bone marrow aspirate samples is optional as detailed in Table 5.6-1.

In addition to efficacy assessments, additional, optional, bone marrow biopsy and aspirate samples may be collected and submitted for biomarker studies as detailed in Table 5.6-1.

5.4.5 Disease Response Evaluation

The determination of disease response to study treatment will be made using Lugano Classification 2014 in subjects with DLBCL, PTCL, PMBL and MGZL (Appendix 2). Responses in CTCL will be evaluated using consensus Global Response Score by the investigators (Appendix 4).

For CTCL Response Evaluation, the consensus Global Response Score will be used incorporating skin, lymph nodes, viscera and blood. The mSWAT score will be used to evaluate and score skin lesions, and to assist in skin response evaluation.

5.5 Pharmacokinetic and Immunogenicity Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving nivolumab and brentuximab vedotin as described in Table 5.5.1-1. All time points are relative to the start of study drug administration. After cycle 1 (once both study drugs of the combination are administered on the same day), predose samples are to be collected relative to the start of brentuximab vedotin. All on-treatment time points are intended to align with days on which study drug is administered, if dosing occurs on a different day, the PK and immunogenicity sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

5.5.1 Pharmacokinetics: Collection and Processing

A detailed schedule of PK and immunogenicity evaluations for nivolumab and brentuximab vedotin is provided in Table 5.5.1-1. PK samples will be analyzed for nivolumab and brentuximab vedotin by validated ligand binding assays. Immunogenicity samples will be analyzed for anti-nivolumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Table 5.5.1-1: Nivolumab Pharmacokinetic and Immunogenicity Sampling Schedule - Cohort A and Cohort B

Study Day	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of the Infusion treatment) Hour:Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 8	Predose[a]	00:00	X	X
Cycle 2 Day 1	Predose[a]	00:00	X	X
Cycle 3 Day 1	Predose[a]	00:00	X	X
Cycle 5 Day 1	Predose[a]	00:00	X	X
Day 1 of every 6th cycle thereafter (every 18 weeks) until discontinuation of study treatment[b]	Predose[a]	00:00	X	X
First 2 Follow-up visits-X01 & X02			X	X

[a] Predose samples should be taken just prior to the administration. It is acceptable to collect the predose sample for nivolumab and brentuximab vedotin at the same time, as long as it is collected prior to the start of the infusion. If the infusion is delayed and a pre-dose sample was already collected, there is no need to collect an additional pre-dose sample.

[b] For subjects during second year of treatment and beyond, PK collections will occur every 24 weeks instead of every 18 weeks.

Table 5.5.1-2: Brentuximab Vedotin Pharmacokinetic and Immunogenicity Sampling Schedule - Cohort A and Cohort B

Study Day	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Brentuximab Vedotin Infusion) Hour:Min	Brentuximab Vedotin PK Blood Sample	Brentuximab Vedotin Immunogenicity Sample
Cycle 1 Day 1	Predose[a]	00:00	X	X
Cycle 2 Day 1	Predose[b]	00:00	X	X
Cycle 3 Day 1	predose[b]	00:00	X	X
Cycle 5 Day 1	predose[b]	00:00	X	X

Table 5.5.1-2: Brentuximab Vedotin Pharmacokinetic and Immunogenicity Sampling Schedule - Cohort A and Cohort B

Study Day	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Brentuximab Vedotin Infusion) Hour:Min	Brentuximab Vedotin PK Blood Sample	Brentuximab Vedotin Immunogenicity Sample
Day 1 of every 6th cycle thereafter (every 18 weeks) until discontinuation of study treatment[a]	predose[b]	00:00	X	X
First 2 Follow-up visits- X01 & X02			X	X

[a] For subjects during second year of treatment and beyond, PK collections will occur every 24 weeks instead of every 18 weeks.

[b] Predose samples should be taken just prior to the administration (preferably within 30 minutes). It is acceptable to collect the predose sample for nivolumab and brentuximab vedotin at the same time, as long as it is collected prior to the start of the infusion. If the infusion is delayed and a pre-dose sample was already collected, there is no need to collect an additional pre-dose sample.

5.6 Biomarker Assessments

Peripheral blood, tumor tissue and bone marrow aspirate/biopsy will be collected prior to therapy and at selected timepoints on treatment as outlined in Table 5.6-1, unless restricted by local requirements.

Table 5.6-1: Biomarker Sampling Schedule (CA209436)

Collection Timing	Plasma and Serum[a]	PBMC	Tumor Biopsy		Bone Marrow Aspirate/Biopsy[b]	Whole Blood
Study Day	Soluble Biomarkers	Immuno-phenotyping	(FFPE)	(Fresh)		SNP
Screening			X[c]	X	X[d]	
Cycle 1 Day 1	X	X		X		X
Cycle 2 Day 1	X	X				
Cycle 3 Day1	X	X				
Cycle 4 Day 1	X	X				
Cycle 7 Day1	X	X				
CR Evaluation	X	X			X[e]	

Table 5.6-1: Biomarker Sampling Schedule (CA209436)						
Collection Timing	**Plasma and Serum**[a]	**PBMC**	**Tumor Biopsy**		**Bone Marrow Aspirate/Biopsy**[b]	**Whole Blood**
Study Day	**Soluble Biomarkers**	**Immuno-phenotyping**	**(FFPE)**	**(Fresh)**		**SNP**
During Treatment (when clinically indicated)			X[f]	X	X[f]	
Follow-up Visit X01	X	X			X[d]	
Upon Progression[g]	X	X	X	X	X	

[a] All biomarker samples may be obtained within 3 days prior to the indicated time.

[b] Fresh tumor biopsy collections may be performed at screening or cycle 1 for flow-cytometry analysis of TILs. Such fresh biopsies for TILs analysis are optional but strongly encouraged. If screening or cycle 1 day 1 fresh tumor collection for TILs flow-cytometry analysis is perform, on-study collections are also optional but encouraged.

[c] Subjects may undergo tumor biopsy during screening or submit archival tumor tissue collected prior to obtaining informed consent. Tumor tissue must have been collected within 20 months from screening, while slides must have been cut within 6 months from screening. Refer to section 5.6.1 for further details. In order to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period.

[d] In subjects with PTCL where clinical suspicion for marrow involvement is high, bone marrow biopsy and aspirate collected within 90 days prior to obtaining consent or fresh sample during screening are acceptable. Submission of bone marrow aspirate is encouraged if available. Submission of bone marrow biopsy specimens is not required at any point in this study.

[e] If the bone marrow was involved by lymphoma prior to or at baseline, a bone marrow biopsy and aspirate will be required to confirm a CR. Submission of bone marrow aspirate is encouraged.

[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 encouraged.

[g] Samples from subjects that have confirmed progression are optional.

5.6.1 Biomarker Sampling

Tumor Biopsy:

Tumor biopsy specimens will be obtained to characterize immune cell populations and expression of selected tumor markers.

Biopsy samples should be excisional, incisional or core needle. Fine needle biopsies are not allowed because the architecture of the tumor in its microenvironment cannot be assessed.

Tumor tissue (obtained during the screening phase or collected as a standard of care procedure prior to obtaining informed consent) must be provided for biomarker analysis. Subjects with relapsed disease must provide a recent biopsy sample within 20 months from screening, while slides have been cut within 6 months from screening.

In order for subjects to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period. Minimum of 1 FFPE tumor tissue block (preferred) OR a minimum of 20 FFPE unstained sections are required for assessment of PD-L1 status and other biomarker evaluations.

All subjects may volunteer to undergo tumor biopsy at any time during therapy if clinically indicated (eg, upon progression). When tumor biopsy is performed, submission of tumor biopsy is optional, but encouraged for the purposes of understanding mechanisms of resistance to therapy.

Fresh tumor biopsy collections may be performed at screening or cycle 1 day 1 for flow-cytometry analysis of TILs. Such fresh tumor biopsies for TILs analysis are optional but strongly encouraged. If screening or cycle 1 day 1 fresh tumor collection for TILs flow-cytometry is performed, on-study collections are also optional but encouraged.

Plasma and Serum

Soluble Biomarkers

Soluble factors, such as cytokines, chemokines, soluble receptors, and antibodies to tumor antigens will be characterized and quantified by immunoassays in serum.

Plasma samples will be collected and assessed for additional cytokines and soluble factors, including soluble PD-L1 if possible.

PBMC

Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory markers in peripheral blood mononuclear cell (PBMC) preparation 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

Whole Blood

Single Nucleotide Polymorphism (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

Bone Marrow Biopsy and Aspirate

If clinical suspicion of bone marrow involvement, disease manifestation in the bone marrow will be evaluated in subjects with PTCL (Section 5.4.4) within 90 days prior to start of study therapy. If disease is observed in the bone marrow prior to or during screening, bone marrow **aspirate** will be required if CR is considered during the treatment phase of the study. Bone marrow aspirates will be obtained using institutional standards for these procedures. Samples will be assessed for

phenotypic and functional status of immune cells and tumor cells. (Screening and during treatment as described in Table 5.6-1).

Samples from bone marrow aspirates that may be performed at screening and during CR evaluation (only for subjects who had marrow involvement at study entry) are encouraged to be submitted for biomarker assessment. These will be utilized to assess the phenotypic and functional status of immune cells and tumor cells.

All subjects may volunteer to undergo bone marrow biopsy and aspirate at any time during therapy if clinically indicated. When bone marrow biopsy is done, submission of bone marrow aspirate is encouraged.

5.6.2 Detailed Biomarkers

The biomarkers described below will be analyzed by third party vendors to the extent possible considering that tumor tissue provided by some of the subjects may be insufficient to complete the full panel of biomarkers proposed in this protocol.

- **PD-L1**: Proprietary IHC analysis (Screening only)
- **Immunecell subsets:** Lymphocyte subsets and expression levels of T cell co-stimulatory markers (by flow cytometry). Analyses may include, but not 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, CD 30, CD153 and Ki67. Analysis of the diversity of the T-cell repertoire in correlation to clinical activity.
- **Tumor gene and phenotype**: Analysis (by IHC, RNASeq, GEP, qRT-PCR, miRNA, methylation, or mutational analyses) of disease heterogeneity and subtypes and implication of the data as response predictors to study therapy. (Screening only)
- **Cell of origin**: Cell of origin evaluation will be done by for subjects with diagnosis of relapsed DLBCL. Additionally, BCL2 and MYC will be assessed for double hit lymphoma. (Screening only)
- **Molecular mechanisms of action and resistance to the study drugs:** Expression profiling of immune-related genes, mutational analysis, and immune related signaling pathway gene expression profiling. Analysis includes, genes associated with immune-related pathways, such as T cell activation and antigen processing and presentation (Screening only and other timepoints if tumor material is made available)
- **PD-1 expression and nivolumab binding** effects of combination therapy on survival pathways (NF-kB,) as well as survival signals from the microenvironment. 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
- **Biomarkers of clinical response**: Multiplex- and enzyme-linked immunosorbent assay (ELISA) of tumor antigen-specific responses associated with clinical response by including cytokines, chemokines, soluble receptors, and antibodies to tumor antigens quantified. Analyses include but are not limited to, soluble CD25, soluble PD-1, soluble LAG 3, CXCL 9, and soluble PD-L1. (Screening and during treatment as described in Table 5.6-1)

- **Single nucleotide polymorphisms** (SNP) associated with safety and efficacy of study therapy. SNP analysis will be limited to genes associated with the PD1/PD-L1 pathway and genes associated with CD30 and TNF receptors and apoptosis.
- **Characterization of tumor infiltrating lymphocytes (TILs)** and tumor antigens. Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin embedded (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.
- **Flow cytometry of TIL** from bone marrow aspirates, tumor biopsies and lymph nodes will be assessed for 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. Where available, immune cells from tumor and lymph node biopsies will be isolated and cryopreserved. For functional assessment, including proliferation and intracellular cytokines such as IFN-gamma and TNF-alpha.
- **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.

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.

5.7 Outcomes Research Assessments

General health-related quality of life will be collected with the EQ-5D 3L during Expansion Phase (Cohort B) as outlined in the assessment schedule in Table 5.1-2 and Table 5.1-3

Outcomes research data including health related quality of life (QoL) and patient reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the subjects' perspective. These data will be used to assess the impact of nivolumab combined with brentuximab vedotin as reported by subjects with DLBCL (cohort B1), PTCL (cohort B2) and CTCL (cohort B3).

The EQ-5D 3L is a standardized instrument for self-reported health status comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety, plus a visual analog rating scale (VAS).

Subjects will be asked to complete the EQ-5D 3L before study drug administration and any clinical activities are performed during visits to the study clinics at on-study visits. . During follow-up and

survival-follow-up assessments, the EQ-5D 3L may be administered via telephone contact. Validated questionnaires will be provided in the subject's preferred language.

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Serum samples collected at time points identified in Table 5.5.1-1 will be analyzed by a validated immunogenicity assays. Additional characterization (ie, neutralizing antibodies) for any detected anti-drug antibodies (ADA) response to nivolumab and/or brentuximab vedotin may also be performed using a validated functional cell-based assay. All on-treatment PK timepoints are intended to align with days on which nivolumab and brentuximab vedotin are administered. If it is known that dose(s) is/are going to be delayed, then the predose sample should be collected just prior to the delayed dose(s). However, if a predose sample(s) is/are collected, but the dose is subsequently delayed, additional predose sample(s) should not be collected. Selected serum samples may be analyzed by an exploratory method that measures antinivolumab 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).

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.)

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 the last dose of *study drug*. 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.

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 must 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 until 100 days from the last dose 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).

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:

- 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 Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with 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).

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

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 of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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. AT (ALT or AST) elevation > 3 times upper limit of normal (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

Not Applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

- In the Dose Evaluation Phase (Cohort A), 6 -12 subjects will be treated (Section 4.5.1). The number of subjects is not based on statistical power considerations. If less than 1/3 of 6 subjects experience a DLT, the upper limit of the 80% 1-sided exact confidence interval for the true DLT rate will not be greater than 42%. If less than 1/3 of 12 subjects experience a DLT, the upper limit of the 1-sided 80% exact confidence interval (CI) for the true DLT rate will not be greater than 41.2%.
- In the Expansion Phase (Cohort B), a total of 130 subjects will be treated, with 40 subjects in cohort B1 (DLBCL), 30 subjects in cohort B2 (PTCL), 20 subjects in B3 (CTCL), 30 subjects in cohort B4 (PMBL) and 10 subjects in cohort B5 (MGZL).
  - Given 40 subjects in DLBCL, the one-sided 90% confidence interval (ie, two-sided 80% confidence interval) for the ORR is 48.6% - 70.6% if we assume an observed ORR rate of 60%. The lower bound of the 90% CI excludes 40%, which is the null hypothesis ORR rate for PTCL.
  - Given 30 subjects in PTCL, the one-sided 90% confidence interval (ie, two-sided 80% confidence interval) for the ORR is 46.7% - 72.3% if we assume an observed ORR rate of 60%. The lower bound of the 90% CI excludes 40%, which is the null hypothesis ORR rate for PTCL.
  - Given 20 subjects in CTCL, the one-sided 90% confidence interval (ie, two-sided 80% confidence interval) for ORR is 63.9% - 91.0% if we assume an observed ORR rate of 80%. The lower bound of the 90% CI excludes 60%, which is the null hypothesis ORR rate for CTCL.
  - Given 30 subjects in PMBL, the one-sided 90 % confidence interval (ie, two-sided 80% confidence interval) for the ORR is 37.0% - 63.0% if we assume an observed ORR rate of 50%. The lower bound of the 90% CI excludes 30%, which is the null hypothesis ORR rate for PMBL.
  - Given 10 subjects in MGZL, the one-sided 90 % confidence interval (ie, two-sided 80% confidence interval) for the ORR is 11.6% - 55.2% if we assume an observed ORR rate of 50%. The lower bound of the 90% CI excludes 10%, which is the null hypothesis ORR rate for MGZL.

  Table 8.1-1 summarizes the 90% exact CI for different targeted ORRs and sample sizes. The targeted ORR of 60% in DLBCL and PTCL and 80% in CTCL, and null hypothesis ORR rate of 40% in DLBCL and PTCL and 60% in CTCL are based on the historical data and the activity of brentuximab vedotin and nivolumab as single agents from phase I and phase II studies. [19,39,86,87]

Table 8.1-1: One-sided 90% Exact CI for different number of subjects in each cohort		
	If the observed ORR rate is 60% in Cohort B1 and B2	**Power**
N=30	[46.7% - 72.3%]	82%
N=40	[48.6% - 70.6%]	87%
	If the observed ORR rate is 80% in Cohort B3	
N=20	[63.9% - 91.0%]	62 %
	If the observed ORR rate is 50% in Cohort B4	
N=30	[37.0% - 63.0%]	81 %
	If the observed ORR rate is 30% in Cohort B5	
N=10	[11.6% - 55.2%]	61%

Also, If we have 20 subjects in Cohort B3, assuming true ORR is 80%, there will be approximately 62% power to reject null hypothesis that the true ORR is <= 60%, considering a one-sided alpha of 10%. Given a very low prevalence of CTCL, 20 subjects in cohort III is considered as feasible and adequate for a phase II signal detecting trial. Sample size of 30 subjects in Cohort B2 and 40 subjects in Cohort B1 are corresponding to power of 82% and 87% respectively to reject null hypothesis that the true ORR is <= 40% assuming true ORR is 60% and considering a one-sided alpha of 10%. If we have 30 subjects in Cohort B4, assuming true ORR is 50%, there will be approximately 81% power to reject null hypothesis that the true ORR is <= 30%, considering a one-sided alpha of 10%. Finally if we have 10 subjects in Cohort B5, assuming true ORR is 30%, there will be approximately 61% power to reject null hypothesis that the true ORR is <= 10%, considering a one-sided alpha of 10%.

If the screening failure rate is 20%, we would need to enroll 170 subjects to have 136 patients treated (130 in Cohort B, 6 in Cohort A). If Cohort A needs 6-12 more treated subjects, we would need to enroll 8-15 more subjects accordingly.

8.2 Populations for Analyses

In 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 any of the study drugs. This is the primary population for safety and efficacy analyses. This dataset will be used for baseline demographics and efficacy and safety analyses.
- PK Subjects: Subjects with available serum time-concentration data from treated subjects dosed with nivolumab and/or brentuximab vedotin.
- HEOR subjects: treated subjects who have an assessment at screening/baseline and at least 1 follow-up assessment

- Immunogenicity subjects: treated subjects who have an assessment at screening/baseline and at least 1 follow-up assessment

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary safety endpoints include incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, drug-related adverse events and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The primary efficacy endpoint is ORR. It is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR 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 or the date of subsequent therapy, whichever occurs first. Allogeneic SCT and ASCT will be considered as subsequent therapy. In subjects with relapsed refractory DLBCL, relapsed refractory PTCL, relapsed refractory PMBL and relapsed refractory MGZL the response (CR, PR, PD, and progression) will be assessed according to Lugano Classification 2014. For subjects with relapsed refractory CTCL, response will be assessed according to consensus Global Response Score as per the consensus statement of the International Society for Cutaneous Lymphoma. A CR must have been confirmed by scans, including a negative Positron Emission Tomography (PET) to be considered for CR in subjects with PTCL, DLBCL, PMBL and MZGL. In subjects with PTCL, if the bone marrow was compromised at baseline, a bone marrow must also be negative at the time of CR. In CTCL CT scans (chest, neck, abdomen and pelvis), blood flow for SS cells and m SWAT skin scoring along with medical photography will be performed at baseline and at the end of the treatment for response evaluation. The investigator will perform tests that will allow evaluation of response to therapy according to corresponding disease criteria in Appendix 2 and Appendix 4. The analysis of the primary endpoint will occur approximately 8 months after the last enrolled subject's first dose of study therapy. Depending on the enrollment for each disease cohort, the analysis may be done at different times for each cohort, or at the same time for the three cohorts.

8.3.2 Secondary Endpoint(s)

The secondary endpoints are DOR, CR rate, duration of CR, PFS and OS.

DOR will be calculated from the date of initial documentation of a response (CR, or PR) to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment. For subjects who received subsequent therapy prior to documented progression, duration of response will be censored on the last tumor assessment date prior to subsequent therapy. Allogeneic SCT and ASCT will be considered as subsequent therapy.

The CR rate is defined as the number of subjects with a BOR of CR 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 to the date of initial documented progression or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition.

PFS is defined as the time from the date of first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever comes first. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment. For subjects who received subsequent therapy prior to documented progression, it will be censored on the last tumor assessment date prior to subsequent therapy.

OS is defined as the time from the date of first dose of study drug until the date of death (any reason). If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive.

8.3.3 Exploratory Endpoint(s)

The Indeterminate response will be assessed per the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC). The exploratory biomaker objectives are to assess CD30 expression and correlate with response, and to assess PD-L1/L2 status and correlate it with response etc. These biomarker endpoints are discussed in detail in Section 5.6. The exploratory objectives also include characterizing pharmacokinetics (PK) and the immunogenicity of nivolumab and brentuximab vedotin following combination therapy. The nivolumab and brentuximab vedotin concentration, PK parameter and inmmunogenicity endpoints are discussed in details in Section 5.5.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics of patient will be summarized for each cohort and also for all treated subjects.

8.4.2 Efficacy Analyses

All analyses will be performed separately for each cohort and also for all treated subjects combined with same treatment dosage (ie, safety cohort subjects with different dose from the expansion cohort will not be combined).

The ORR will be summarized by binomial response rates and their corresponding two-sided 80% exact CIs using the Clopper-Pearson method. The same analysis will be performed for CR rate.

The DOR will be summarized by cohort for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using log-log transformation method and range, will also be calculated. The same analysis will be performed for duration of CR, PFS and OS at 1 year. Detailed analyses on efficacy endpoints will be presented in the statistical analyses plan.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.03 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 v4.03 criteria.

In addition to separate analyses per cohort, safety analyses will be performed all treated subjects combined. If safety cohorts subject have different doses, the safety results will be presented by cohorts and by dose.

8.4.4 Pharmacokinetic Analyses

The nivolumab and brentuximab vedotin concentration data obtained in this study may be combined with data from other studies in the clinical development programs to develop or refine existing population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab or brentuximab vedotin 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 exposure-response analyses. Results of population PK and exposure response-analyses will be reported separately.

8.4.5 Biomarker Analyses

Summary statistics for peripheral blood and tumor biomarker activity such as, but not limited to CD30, PD-L1/L2 expression levels and their corresponding changes (or percent changes) from baseline will be tabulated by planned study visit to assess pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically; if there is indication of meaningful pattern across time, further analysis may be performed to characterize the relationship. Results from peripheral blood and tumor biomarkers will be tabulated and associations between biomarkers and efficacy or safety measures will be assessed. Methods such as, but not limited to, logistic regression will be used to explore possible associations between measures of peripheral blood, tumor biopsies and clinical outcome. More details of biomarker analyses will be described in the statistical analysis plan.

8.4.6 Outcomes Research Analyses

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 3L 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 3L 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.

8.4.7 Other Analyses

8.4.7.1 Immunogenicity Analyses

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

No formal interim analysis is planned. 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. Interim analyses will not impact the study conduct and the trial will continue as planned.

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

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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.

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 to include investigational product and the following non-investigational product(s). 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 paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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, including any paper or electronic 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
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

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

Not applicable.

11 LIST OF ABBREVIATIONS

Term	Definition
ABC	Activated B cell like
ACTH	Adrenocorticotropic Hormone
ACVBP	Doxorrubicin, cyclophosphamide, vindesine, bleomycin and prednisone
ADC	Antibody-drug conjugate
AE	adverse event
AIDS	Acquired immunodeficiency syndrome
AITL	Angioimmunoblastic T Cell Lymphoma
ALCL	Anaplastic Large Cell Lymphoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	Autologous Stem Cell Transplant
AST	aspartate aminotransferase
AT	Aminotransferase (ALT or AST)
BA	Bioavailability
BCNU	bis-chloroethylnitrosourea (Carmustine)
BE	Bioequivalence
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
BV	Brentuximab Vedotin
C	Celsius
Ca	Calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1	Chloride
CrCl	creatinine clearance

Term	Definition
CL/CLR	Clearance/renal clearance
Cm	Centimeter
CMV	Cytomegalovirus
CNS	Central nervous system
COO	Cell of Origin
CR	Complete remission
CRC	Colorectal Cancer
CrCl	Creatinine Clearance
CRF	Case Report Form, paper or electronic
CRR	Complete response rate
CT	Computed tomograhpy
CTLA	Cytotoxic T-Lymphocyte Antigen
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T Cell Lymphoma
DILI	drug induced liver injury
dL	Deciliter
DLBCL	Diffuse large B-Cell lymphoma
DLT	Dose Limiting Toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event Free Survival
eg	exempli gratia (for example)
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organization of Research and Treatment of Cancer
ER	Endoplasmic Reticulum Stress
eSAE	Electronic Serious Adverse Event
ESR	Expedited Safety Report

Term	Definition
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
FFPE	Formalin-Fixed Parafin-Embedded
FSH	follicle stimulating hormone
g	Gram
GC	Germinal Center subtype
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
G-CFS	Growth factor support
GVHD	Graft versus host disease
h	Hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	hepatitis C virus
HCO3-	Bicarbonate
HDACi	Histone deacetylase Inhibitor
HD-ASCT	High dose autologous stem cell transplant
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
HR	heart rate
HRT	hormone replacement therapy
HuMAb	Fully-human monoclonal antibody
IB	Investigational Brochure
ICD	Immunogenic cell death
ICR	Immune checkpoint receptors
ICH	International Conference on Harmonisation

Term	Definition
ICF	Informed Consent Form
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	Immuneglobulin
IHC	Immunohistochemistry
IMP	investigational medicinal products
IND	Investigational New Drug
INN	International Nonproprietary Name
IPI	International prognostic index
IR	Indeterminate Response
IRB	Institutional Review Board
ISCL	International Society for Cutaneous Lymphoma
IU	International Unit
IUD	Intrauterine device
IV	Intravenous
IVRS	Interactive voice response system
JCV	John Cunningham virus
K+	Potassium
kg	Kilogram
L	Liter
LDH	lactate dehydrogenase
LFT	Liver function test
LPFT	Last Patient First Treatment
mAbs	monoclonal antibodies
mCRPC	Metastatic Castration-Resistance Prostate Cancer
MF	Mycosis Fungoides
mg	Milligram
Mg++	Magnesium
MGZL	Mediastinal Gray Zone Lymphoma
MHC	Major Histocompatibility Complex

Term	Definition
min	Minute
MRI	Magnetic resonance imaging
mL	Milliliter
MLR	mixed lymphocyte reaction
mm	Millimeter
MMAE	Monomethyl auristatin E
mmHg	millimeters of mercury
mSWAT	Modified Severity Weighted Tool
MTD	maximum tolerated dose
µg	Microgram
N	number of subjects or observations
Na	Sodium
N/A	not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NFkB	Natural Factor κB
ng	Nanogram
NIMP	non-investigational medicinal products
NIV	Nivolumab
NHL	Non-Hodgkin lymphoma
NK	Natural Killer
Non GC	Non germinal center subtype
NOS	Not otherwise specified
NSCLC	Non small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cells
PD	Progressive Disease
PD-1	Programmed death-1 receptor
PET	Positron emission tomography

Term	Definition
PFS	Progression free survival
PK	pharmacokinetics
PPK	Population PK
PMBL	Primary Mediastinal B Lymphoma
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PRR	Partial response rate
PS	Performance Status
PTCL	Peripheral T Cell Lymphoma
q	Every
Q2W	Every 2 weeks
qPCR	Quantitative real-time polymerase chain reaction
RBC	red blood cell
RCC	Renal cell carcinoma
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone
RO	Receptor Occupancy
RT-PCR	Reverse transcription- polymerase chain reaction
SAE	serious adverse event
SCT	Stem cell transplant
SD	Stable Disease
SmPC	Summary of product characteristics
SNP	Single nucleotide polymorphisms
SOP	Standard Operating Procedures
SS	Sézary Syndrome
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
TFH	T Follicular helper cells

Term	Definition
T-HALF	Half life
TIL	tumor infiltrating lymphocytes
USAN	United States Adopted Name
USP	Unites States Pharmacopeia
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 1 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, eg, 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

Toxicity and Response Criteria of the Eastern Cooperative Oncology Group.

APPENDIX 2 2014 LUGANO CLASSIFICATION: STAGING AND RESPONSE EVALUATION (DIFFUSE LARGE B CELL LYMPHOMA, PERIPHERAL T CELL LYMPHOMA, PRIMARY MEDIASTINAL B LYMPHOMA & MEDIASTINAL GRAY ZONE LYMPHOMA).

Table 1: Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology, if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

*The recommendations from Lugano Classification is to use a 5 point scale to assess the metabolic response in PET-CT based response.

Response Evaluation in DLBCL, PTCL, PMBL & MGZL:

CR (Complete Remission)

The designation of CR requires all of the following be met:

1) Complete disappearance of all detectable clinical evidence of disease.
   a) PET-CT-based response: A score of ≤ 3 is considered to represent complete metabolic response.
   b) CT based response: Target node/nodal masses must regress to ≤ 1.5 cm in LDi, with no extrlymphatic sites of disease.

Organ involvement: Absence of organomegaly (Table 3).

2) Bone marrow: No evidence of FDG- avid disease in marrow. If there was evidence of involvement of bone marrow with lymphoma at screening/baseline and a biopsy was performed (PTCL), a bone marrow biopsy will be required to confirm CR.
3) The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation of CR.

PR (Partial Remission)

The designation of PR requires all of the following:

1) PET-CT based response: Score of 4 or 5, provided reduced uptake compared with base line and absence of structural progression development on CT Scan.

2) CT based response: ≥ 50% regression in SPD of upto 6 measurable nodal and extranodal lesions (Table 3) .
3) Splenic and hepatic nodules must regress by ≥ 50% in length beyond normal.

Bone marrow : reduced uptake compared with baseline. If there is evidence of nodal response but persistent focal changes in the marrow consider further evaluation (Table 3).

SD (Stable Disease)

SD is defined as the following:

1) PET-CT based response: no metabolic response, score of 4 or 5 with no significant changes from baseline.
2) CT based response: < 50% decrease from baseline, absence of new lesions (Table 3).
3) Bone marrow: no change from baseline.

PD: Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

1) PET-CT based response: Score of 4 or 5 with increase in intensity from baseline or interim scan/ or any new FDG avid focus consistent with malignant lymphoma (Table 3).
2) CT based response: New node, new or recurrent splenomegaly,progression of existing lesions (Table 3).

IR (INDETERMINATE RESPONSE)

A patient will be considered to have Indeterminate Response (IR) in one or more of the 3 following circumstances

1) Increase in overall tumor burden (as assessed by SPD) of ≥ 50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration (IR(1))
2) Appearance of new lesions; or growth of one or more existing lesion(s) of ≥ 50% at any time point during treatment occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment (IR(2))
3) Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number (IR(3))

It is possible that, at a single time point a subject could fulfill criteria for both IR(1 or 2) AND IR(3): for example, there could be a new FDG-avid lesion in the absence of overall progression (IR(2)), and, at the same time, increase in FDG uptake of a separate lesion (IR(3)). In such cases, the designation of IR(1 or 2) should take priority (eg, IR(2))

Follow-up of IR

1) In patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated and the patient should be considered to have true PD if the SPD of target lesion has increased further, with the considerations below:
2) In the case of IR(1), the comparison should be between the first IR(1) and the current SPD, with an increase of >10% constituting PD. In addition there should be an increase of > 5 mm (in either dimension) of at least one lesion for lesions < 2 cm, and 10 mm for lesions > 2 cm, to be consistent with the Lugano classification (3)(Table 2). The 10% threshold is empiric but designed to account for variability in measurement (37), especially when taken along with the minimum increase. If the target SPD increase is < 10%, the response would still be categorized as IR(1), and the patient could continue treatment until a subsequent scan shows either true PD (> 10% increase from first IR(1) time point and an increase of > 5mm in either dimension of at least one lesion) or response (>50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4-8 weeks of the original IR(1) timepoint to ensure absence of significant further increase.
3) In the case of IR(2), the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increased > 50% from the nadir value which may precede the IR time point. The patients is considered to have PD.
4) In the case of IR(3), since inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted above
5) Importantly, if a patient is assessed as having IR and then “true” PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR

APPENDIX 3 CUTANEOUS T CELL LYMPHOMA ISCL/EORTC STAGING CRITERIA

Table 2: Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

*Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

†Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions[1] to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.

‡The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

APPENDIX 4 MODIFIED SEVERITY WEIGHTED ASSESSMENT TOOL / GLOBAL RESPONSE SCORE

Table 3: Modified Severity Weighted Assessment Tool

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.
Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.
*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Table 4: Response in Skin

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.
*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides[7]), the response should be considered a partial response only.
†Whichever criterion occurs first.

Table 5: Response in Lymph Nodes*

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
*Peripheral and central lymph nodes.
†Whichever criterion occurs first.

Table 6: Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or New organ involvement or Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
*Whichever criterion occurs first.

Table 7: Response in Blood*

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL[36] or Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to $\geq B_1$ in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

*As determined by absolute numbers of neoplastic cells/μL.

†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.

‡There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.

§Whichever occurs first.

Table 8: Global Response Score

Global Score*	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.
*It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval during which each patient is under observation also be generated.

Response Evaluation in CTCL:

Response in CTCL will be evaluated based on the involvement of different sites (lymph nodes, viscera, skin and blood) using the TNMB staging (as clinically indicated) and will be incorporated in the Global Response Score. The m SWAT will be used for skin scoring.

All responses to be designated as CR or PR, should be documented for at least 4 weeks in duration. No CR can be ascribed to a study drug while a patient remains on concomitant therapy (such as topical steroids) with known efficacy in MF/SS.

In certain cases to document CR a biopsy may be required if there are limitations on Spiral CT scan or MRI examination for lymph node or viscera evaluation and if it is deemed necessary.

Blood evaluation for Sezary syndrome: The absolute number of CD4+ CD26- determined on flow cytometry will be used to assess blood involvement. A normal value for CD+ CD26- or CD4+CD7- cells by flow cytometry is lower than 15%.

Response in skin:

m SWAT for skin soring/evaluation, to track skin tumor burden.

CR: 100% clearance of skin lesions.

PR: 50%-99% clearance of skin disease from baseline without new tumors (T3) in patients with T1, T2 or T4 only skin disease. (≥ 50% reduction in the mSWAT score compared with baseline).

Stable disease: < 25% increase to < 50% clearance in skin disease.from baseline without new tumors (T3) in patients with T1, T2, or T4 only skin disease. (Less than 50% reduction to less than 25% increase in the mSWAT score compared with baseline).

Progressive disease: > 25% increase in skin disease from baseline or new tumors (T3) in patients with T1, T2 or T4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score. Relapse is any disease recurrence in those with complete response. (≥ 25% increase in the mSWAT score from baseline).

Response in the lymph nodes will be assessed using a Spiral CT Scan or MRI.

CR: all lymph nodes ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must be ≤ 1 cm in their short axis or biopsy negative for lymphoma.

PR: cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymphnode > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter.

SD: fails to attain the criteria for CR, PR, and PD.

PD: > 50% increase in SPD from baseline of lymph nodes or any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically or loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR.

Relapse is any new lymph node > 1.5 cm in the long axis in those with CR proven to be N3 histologically.

Response in the viscera will be assessed using a Spiral CT Scan or MRI:

CR: (viscera): liver , spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma.

PR: ≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement.

SD: Fails to attain the criteria for CR, PR, or PD.

PD: > 50% increase in size (SPD) of any organs involved at baseline or new organ involvement or loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR.

Relapse new organ involvement in those with CR.

Response in blood will be performed with peripheral blood flow cytometry.

CR: B0 (absence of blood involvement).

PR: > 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B2).

SD: Fails to attain criteria for CR, PR, or PD.

PD: B0 to B2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL[36] or loss of response: in those with PR who were originally B2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL.

Relapse Increase of neoplastic blood lymphocytes to ≥ B1 in those with CR.

* SPD: sum of the maximum linear dimension major axis x longest perpendicular dimension minor axis.

*B1: Low tumor burden (> 5%, B1a=clone negative, B1b= clone positive).

B2: High tumor burden ≥ 1000/μL Sezary cells with positive clone.

IR (INDETERMINATE RESPONSE)*

A patient will be considered to have Indeterminate Response (IR) in one or more of the 3 following circumstances

1) Increase in overall tumor burden (as assessed by SPD) of ≥ 50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration (IR(1))
2) Appearance of new lesions; or growth of one or more existing lesion(s) of ≥ 50% at any time point during treatment occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment (IR(2))
3) Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number (IR(3))

It is possible that, at a single time point a subject could fulfill criteria for both IR(1 or 2) AND IR(3): for example, there could be a new FDG-avid lesion in the absence of overall progression (IR(2)), and, at the same time, increase in FDG uptake of a separate lesion (IR(3)). In such cases, the designation of IR(1 or 2) should take priority (eg, IR(2)

Follow-up of IR

1) In patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated and the patient should be considered to have true PD if the SPD of target lesion has increased further, with the considerations below:
2) In the case of IR(1), the comparison should be between the first IR(1) and the current SPD, with an increase of >10% constituting PD. In addition there should be an increase of > 5 mm (in either dimension) of at least one lesion for lesions < 2 cm, and 10 mm for lesions > 2 cm, to be consistent with the Lugano classification (3)(Table 2). The 10% threshold is empiric but designed to account for variability in measurement (37), especially when taken along with the minimum increase. If the target SPD increase is < 10%, the response would still be categorized as IR(1), and the patient could continue treatment until a subsequent scan shows either true PD (> 10% increase from first IR(1) time point and an increase of > 5mm in either dimension of at least one lesion) or response (>50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4-8 weeks of the original IR(1) timepoint to ensure absence of significant further increase.
3) In the case of IR(2), the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increased > 50% from the nadir value which may precede the IR time point. The patients is considered to have PD.
4) In the case of IR(3), since inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted above
5) Importantly, if a patient is assessed as having IR and then “true” PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should

subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR

*Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) (Appendix 2) will be applied as clinically applicable

APPENDIX 5 ACUTE GVHD GRADING AND STAGING

Table 9: 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 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 10: 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%

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.

APPENDIX 6 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.

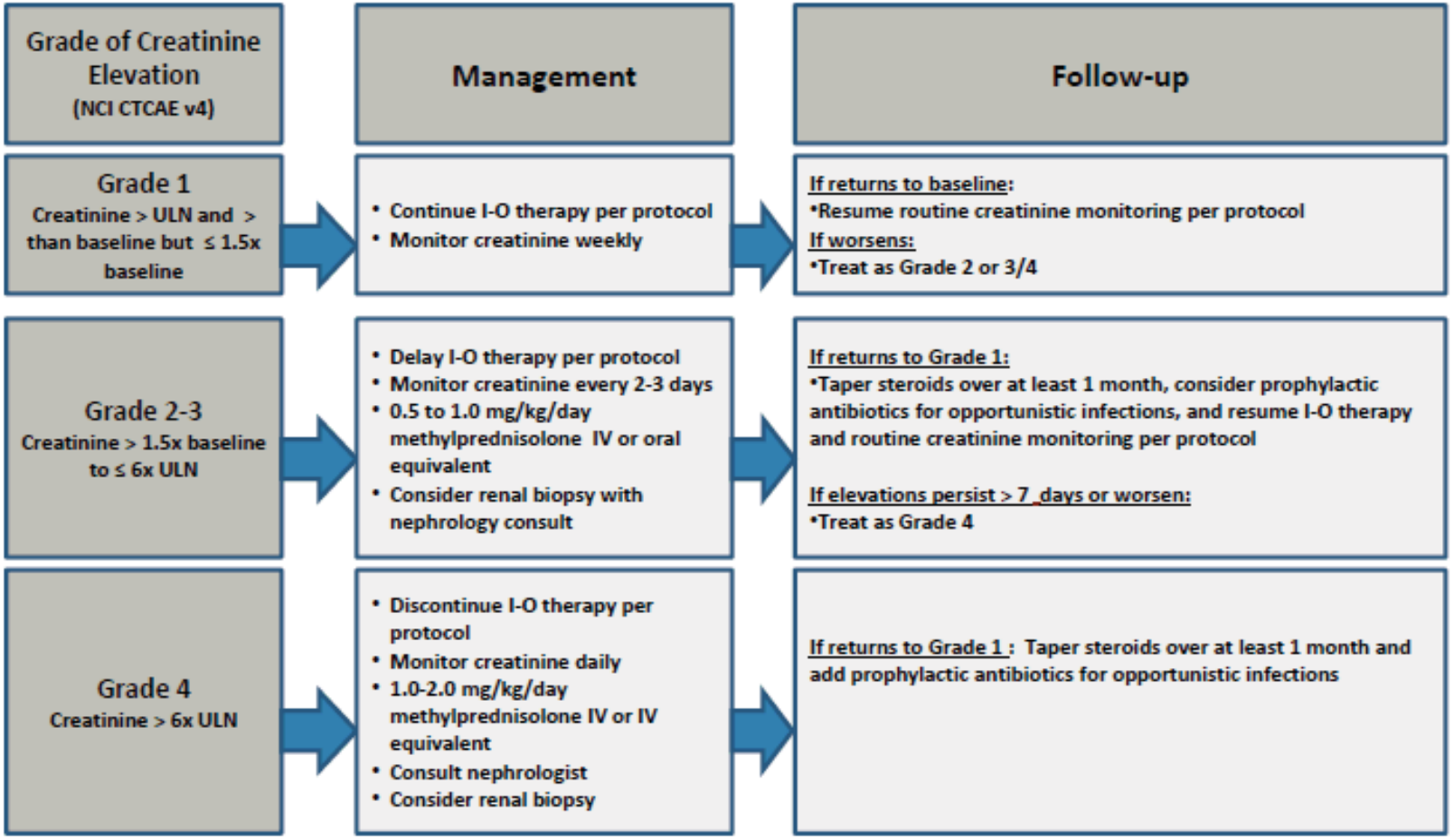
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat 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.

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

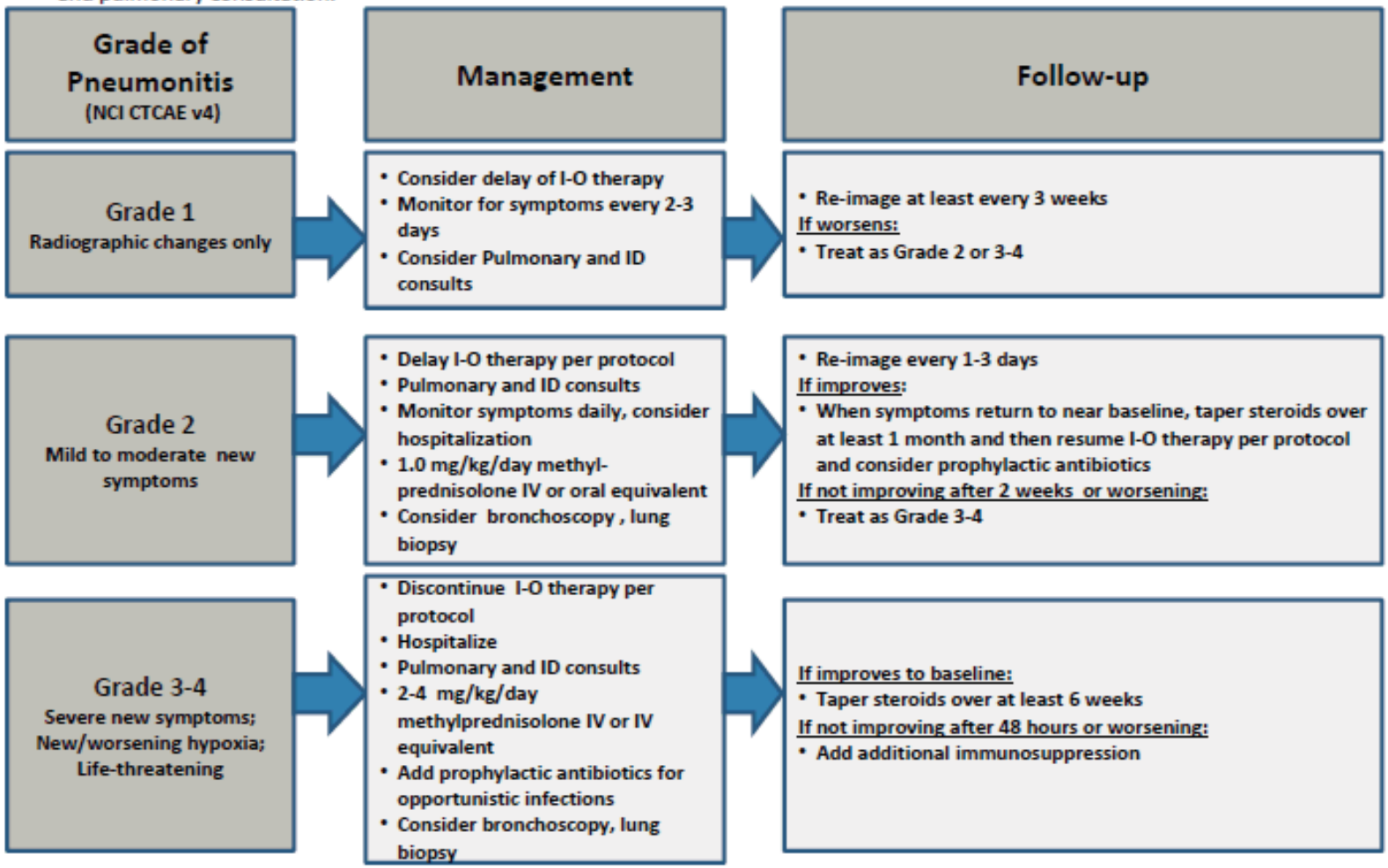


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

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.

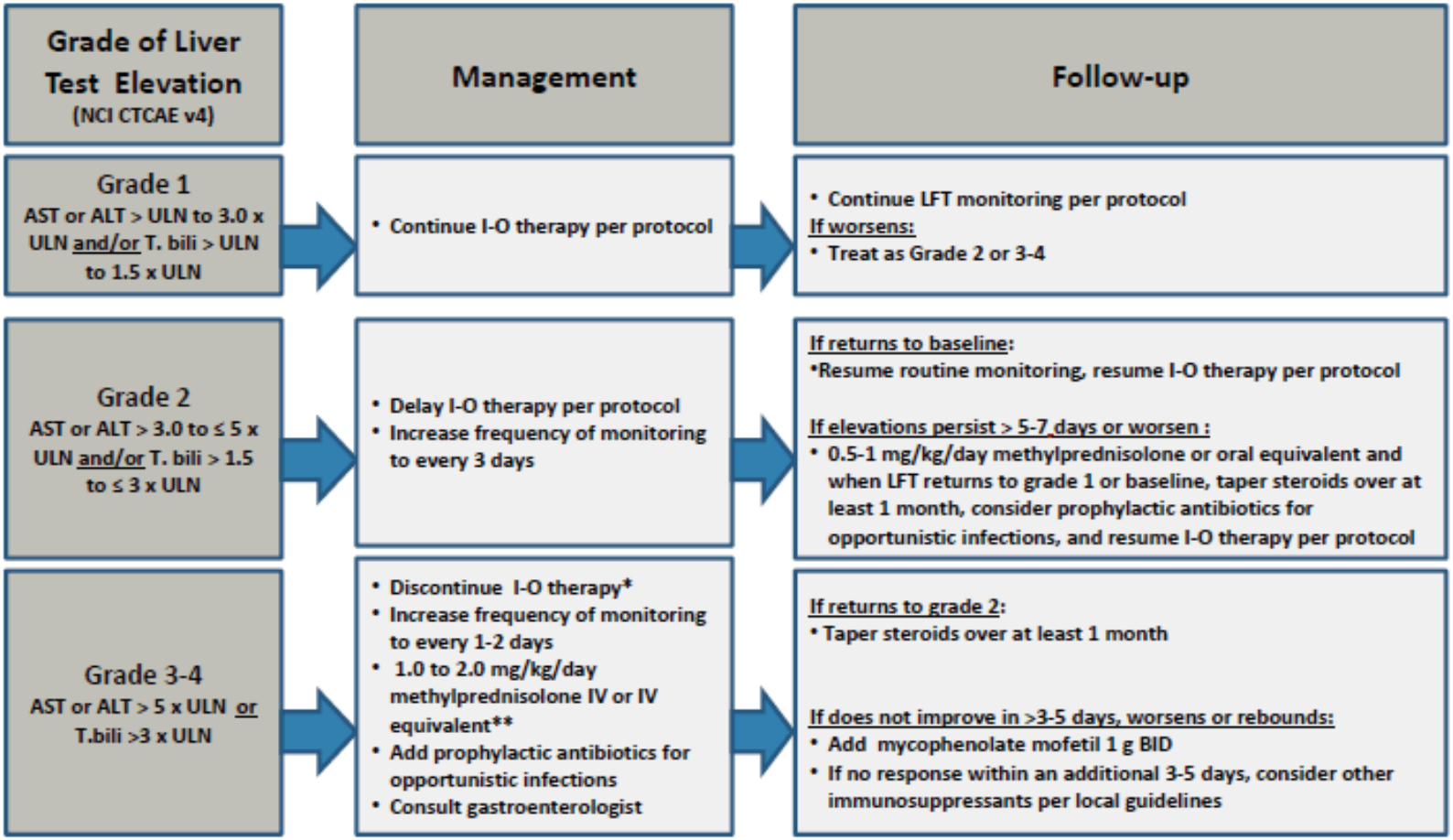


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

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.

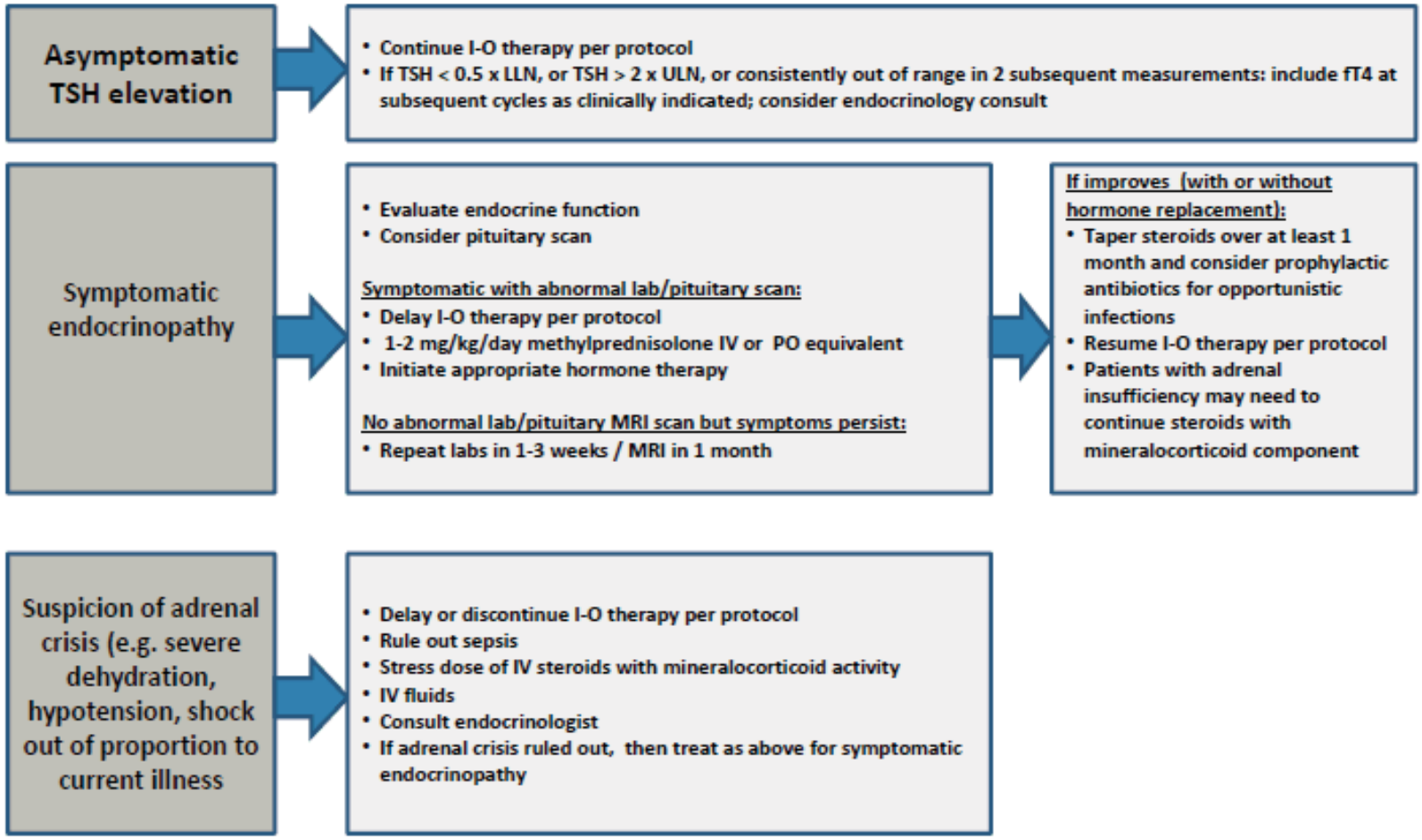
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Endocrinopathy 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.

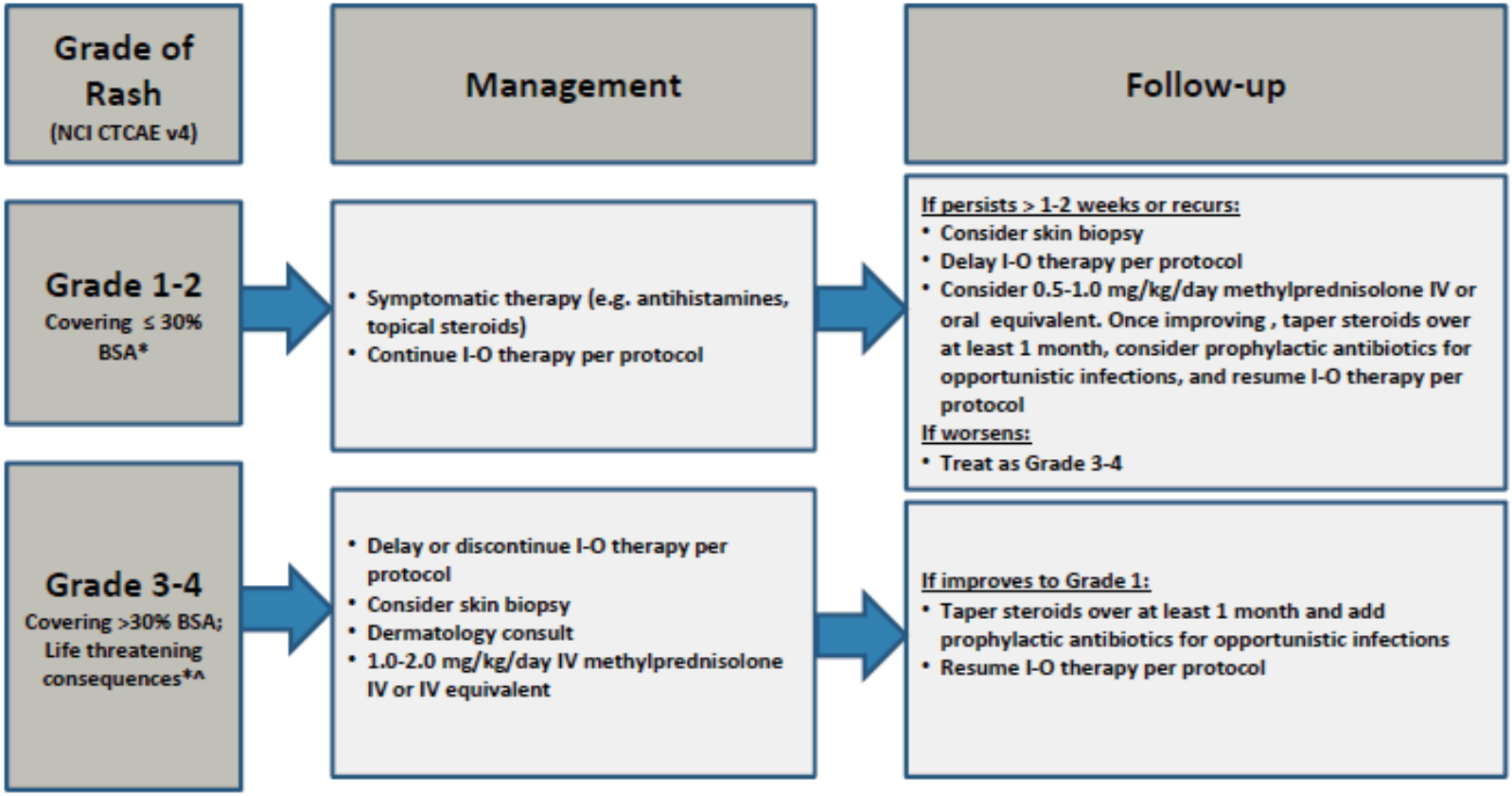


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

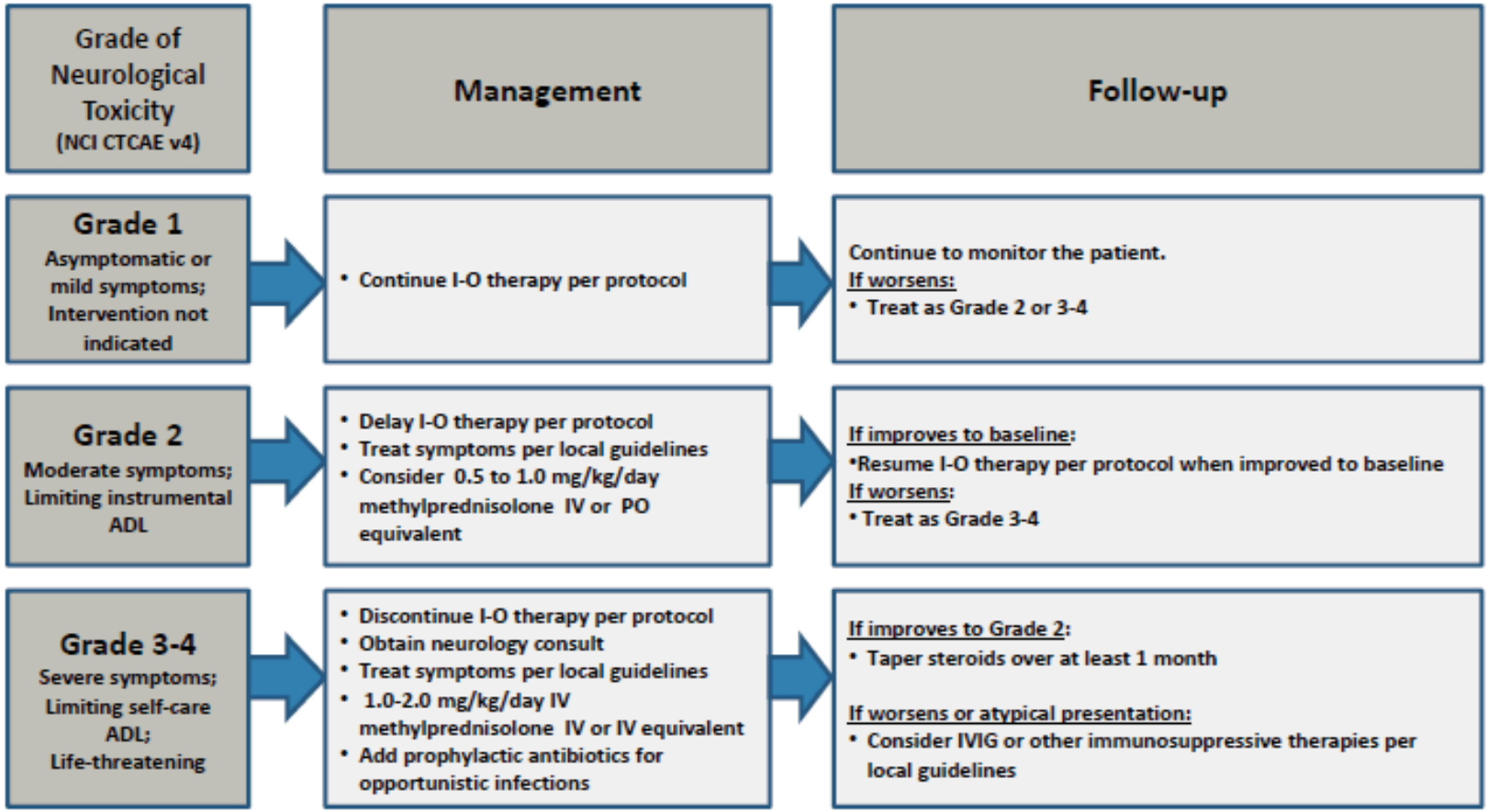


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of 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.

Updated 05-Jul-2016

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.

Updated 05-Jul-2016