Statistical Analysis Plan 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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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

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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2 STUDY DESCRIPTION

2.1 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 NHL subtype of DLBCL, PTCL (excluding ALCL), PMBL, MGZL and CTCL(MF/SS).

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 1.8mg/kg intravenously in combination with nivolumab 240mg flat dose intravenously in a q 3 week cycle.

In cycle 1, brentuximab vedotin 1.8mg/kg will be administered on day 1 where as nivolumab 240mg 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 1.8mg/kg in combination with nivolumab 240mg flat dose intravenously every 3 weeks or at a reduced dose of brentuximab vedotin at 1.2mg/kg will be based on the safety data reviewed throughout the DLT evaluation period. 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 recommendations.

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 in MGZL (cohort B5) will be enrolled to complete this evaluation.

All subjects in Cohort A and Cohort B will be allowed to be treated until disease progression or unacceptable toxicity as described in Protocol Section 4.5.3 and Section 4.5.5. If during therapy it

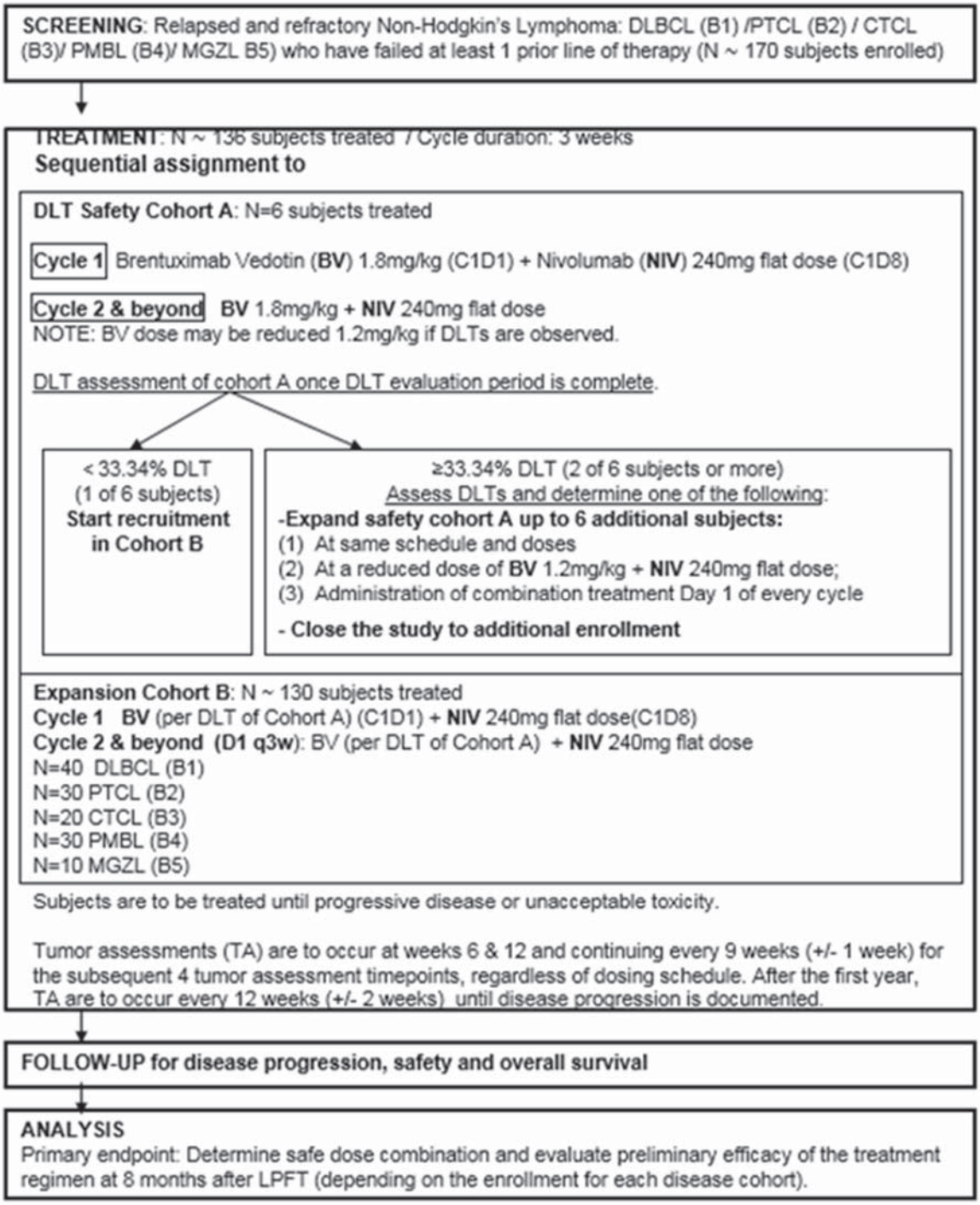
appears that a subject is benefiting from the combination but experiencing toxicities related to one agent that would require permanent treatment discontinuation, then they have the option to continue therapy with the single agent not attributing to toxicities.

Subjects that present progressive disease during treatment may be allowed to be treated beyond progression until further progression is observed.

Once subjects discontinue from study treatment for any reason, subjects will enter the follow-up phase of the study.

The study design schematic is presented in Figure 2.1-1

Figure 2.1-1: Study Design Schematic



2.2 Treatment Assignment

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an 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.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

Amendments 01, 02 and 03 are site specific.

This SAP is based on the Revised Protocol 01 dated 14-Sep-2016. It incorporates Amendment 04. This amendment allowed additional cohorts of subjects with relapsed PMBL & MGZL to participate in the expansion cohort. Additionally, the amendment also defined Indeterminate response (IR) criteria and described 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 have also been made.

The SAP will be updated in the future if any amendment to the protocol is made that has impact on the analyses.

2.5 Data Monitoring Committee

Not applicable.

3 OBJECTIVES

3.1 Primary

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) and 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.

3.2 Secondary

- 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 PFS based on investigator assessment and OS of the brentuximab vedotin and nivolumab combination regimen.

4 ENDPOINTS

4.1 Primary Endpoints

The primary safety endpoints include DLT, 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 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 PMBL, relapsed refractory MGZL and relapsed refractory PTCL the response (CR, PR, SD and progression) will be assessed according to Lugano Classification 2014. A CR must have been confirmed by scans, including a negative Positron Emission Tomography (PET) to be considered for CR in subjects with PTCL, PMBL, MGZL and DLBCL. 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.

4.2 Secondary Endpoints

The secondary endpoints are DOR, CR rate, duration of CR, PFS and OS. All these endpoints are based on Lugano classification 2014 and Global Response score for the CTCL subjects.

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 due to any cause, whichever occurs 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, duration of response will be censored on the last tumor assessment date prior to or on 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 relapse 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 due to any cause, whichever comes first. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date of first treatment. For subjects who received subsequent therapy prior to documented progression, it will be censored on the last tumor assessment date prior to or on subsequent therapy.

Table 4.2-1: Censoring Scheme for PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	First dose date	Censored
No on study tumor assessments and no death	First dose date	Censored
New anticancer treatment started without a prior reported progression or death	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Progression documented at scheduled or unscheduled visit and no new anticancer treatment started before	Date of the first documented tumor progression	Progressed
Subject progression free and no new anticancer treatment started	Date of last tumor assessment	Censored
Death without prior progression and no new anticancer treatment started	Date of death	Progressed

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.

[redacted]

5 SAMPLE SIZE AND POWER

5.1 Sample Size Determination

- 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 one or less (<=1) 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 3 or less (≤ 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) and 20 subjects in B3 (CTCL), 30 subjects in cohort B4 (PMBL) and 10 subjects in cohort B5 (MGZL).
  - Given 40 subjects in DLBCL, the 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 CI excludes 40%, which is the null hypothesis ORR rate for PTCL.
  - Given 30 subjects in PTCL, the 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 CI excludes 40%, which is the null hypothesis ORR rate for PTCL.
  - Given 20 subjects in CTCL, the 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 CI excludes 60%, which is the null hypothesis ORR rate for CTCL.
  - Given 30 subjects in PMBL, the 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 CI excludes 30%, which is the null hypothesis ORR rate for PMBL.
  - Given 10 subjects in MGZL, the two-sided 80% confidence interval for the ORR is 11.6% - 55.2% if we assume an observed ORR rate of 30%. The lower bound of the CI excludes 10%, which is the null hypothesis ORR rate for MGZL.

Table 5.1-1 summarizes the 80% exact CI for different targeted ORRs and sample sizes.

Table 5.1-1:	Two-sided 80% Exact CI for different number of subjects in each cohort
	If the observed ORR rate is 60% in Cohort B1 and B2
N=30	[46.7% - 72.3%]
N=40	[48.6% - 70.6%]
	If the observed ORR rate is 80% in Cohort B3
N=20	[63.9% - 91.0%]
	If the observed ORR rate is 50% in Cohort B4
N=30	[37.0% - 63.0%]
	If the observed ORR rate is 30% in Cohort B5
N=10	[11.6% - 55.2%]

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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

See Core Safety SAP.

6.2 Treatment Regimens

Subjects will receive brentuximab vedotin (BV) 1.8mg/kg and nivolumab 240mg flat dose or BV 1.2mg/kg and nivolumab 240mg flat dose.

6.3 Populations for Analyses

- **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.
- **Response Evaluable Subjects**: Treated subjects whose tumor measurements (PET CT or CT/MRI) were made at baseline and at least one on-study tumor assessment.

[redacted]

7 STATISTICAL ANALYSES

7.1 General Methods

All analyses will be performed on the all treated subjects and will be conducted separately for the NHL subtype groups (DLBCL, CTCL, PTCL, PMBL, MGZL).

As there was only one dose explored in the dose evaluation cohort A (brentuximab vedotin 1.8mg/kg and nivolumab 240mg) subjects from cohort A (dose evaluation) and cohort B (dose expansion) will be combined for all analyses, unless otherwise noted. A couple of safety analysis will be conducted on the cohort A subjects only to support the dose evaluation process (see Section 7.6.1).

The bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, grouped by cohort. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by cohort using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution (i.e. progression free survival, overall survival and duration of response) will be estimated using Kaplan Meier techniques.

Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function S(t)[4,5]. Rates at fixed timepoints will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[6] for variance derivation and on log-log transformation applied on the survivor function S(t)[7].

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site and per month for all enrolled subjects. First dosing date, country, investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

The relevant Protocol Deviations will be summarized for all treated subjects. A subject listing will also be produced. Relevant deviation implies a potential major impact on the interpretability of the main results of the study. Criteria for relevant deviations are listed below:

At entrance:

- Wrong diagnosis based on Exclusion/inclusion
- Do not have Measurable disease at baseline (not appliacable to CTCL)
- [redacted]

On-study:

Use of the following prohibited medications during the study (unless utilized to treat a drug related adverse event):

- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents)

7.3 Study Population

7.3.1 Subject Disposition

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

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated.

A subject listing for all treated subjects will be provided showing the subject's first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not treated will also be provided, showing the subject's race, gender, age, consent date and reason for not being treated.

7.3.2 Demographics and Other Baseline Characteristics

The following demographic and baseline characteristics of patient will be summarized. Listings will also be provided.

Baseline demographics:

- Age (descriptive statistics)
- Age category (< 65, ≥ 65 to <75, ≥ 75 to <85, ≥85)
- Gender, race, ethnicity

Baseline physical measurements

- ECOG, height, and weight

Other baseline characteristics:

- smoking status
- region (US/Canada, Europa and rest of the world)
- initial disease diagnosis
  - DLCL: DLCL or transformed lyphoma,
  - CTCL: Mycosis Fungoides (MF), Sezary Syndrome (SS)
  - PTCL: Angioimmunoblastic T Cell Lymphoma, Peripheral T Cell Lymphoma-NOS, Peripheral T Cell Lymphoma-Other
- stage of disease at initial diagnosis
- Disease status at study entry(relapsed, refractory or relapsed and refractory).
- Some disease characteristics will be reported depending on the NHL subtype:

DLBCL:

- international prognostic index (IPI) score at diagnosis,
- cell type involved at diagnosis and study entry.

CTCL:

- disease diagnosis at study entry: Mycosis Fungoides (MF), Sezary Syndrome (SS), other.

PTCL: no specific characteristics

PMBL: no specific characteristics

MGZL: no specific characteristics

- Time from Initial Disease Diagnosis to (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year)
- Lymphoma PET scan (yes/no), Lugano classification 5 point scale Lesion sites, Max SUV

- All lesions (Investigator Tumor Assessments at Baseline): sites of diseases, number of disease sites per subject
- Target Lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of product diameters of target lesions.
- Lymphoma involvement in bone marrow at baseline (Yes/No/Not Available)
- baseline efficacy assessement for CTCL: % BSA involvement, blood involved by peripheral blood cytometry, lymph node involved and tumor involved

7.3.3 Medical History

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

7.3.4 Prior Therapy

The following will be summarized:

- Number of subjects by type of prior therapy received (excluding preparative regimen for ASCT):
  - Immunotherapy by Monoclonal Antibodies
  - Steroid
  - Chemotherapy – Anthracyclines
  - Chemotherapy – Other than Anthracyclines
  - Kinase Inhibitors
  - Immunomodulary Derivatives
  - Radioimmunotherapy
  - Other
- Number of prior systemic regimen received (0, 1, 2, 3, ≥ 4), excluding preparative regimen for ASCT subjects
- Number of subjects per type of regimen for first and second lines of therapy (e.g. R-CHOP, ICE).For CTCL number of subjects per type of regimen by line of therapy where the combination of drugs within a regimen will be the concatenation of drugs by alphabetical order (e.g. gemcitabine)
- Number of subjects with prior ASCT and type of regimen received for preparation to ASCT (e.g. Carmustine / Cytarabine / Etoposide / Mephalan) and number of subjects ASCT ineligible.
- Best response to most recent prior regimen (CR vs. PR vs. SD vs. Relapse/PD vs. Unable to Determine vs. Not reported)
- Prior radiotherapy (yes or no)
- Prior surgery (yes or no)

By subjects will also list the systemic therapy, details about ASCT and details about surgery and radiotherapy.

7.3.5 Baseline Examinations

Percentage of subjects with abnormal baseline physical examination will be tabulated by examination criteria. A by-subject listing will also be provided.

7.4 Extent of Exposure

Analyses in this section will be performed on all treated subjects.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) for each drug separately:

- Number of doses received
- Cumulative dose
- relative dose intensity
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who discontinued study therapy. Subjects who are still on study therapy will be censored on their last dose date. Median duration of treatment and associated 95% CI will be provided.

A by-subject listing of dosing of study medication (record of study medication, infusion details, dose change) and a listing of batch number will be also provided.

Below table summarizes the key parameters used to calculate dosing data.

Table 7.4.1 -1: Administration of Study Therapy: Definition of Parameters

	Nivolumab	**Brentuximub Vedotin**
Dosing schedule per protocol	Day 1, 240mg every 3 weeks (except cycle 1 C1D8)	1.8mg/kg (or 1.2mg/kg) every 3 weeks
Dose	Dose is defined as total dose administered. Dose administered in mg at each dosing date are collected on the CRF.	Dose (mg/kg) is defined as total dose administered (mg)/most recent weight. Dose administered in mg at each dosing date and most recent weight are collected on the CRF.
Cumulative Dose	Cum dose (mg) is sum of the doses (mg) administered to a subject during the treatment period.	Cum dose (mg/kg) is sum of the doses (mg/kg) administered to a subject during the treatment period.
Duration of treatment	Last dose date - Start dose date + 1	Last dose date - Start dose date + 1
Relative Dose intensity	If only one dose of nivolumab Cum dose (mg)/[(Last dose date of nivolumab - Start dose date of nivolumab + 14) x 240 /14] x 100	Cum dose (mg/kg)/[(Last dose date of BV - Start dose date of BV + 21) x 1.8 /21] x 100 or

Table 7.4.1 -1: Administration of Study Therapy: Definition of Parameters

	Nivolumab	Brentuximub Vedotin
	If more than 1 dose of nivolumab [Cum dose (mg) / (Last dose date of nivolumab - Start dose date of nivolumab + 21)] x [(14+(number of nivolumab doses-1) * 21 / 240 * number of nivolumab doses] x 100	

7.4.2 Modifications of Study Therapy

There will be no dose escalations or reductions of nivolumab allowed. Brentuximab Vedotin may reduce dose to 1.2mg/kg. Brentuximab. Dose reduction as reported by the investigator will be summarized along with reason for reduction.

7.4.2.1 Dose Delays

Treatment may be delayed for up to a maximum of 6 weeks from the last dose. If one of the study drug is delayed for any reason the other drug must also be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days as of cycle 2 onwards (i.e., greater than or equal to 4 days from scheduled dosing date). Length of delay is defined as (duration of previous cycle in days - 21). Dose delays will be divided into following categories: 4 - < 8 days, 8 - < 15 days, 15 - < 42, ≥ 42 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by drug:

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

7.4.2.2 Infusion Interruptions and Rate Changes:

Each nivolumab or brentuximab vedotin infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF. The following parameters will be summarized for each drug:

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

7.4.2.3 Discontinuation of Study Therapy

The number and percentage of subjects who have discontinued all study drugs and reason for discontinuation will be summarized by treatment group and overall using the subject status eCRF page from end of treatment.

In addition, subjects who discontinued one drug, while continuing treatment with the other study drug, will be summarized based on the dose modification CRF. The reason for discontinuing a specific drug from the combination will also be summarized.

[redacted]

7.5 Efficacy Analyses

7.5.1 Primary Efficacy Endpoint

The primary endpoint ORR will be summarized for all treated subjects by binomial response rate and its corresponding two-sided 80% exact CIs using the Clopper-Pearson method.

BOR categories will be tabulated.

7.5.2 Secondary Efficacy Endpoints

The CR will be analyzed using the same statistical method as ORR.

The DOR will be summarized for subjects who achieve 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. Range of DOR will also be calculated. The same analysis will be performed for duration of CR.

The time to response (TTR), time from the first dose to the first response date will also be summarized. Note that TTR was not listed as a secondary endpoint in the protocol.

PFS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. KM curve of PFS will be generated. Median values of PFS, along with two-sided 95% CIs (based on the log-log transformation), will be calculated. PFS rates at 6 and 12 months (and two-sided 95% CIs) may be reported in function of the the minimum follow-up at time of analyses. Subject listings of PFS will be produced.

The source of progression (death vs. progression) will be summarized. The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated using following categories:

- Received subsequent anti-cancer therapy
- Still on-treatment

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

OS will be analyzed using the same statistical method as PFS. Median values of OS, survival rates at 6 and 12 months along with two-sided 95% CIs may be reported in function of the minimum follow-up at time of analyses.

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

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

Subject Follow-up

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

Follow-Up Therapy

The following information pertaining to subsequent therapies will be summarized:

- Systemic therapy by drug name
- Hematopoietic stem cell transplantation (Allogeneic, Autologous)
- Surgery
- Radiotherapy

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

[redacted]

[redacted]

7.6 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. Details are in the Core Safety SAP v3.0.

7.6.1 Dose Limiting Toxicities

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.

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.

Cohort A subjects who have a related AE that require either discontinuation, dose reduction or delay of more than 7 days of either study drug in Cycle 2 or delays the Cycle 3 Day 1 will be categorized as experiencing DLT.

- Number of subjects with dose limiting toxicities will be tabulated (cohort A, all treated subjects)
- A listing will be provided of those subjects containing their reasons for drug discontinuations, delay or reduction and total number of courses received (Cohort A, All treated subjects)

7.6.2 Deaths

See Core Safety SAP

7.6.3 Serious Adverse Events

See Core Safety SAP

7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP

7.6.5 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP

7.6.6 Adverse Events

See Core Safety SAP

7.6.7 Adverse Events by Subgroups

See Core Safety SAP

7.6.8 Multiple Events

See Core Safety SAP

7.6.9 Adverse Events of Special Interest

See Core Safety SAP

7.6.9.1 Transplant

Number and percentage of subjects by response category (CR, non-CR, unable to determine) will be provided at the time of transplant and at the 100 days, 6 months and 1 year timepoints after transplant for subjects undergoing subsequent allogeneic SCT and autologous SCT separately. Denominators will be based on subjects with assessment available by timepoint.

For subjects undergoing allogeneic SCT, number and percentage of subjects with GVHD will be provided at the 100 days, 6 months and 1 year timepoints: chronic limited, chronic extensive, acute (grade I, II, III, IV, unknown). Denominators will be based on subjects undergoing allogeneic SCT with assessment available by timepoint.

7.6.10 Clinical Laboratory Evaluations

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test.

7.6.10.1 Hematology

See Core Safety SAP

7.6.10.2 Serum Chemistry

See Core Safety SAP

7.6.11 Vital Signs and Pulse Oximetry

See Core Safety SAP

[redacted]

7.6.13 Pregnancy

By-subject listing of pregnancy tests results will be provided

7.6.14 Clinical Safety Program (CSP)

See Core Safety SAP

[redacted]

[redacted]

[redacted]

[redacted]

7.8.2.2 Evaluation of associations between CD30 at baseline and efficacy measures

Analyses for ORR (BOR):

- Box plots of CD30 expression versus BOR will be generated for all CD30 evaluable subjects
- A logistic regression model of ORR (responder, non-responder) will be produced with baseline CD30 expression as continuous covariate.

Analyses of PFS and OS:

- A Cox proportional hazards model of OS will be produced with Baseline CD30 expression as continuous variable.
- A Cox proportional hazards model of PFS will be produced with Baseline CD30 expression as continuous variable.

[redacted]

7.10 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.

8 CONVENTIONS

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

- For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[9].
- Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[10].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive. If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.
- In case of the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
- For other partial/missing dates, the following conventions may be used:
- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, “July 1” will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years:

1 month = 30.4375 days and 1 year = 365.25 days.

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

Duration = (Last date - first date + 1)

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

9 CONTENT OF REPORTS

All analyses describe in this SAP will be included in the final Clinical Study Report. Refer to the Data Presentation Plan for mock-ups of all tables and listings. Analyses of the different NHL subtype may not be conducted all at the same time depending on accrual in the different group.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Initial version: January 31, 2017

[redacted]