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Revised Date 08-Jan-2020

Clinical Protocol CA209812

Randomized, Open-label, Phase 3 Trial of Nivolumab plus Brentuximab vedotin versus Brentuximab vedotin alone in Participants with Relapsed Refractory or Ineligible for Autologous Stem Cell Transplant (ASCT) Advanced Stage Classical Hodgkin Lymphoma (CheckMate 812: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 812)

Revised Protocol Number: 01
Incorporates Administrative Letters 01, 02, and 03.

[redacted]

24-hr Emergency Telephone Number

[redacted]

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Approved v4.0 [redacted]

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	08-Jan-2020	As of 17-Oct-2019, the Sponsor informed all study sites that enrollment into the study was permanently discontinued. • Efficacy assessments are now based on investigator assessments. [redacted] • Survival follow-up will stop at the last safety follow-up visit. Changes per Administrative Letters 01, 02 and 03, as applicable, are now incorporated into the protocol. Appendix 5, Management Algorithms For Immuno-Oncology Agents, has been updated.
Administrative Letter 03	07-Jan-2020	[redacted]
Administrative Letter 02	21-Aug-2017	[redacted] correction of inconsistencies between synopsis and protocol language; addition of SAE assessments during screening; clarification of version 4.03 is used for CTCAE; removal of inconsistent reference to the Bv Investigator Brochure.
Administrative Letter 01	13-Apr-2017	Updated the schedule of activities table by adding an omitted measurement of cardiac ejection fraction at screening. Minor clarification to the ejection fraction inclusion criteria language was nade.
Original Protocol	22-Feb-2017	Not Applicable

Approved v4.0 [redacted]

OVERALL RATIONALE FOR REVISED PROTOCOL 01:

On 17-Oct- 2019, the Sponsor, BMS, notified all study sites that enrollment into CheckMate 812 was permanently discontinued. The Sponsor's decision was based on discussions [redacted] regarding the feasibility of completing enrollment into CheckMate 812 in the rapidly evolving treatment landscape for Classical Hodgkin Lymphoma (cHL). The decision to discontinue enrollment is not related to any efficacy or safety concerns in CheckMate 812.

For currently enrolled participants, at the investigator's discretion, the same study treatment can be continued if the participant is considered to have clinical benefit. Assessments of efficacy and safety will continue at the time points defined in the protocol; however, efficacy assessments are now based on investigator assessments. [redacted] For participants who continue study treatment, BMS will continue to provide study drugs, per country requirements, until the participant meets the protocol discontinuation criteria. Participants who discontinue all study drugs will continue safety follow-up per protocol requirements. Survival follow-up stops at the last safety Follow-up Visit 2 as presented in the Schedule of Activities.

Additional changes include the incorporation of changes per Administrative Letters 01, 02, and 03 that remain applicable and the update of Appendix 5: Management Algorithms For Immuno-Oncology Agents.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
• Synopsis • Section 2 Schedules of Activities: Tables 2-1, 2-2, 2-3. [redacted] • Section 3.3 Benefit/Risk Assessment • Section 5.1 Overall Design, Figure 5.1-1 • Section 5.2 Number of Participants. • Section 6 Study Population • Section 6.4.1 Retesting During Screening or Lead-in [redacted]	On 17-Oct- 2019 all study sites were notified that enrollment into CheckMate 812 was permanently discontinued. [redacted] Survival follow-up will stop at the last safety Follow-up Visit 2. All efficacy assessment will be based on investigator assessment.	The Sponsor's decision was based on discussions [redacted] regarding the feasibility of completing enrollment into CheckMate 812 in the rapidly evolving treatment landscape for Classical Hodgkin Lymphoma (cHL). The decision to discontinue enrollment is not related to any efficacy or safety concerns in CheckMate 812. Modification of study assessments, based on the close in enrollment for this study.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 2 Schedule of Activities Table 2-1, Screening Procedural Outline (BMS-936558)	Per Administrative Letter 02 (21-Aug-2017), cardiac ejection fraction and monitor for serious adverse events were added to the screening assessments.	These assessments have been incorporated into the protocol text per BMS standard practice for incorporating changes of administrative letters into the subsequent revised protocol.
• Section 4 Objectives and Endpoints, Table 4-1 Objectives and Endpoints • Section 5.1 Overall Design, Figure 5.1-1 • Section 5.1.1 Data Monitoring Committee [redacted] • Section 9.1 Imaging Assessment for the Study	Per Revised Protocol 01, efficacy assessment will be based on investigator assessment.	As enrollment was discontinued, the Sponsor decided to discontinue efficacy assessments by BICR.
Section 6.1 Inclusion Criteria 4) Physical and Laboratory Test Finding b)	Per Administrative Letter 02 (21-Aug-2017), echocardiography was no longer required for evaluation of left ventricular ejection fraction over 50% at rest.	This change has been incorporated into the protocol text per BMS standard practice for incorporating changes of administrative letters into the subsequent revised protocol.
Section 7.1.4, Management Algorithms for Immuno-Oncology Agents	Addition of myocarditis to the list of management algorithms for immuno-oncology agents	Alignment with updates in Appendix 5: Management Algorithms for Immuno-oncology Agents
Section 7.1.6, Dose Discontinuation Criteria (Nivolumab)	Neurologic toxicity and myocarditis added to the list of Grade 3 study treatment-related adverse events of any duration that require discontinuation	Alignment with current standard for nivolumab.
Section 9. Study Asssesements and Procedures	Documentation of GvHD for participants who discontinue study therapy by proceeding to allogeneic SCT will stop at Follow-up Visit 2.	Modification of study assessments, based on the close in enrollment for this study

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.5 Pregnancy	The length of time for reporting of pregnancy by the investigator as detailed in this section of the protocol has been changed from 5 half-lives after product administration, to 5 half-lives plus 30 days after product administration.	Alignment with contraceptive requirements that are presented in inclusion criteria.
Section 10 Statistical Considerations	Added paragraph to address close of enrollment, total number of participants randomized and changes to the statistical section. Minor revisions to align with the Sponsor's decision to stop enrollment in the sudy and the change from BICR to investigator assessments for efficacy.	Alignment of statistical section to protocol changes previously described.
[redacted]		
Section 11: References.	Reference 27 from original protocol deleted and all subsequent references renumbered	Corrections for references for product information for brentuximab vedotin.
Appendix 5: Management Algorithms For Immuno-Oncology Agents	Management algorithm for hepatic adverse events - deletion of footnote: I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN. Addition of Myocarditis Adverse Event Management Algorithm.	Updated per nivolumab program standard.

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1 SYNOPSIS

Protocol Title: Randomized, Open-label, Phase 3 Trial of Nivolumab plus Brentuximab vedotin versus Brentuximab vedotin alone in Participants with Relapsed Refractory or Ineligible for Autologous Stem Cell Transplant (ASCT) Advanced Stage Classical Hodgkin Lymphoma

(CheckMate 812: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 812)

Study Phase: 3

Rationale:

The programmed death-1 (PD-1) cell surface membrane receptor is a member of the CD28 family of T-cell co-stimulatory receptors.[1] PD1 expression is a marker of T cell exhaustion and is associated with immune evasion in tumors. Hodgkin Lymphoma (HL) is characterized by genetic predisposition for over expression of programmed death (PD)-1 ligands. There are multiple mechanisms identified for upregulation of PD-L1 & PD-L2 in HL. Additionally CD30 is a cell membrane protein of the tumor necrosis factor family. CD30 is highly expressed in HL on the Reed Sternberg cells. Given the abundant expression of PD-1 ligands and CD30 in HL, the two proteins provide opportunity to target specific molecules associated with tumor growth and progression. Ongoing trials with the combination of brentuximab vedotin (BV) and nivolumab appear promising. Nivolumab and BV have demonstrated encouraging single agent activity in the treatment of relapsed HL. Since both drugs are effective as single agents, it is likely that the combination may have better efficacy as compared to either agent alone. A Phase 1/2 trial of the BV and nivolumab combination is ongoing in adults with Relapsed/Refractory Hodgkin Lymphoma after failure of first-line therapy. This study is actively enrolling (ClinicalTrials.gov identifier: NCT02572167). In this study, patients have been treated for a total of 4 cycles with combination regimen. Overall, the combination has been well tolerated with none of the participants requiring dose discontinuation due to toxicities. All patients were able to tolerate 4 cycles of combination regimen. The majority of adverse events including immune-related adverse events were low grades (1 and 2). Preliminary results are indicative of a highly efficacious regimen in a sample size n= 20, with an Objective Overall Response Rate of 90% and Complete Metabolic Response of 62%. Similar findings have been observed in another ongoing trial, the ECOG ACRIN trial E4412 (ClinicalTrials.gov identifier: NCT01896999). The preliminary data from the E4412 trial with a sample size (N=10) for relapsed/refractory patients has demonstrated an ORR of 100% and CR of 63%. Although the studies are ongoing and numbers are small, preliminary findings are suggestive of an effective and tolerable regimen in a refractory patient population with high unmet need.

On 17-Oct- 2019, all study sites were notified that the Sponsor, Bristol-Myers Squibb, had decided to permanently discontinue enrollment in CheckMate 812. The Sponsor's decision was based on discussions [redacted] regarding the feasibility of completing enrollment into CheckMate 812 as designed. Difficulty in enrollment of this study is linked to the rapid evolution in the US cHL treatment landscape and particularly with respect to the use of BV in earlier lines of treatment. This evolution has led to a decrease in the pool of patients potentially eligible for CheckMate 812.

The decision to discontinue enrollment is not related to any efficacy or safety concerns in CheckMate 812. For currently enrolled participants, at the investigator's discretion, the same study treatment can be continued if the participant is considered to have clinical benefit. Assessments of efficacy and safety will continue per protocol; however, efficacy assessments will be done by investigator. [redacted] For participants who continue study treatment, BMS will continue to provide study drugs, per country requirements, until the participant meets the protocol discontinuation criteria. Participants who discontinue all study drugs will continue safety follow-up per protocol requirements. Survival follow-up will stop at safety follow-up Visit 2, as presented in the Schedule of Activities.

Study Population:

As of 17-Oct-2019 enrollment in this study was stopped at the decision of the Sponsor. A total of 23 participants have been randomized.

Males and females, ages 18 and above, with relapsed/refractory cHL, with one of the following:

a) Autologous Stem Cell Transplant (ASCT) ineligible patients

Chemo-resistant disease (unable to achieve CR or PR to salvage chemotherapy) or any significant coexisting medical condition (cardiac, renal, pulmonary, or hepatic dysfunction) are likely to have a negative impact on tolerability of ASCT. Note: Sponsor review and approval of participants < 65 years of age who are not ASCT candidates is required before randomization. Participants must have received at least 2 prior chemotherapy regimens (BV can be included as one regimen)

b) Patients after failure of ASCT:

- Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT
- Documented relapsed disease (after CR) or disease progression (after PR or SD)

Both for a) and b), participants who are naïve to BV or who were sensitive to the most recent BV treatment are eligible. Participants must demonstrate BV sensitivity as defined by documented PR or CR from the most recent BV treatment, and by no disease progression during the most recent BV treatment or no early relapse within 3 months after last dose of the most recent BV based on medical record. For b), prior treatment with BV may have been as a single agent or in combination with chemotherapy and may have occurred during any line of therapy (eg, induction, salvage, or consolidation post-ASCT). Of note, documentation of response following consolidation therapy with BV is not required, as it is assumed that the patients are in remission at the time of consolidation.

Other key inclusion criteria include ECOG PS 0-1 and biopsy confirmation of cHL prior to initiation of study drug. Key exclusion criteria include known CNS lymphoma, nodular lymphocyte-predominant HL, and active interstitial pneumonitis or CT evidence of Grade 1 pneumonitis. See Section 6 of the protocol for full list of criteria.

Objectives and Endpoints:

Objectives	Endpoints
Primary • To compare progression free survival of nivolumab+BV vs. BV based on investigator assessments	• Progression Free Survival (PFS): defined as time from date of randomization to death, or disease progression.
Secondary • To compare the complete response rate of nivolumab+BV vs. BV based on investigator assessments • To assess objective response rate and duration of response based on investigator assessments. • To assess duration of complete response based on investigator assessments. • To assess overall survival of participants treated with nivolumab + BV vs BV.	• Complete Response Rate (CRR): defined as proportion of participants who have achieved complete response (Lugano 2014 conference) • Objective Response Rate (ORR): defined as the proportion of participants who have achieved complete response or partial response (Lugano 2014 classification) • Duration of response or duration of complete response (DOR or DOCR): defined as the time from first response or complete response to the date of initial objectively documented progression as determined using the 2014 Lugano classification or death due to any cause • Overall Survival (OS): defined as the time between the date of randomization and the date of death..

Overall Design:

This is a 1:1 randomized, open-label phase 3 study in advanced cHL participants ≥ 18 years old who are relapsed refractory or ineligible for autologous stem cell transplant (ASCT). Patients will be balanced in the 2 groups in regards to prior therapies. Approximately 340 participants will be treated in one of two arms: 1) nivolumab 360 mg IV every 3 weeks until progression or unacceptable toxicity (except for patients in CR who can discontinue at 2 years) plus BV 1.8 mg/kg IV every 3 weeks for 16 cycles, or until progression or unacceptable toxicity, whichever occurs first or 2) BV alone 1.8 mg/kg every 3 weeks for 16 cycles, or until progression or unacceptable toxicity, whichever occurs first. Treatment may also be discontinued if the participant meets other criteria for discontinuation of study drug outlined in Section 8.1 of the protocol. Participants receiving nivolumab who achieve CR may discontinue treatment after a maximum of 2 years of therapy, provided that there is no prohibitive toxicity. Participants can be BV- naïve, or can have prior BV treatment as a single agent or in combination in any line of therapy. Randomization stratification will be performed on the following two factors: 1) Prior ASCT status (YES/NO). 2) Prior BV use (YES/NO). Participants will be balanced based on the stratification factors per arm.

Participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 21-day dosing period will constitute a cycle.

Study visits and endpoint measurements will occur as indicated in Table 2-1 though Table 2-3 in the protocol.

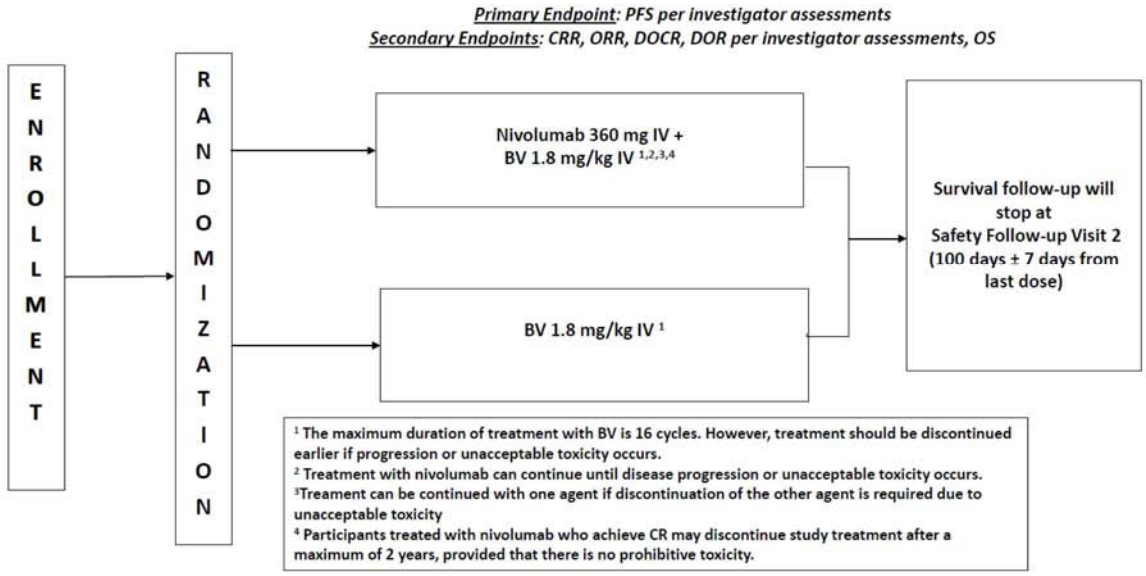
Any participant who discontinues the study treatment prior to progression will be followed for progression, then survival, in the follow up phase of the study.

As of 17-Oct-2019, enrollment in this study was stopped at the decision of the Sponsor. For currently enrolled participants, at the investigator's discretion, the same study treatment can be continued if the participant is considered to have clinical benefit. Assessments of efficacy and safety will continue per protocol; however, efficacy assessments will be done by investigator. [redacted] For participants who continue the study treatment, BMS will continue to provide study drugs, per country requirements, until the participant meets the protocol discontinuation criteria. Participants who discontinue all study drugs will continue safety follow-up per protocol requirements. Survival follow-up will stop at safety follow-up visit 2 as presented in the Schedule of Activities.

Number of Participants:

- **# Screened:** Approximately 400 were planned to be screened.
- **# Randomized:** Approximately 340 with 170 participants in the nivolumab + BV arm, 170 in the BV arm were antipated. A total of 23 participants were randomized before enrollment was stopped (17-Oct-2019) per the decision of the Sponsor..
- **Screen Failure Rate:** 15%

Treatment Arms and Duration:



Approved v1.0 [redacted]

Abbreviations: BV = brentuximab vedotin; PFS = progression-free survival; CRR = complete response rate; OS overall survival; ORR = objective response rate; DOCR = duration of complete response; DOR = duration of response

Study treatment:

- Randomized Investigational Arm: Nivolumab (360 mg flat dose) every 3 weeks until progression or unacceptable toxicity+ BV (1.8 mg/kg) every 3 weeks for 16 cycles, progression, or unacceptable toxicity, whichever occurs first
- Randomized Control Arm: BV (1.8 mg/kg) every 3 weeks for 16 cycles, progression, or unacceptable toxicity, whichever occurs first

Study Drug for CA209812		
Medication	**Potency**	**IP/Non-IP**
Nivolumab (BMS-936558) Solution for Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IP
Brentuximab Vedotin Powder for Solution for Injection	50 mg	IP

Other medications used as support 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.

Study drug preparation and administration instructions will be provided in a separate manual.

Statistical Considerations

As of 17-Oct-2019, enrollment in this study was stopped at the decision of the Sponsor. At the time enrollment was stopped, 23 participants had been randomized. No formal statistical testing or inferential analyses will be performed. The statistical analyses as previously planned will only be conducted if appropriate in the final analysis. Further details are presented in the SAP.

Sample Size:

The planned sample size for this study was to be approximately 340 randomized participants. The sample size of the study accounts for the primary efficacy endpoint, PFS. PFS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided) with 90% power.

[redacted]

Approved v4.0 [redacted]

[redacted]

EAST version 6.3 was used for sample size/power computations.

As of 17-Oct-2019 enrollment in this study was stopped at the decision of the Sponsor. At the time enrollment was stopped, 23 participants had been randomized.

Endpoints:

Primary Endpoints:

The primary objectives in the study will be measured by the primary endpoint of PFS by investigator assessments.

Secondary Endpoints:

The secondary objectives in the study will be measured by:

- CRR, ORR, DOR, and DOCR assessed by investigator.
- OS

Analyses:

PFS Analysis

The primary endpoint PFS based on investigator assessment will be compared in two randomized arms via a two-sided, log-rank test stratified by the same factors used in randomization. Participants who die without a reported progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last tumor assessment. Participants who did not have any on study assessments and did not die will be censored on the randomization date. A participant who initiates a subsequent anti-cancer therapy will be censored on the date of last tumor assessment prior or on the start date of their subsequent anti-cancer therapy. Sensitivity analyses will be performed using different PFS definitions to assess the robustness of the primary analysis. The PFS curve, median and PFS rate at 6, 12, 18, and 24 months for each randomized arm will be estimated using the Kaplan-Meier product-limit method. Two sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method. A two-sided, 95% confidence interval for the PFS rates will be computed by Greenwood method. The HR and corresponding two-sided 100 * (1-α)% (α adjusted

for the interim analysis) confidence interval will be estimated in a Cox proportional hazards model using randomized arm as a single covariate, stratified by the same factors used in randomization

CRR/CMR Analysis

CRR/Complete Metabolic Response (CMR) based on investigator assessment will be compared in two randomized arms via a two-sided, Cochran-Mantel-Haenszel (CMH) test stratified by the same factors used in randomization. An estimate of the treatment odds ratio between the nivolumab + BV and BV arm along with corresponding two-sided 95% CIs and p-value will be presented. The estimate of the CRR/CMR and associated exact two-sided 95% CIs (by Clopper and Pearson method) will be presented for both arms.

When the primary endpoint, PFS, is statistically significant, the secondary endpoint CRR/CMR will be tested. The hierarchical testing procedure that ensures the study-wise type I error is controlled at 5% levels will be described in the SAP.

ORR, DOR, DOCR and OS Analysis

ORR will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method.

Duration of response (or complete response) in each treatment group will be estimated using KM product-limit method for participants who achieve PR or CR (or CR only). Median values along with two-sided 95% CI will be calculated.

The OS curves for each treatment group will be estimated using the Kaplan-Meier product-limit method. Two-sided, 95% confidence intervals for median OS will be provided. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive.

Safety Analysis

Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE version 4.03. All on-study AEs, treatment-related, AEs, SAEs and treatment-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 1grade per NCI CTCAE v4.03 criteria.

[1] Pardoll D: Does the immune system see tumors as foreign or self? Ann Rev Immunol. 2003; 21:807-39.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (BMS-936558)

Procedure	Screening Visit[a]	Notes Enrollment was stopped as of 17-Oct-2019.
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Include Height, Weight, and ECOG performance Status (Appendix 7)
Hasenclever-Index for Hodgkin's Disease also known as IPS at Initial Diagnosis	X	Composite score, see Appendix 8.
Vital Signs	X	Includes body temperature, seated blood pressure (BP) and heart rate. Should be performed 14 days prior to first dose
Cardiac Ejection Fraction	X	Assessment of cardiac ejection fraction within 28 days prior to first dose (Added as part of Administrative Letter 02 [21-Aug-2017])
Monitor for Serious Adverse Events	X	(Added as part of Administrative Letter 02 [21-Aug-2017])
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose

Approved v4.0 [redacted]

Table 2-1: Screening Procedural Outline (BMS-936558)

Procedure	Screening Visit[a]	Notes Enrollment was stopped as of 17-Oct-2019.
Laboratory Tests	X	Complete blood count (CBC) with differential, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, P, glucose, albumin, amylase, lipase, thyroid stimulating hormone (TSH) (reflex to free T3, free T4 for abnormal TSH result), c-reactive protein ,hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA) within 14 days prior to first dose.
Urinalysis	X	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH, within 14 days prior to first dose.
Pregnancy Test	X	For WOCBP only (serum or urine - local/site)
ECG	X	Within 28 days prior to first dose
Pulmonary Function Test (PFT)	X	Must include testing for diffusing capacity of the lung for carbon monoxide (DLCO). Within 28 days prior to first dose
Efficacy [redacted] Assessments		
Radiographic Tumor Assessment FDG PET-CT or PET-MRI scan from vertex to toes	X	Must be performed within 28 days prior to first dose. FDG-PET scan from vertex to toes is required at screening. CT portion of PET-CT must be of diagnostic quality. If low dose CT used, then a separated dedicated CT or MRI of the chest, abdomen and pelvis and other known sites of disease must be acquired.
[redacted]		
Collection of tumor tissue	X	Submission of tumor tissue (FFPE tumor tissue block or 25 unstained slides) from a biopsy performed during screening is mandatory. If this is not possible, the following exceptions are allowed:

Approved v4.0 [redacted]

Table 2-1: Screening Procedural Outline (BMS-936558)

Procedure	Screening Visit[a]	Notes **Enrollment was stopped as of 17-Oct-2019.**
		1) Participants who do not have any accessible lesions, or 2) Participants who have archival tissue from a previous tumor biopsy [redacted]. These participants must submit archival tissue from the most recent tumor biopsy if archival tissues are available from tumor biopsies at multiple timepoints. While submission of archival tissue from the most recent tumor biopsy is mandatory, archival tissue from other tumor biopsy is strongly encouraged. For example, participants who mandatorily submit archival tissue from a tumor biopsy at relapse may optionally submit archival tissue for tumor biopsy at initial diagnosis. [redacted] Biopsy samples should be excisional, incisional, or core needle. Tumor biopsies (FFPE) for IHC of tumor and TIL and RNALater for gene expression.
IVRS/Clinical Drug Supplies		
Phone calls to IVRS/Randomize	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.

[a] Within 28 days prior to first dose

Approved v4.0 [redacted]

Table 2-2: Procedural Outline During the Treatment Period (CA209812)

Procedure	Cycle 1 Day 1 - Disease Progression or Unacceptable Toxicity	Notes All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified. Dosing is to be performed every 3 weeks
Safety Assessments		
Targeted Physical Examination	X	Lymph node areas (for example, but not limited to, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver)
Vital Signs	X	Includes body temperature, respiratory rate (RR), and seated blood pressure (BP) and heart rate.
Physical Measurements	X	Within 72 hours prior to dosing. Includes Weight and ECOG performance status (Appendix 7)
Adverse Events Assessment	Continuously	See Appendix 2/Section 9.2. Assessed using NCI CTCAE v. 4.03.
Serious Adverse Events Assessment	Continuously	See Appendix 2/Section 9.2. Assessed using NCI CTCAE v. 4.03
Review of Concomitant Medications	X	See section 7.7
Laboratory Tests	X	Within 72 hours prior to dosing to include CBC w/differential, AST, ALT, ALP, TBili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, lipase, c-reactive protein, albumin
Thyroid Function Testing	See note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 9 weeks (± 7 days) from first dose regardless of dosing schedule.
Pregnancy Test for WOCBP	X See note	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (± 7 days) regardless of dosing schedule.
Efficacy Assessments		
Radiographic Tumor Assessment FDG-PET-CT or PET-MRI scans from vertex to toes	See note	FDG PET-CT or PET-MRI will be performed at the end of cycle 5, 10, 15, and every 5 cycles until disease progression. FDG PET-CT or PET-MRI can be performed as clinically warranted for suspicion of recurrence during the non-protocol specified time points
B symptoms	See note	Collected Day 1 (prior to dosing) of every other cycle (cycle 1, 3, etc)

Approved v4.0 [redacted]

Table 2-2: Procedural Outline During the Treatment Period (CA209812)

Procedure	Cycle 1 Day 1 - Disease Progression or Unacceptable Toxicity	Notes All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified. Dosing is to be performed every 3 weeks
[redacted]		
Clinical Drug Supplies		
Administer Study Drug	X	IVRS should be called within 3 days prior to study treatment administration to receive vial assignment.

Approved v4.0 [redacted]

Table 2-3: Procedural Outline after the Treatment Period (CA209812) - Follow Up

Procedure	X, Follow-Up, Visits 1 and 2[a]	Notes
Safety Assessments		
Targeted Physical Examination	X	Lymph node areas (for example, but not limited to, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver)
Serious Adverse Events Assessment	X	SAEs related to any later protocol-specified procedure must be collected
Adverse Events Assessment	X	Non-serious AEs and SAEs must be collected up to 100 days after study treatment discontinuation.
Peripheral Neuropathy	X	Any AEs of peripheral neuropathy must be followed until resolution or end of study, whichever occurs first.
Monitoring for (in)fertility	X	Completion of CRF through Safety Follow-up Visit 2.
Monitoring for cardiotoxicity and pulmonary toxicities	X	Completion of CRF through Safety Follow-up Visit 2 and work up as indicated (for clinical symptoms)
Monitoring for secondary neoplasms	X	Completion of CRF through Safety Follow-up Visit 2.
Laboratory Tests	X	During Follow-up visit 1 and Follow-up visit 2: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
Thyroid Function Testing	X	TSH (reflex to free T3 and free T4 if abnormal result) Every 9 weeks
Pregnancy Test (WOCBP only)	X	Serum or urine (WOCBP only)
[redacted]		

Approved v4.0 [redacted]

Table 2-3: Procedural Outline after the Treatment Period (CA209812) - Follow Up

Procedure	X, Follow-Up, Visits 1 and 2[a]	Notes
[redacted]		
Efficacy Assessments		
B Symptoms	X	To be collected only at Follow-up Visit 1
Radiographic Assessments		
FDG-PET CT or FDG MRI scan from vertex to toes [b]	See note	For participants who discontinue study treatment prior to disease progression, no further FDG-PET CT or PET MRI will be obtained.
[redacted]		
Participant Status		
Survival Status	X	Survival follow-up will stop after safety Follow-up Visit 2.

Approved v4.0 [redacted]

Table 2-3: Procedural Outline after the Treatment Period (CA209812) - Follow Up

Procedure	X, Follow-Up, Visits 1 and 2[a]	Notes
Subsequent anti-lymphoma therapies	X	It can be accomplished by visit or phone contact to assess subsequent anti-cancer therapy. Per Revised Protocol 01, stop after safety Follow-up Visit 2.
Post-nivolumab stem cell transplant follow-up (if applicable)	X	Completion of associated eCRF page. Per Revised Protocol 01, stop after safety Follow-up Visit 2.
GVHD Assessments	X	Only for participants who discontinued study therapy by proceeding to allogeneic SCT. See Section 9 and Appendix 9. Per Revised Protocol 01, stop after safety Follow-up Visit 2.

[a] X, Follow-up visit 01 occurs 35 days ± 7 days from last dose and Follow-up visit 02 occurs 100 days ± 7 days from the last dose.

[b] Should a participant 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. CTs and MRIs should be acquired with a slice thickness of 5 mm or less with no gap (contiguous).

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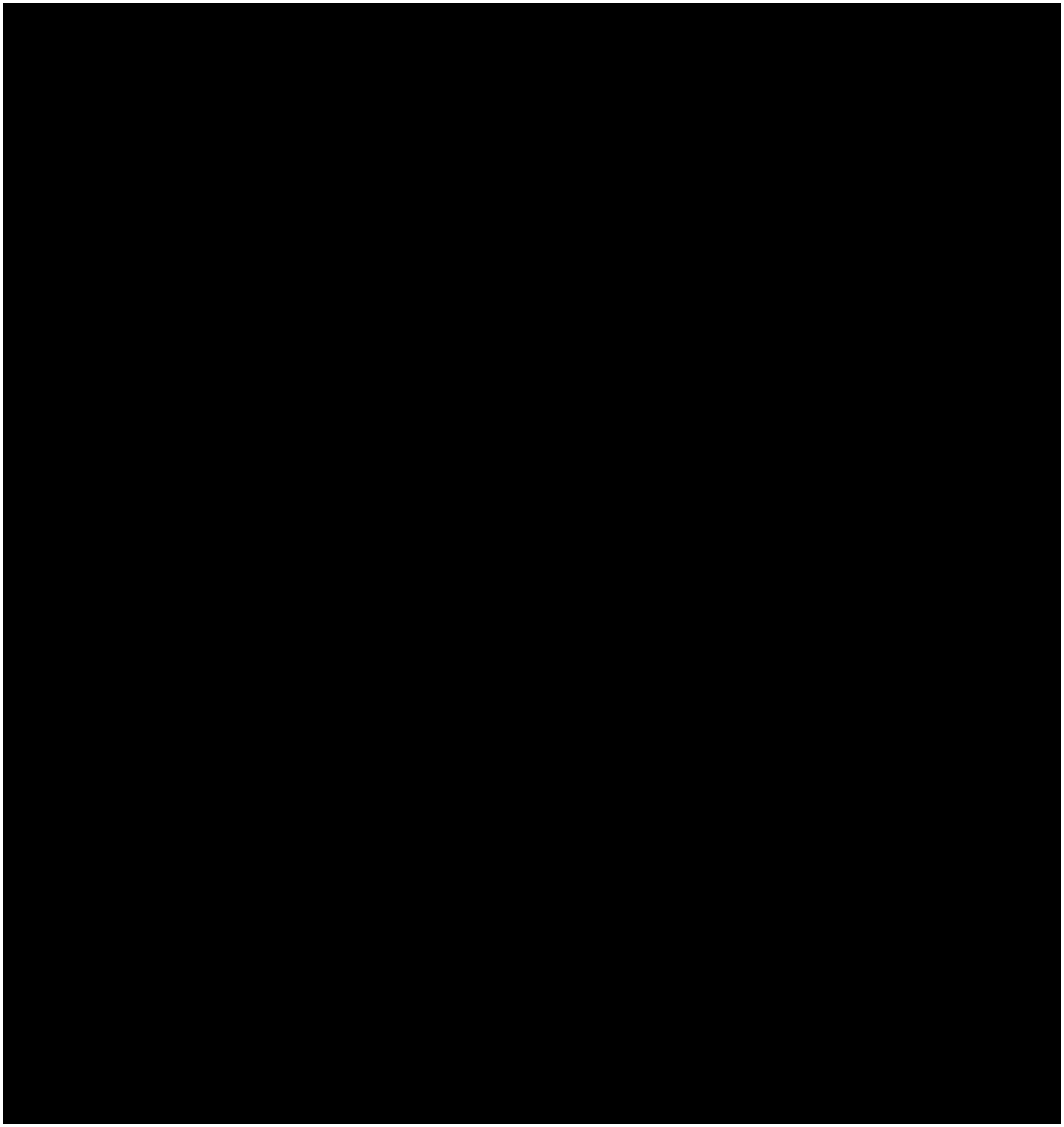
3 INTRODUCTION

This study strives to improve disease control while minimizing treatment burden by incorporating two novel agents, nivolumab and brentuximab vedotin (BV), as salvage therapy in patients with relapsed Hodgkin Lymphoma (HL).The study targets patients who have relapsed after autologous stem cell transplant (ASCT) or are ineligible for ASCT.

Hodgkin lymphoma is a lymphoid malignancy characterized by the presence of multinucleated Reed-Sternberg cells, which are generally accepted to be of B-cell origin and usually account for only 1% to 10% of the cells in the tumor tissue.[1] The majority of cells in HL tumor tissue are a mixed infiltrate of various lymphoid cells, including regulatory T-cells and macrophages.[1] The updated 2008 WHO classification recognizes two histologic groups: nodular lymphocyte predominant, which accounts for about 5% of all HL cases, and "classical" HL (cHL) which accounts for the remainder.[1]

In the totality of cancer epidemiology, HL represents a small percentage of all patients diagnosed with malignancy, yet it affects many considered as young adults. Approximately 8,500 new cases of HL are estimated to be diagnosed in the US in 2016 and more than 1,100 deaths from HL are expected.[2] The prevalence of HL in the US in 2013 was estimated to be 193,545. The median age of diagnosis of HL in the US is 38 years; there is a bimodal age-specific incidence pattern, in which the incidence is highest between 15 and 34 years, declines between ages 35 and 54, and increases again after 55 years.[3]

Improvements in the use of combined chemotherapy and radiotherapy in advanced stage newly diagnosed cHL have resulted in durable remission rates of approximately 60% to 80%.[2,4] However, the remaining approximately 30% of patients will either relapse or have primary refractory disease. Failure to achieve complete response (CR) at the end of first-line therapy is considered as treatment failure. Salvage multi-agent chemotherapy, followed by ASCT, can only provide long-term disease control in approximately half of the patients with relapsed or refractory disease but at the price of additional acute and long-term toxicity. Patients who relapse after ASCT have an extremely poor prognosis and constitute a group with high unmet medical need.



3.2 Background

High-dose chemotherapy with ASCT remains the optimal option to achieve a durable remission in patients with HL who have relapsed or are refractory to the standard frontline combination chemotherapy.[12] Furthermore with ASCT approximately 50% of the patients are cured.[4] Unfortunately, the remaining 50% of ASCT patients do not experience long-term disease control with median overall survival of approximately 27 months.[13] In particular, the prognosis remains exceedingly poor for patients who experience relapse or progressive HL within one year after ASCT where the median survival time is approximately 1.2 years.[14] Several small clinical studies

have examined various agents in the ASCT relapsed HL population with uniformly poor results. Therefore, the therapeutic options for these patients remain very limited. This underscores the need for more effective regimens for the treatment of relapsed, refractory HL.

Brentuximab vedotin is approved for patients who have progressed after ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. In a pivotal phase 2 study of 102 patients with relapsed or refractory HL following ASCT, treatment with BV 1.8 mg/kg every 3 weeks resulted in an objective response rate (ORR) of 75% (95% CI: 64.9, 82.6). [15] The CR rate was 34% (95% CI: 25.2, 44.4) and the median progression-free survival (PFS) for all patients on study was 5.6 months (95% CI: 5.0, 9.0). Longer follow up showed that the median overall survival (OS) and median PFS were 40.5 months (95% CI: 28.7, 61.9) and 9.3 months (95% CI: 7.1, 12.2), respectively. The estimated 5-year OS and PFS rates were 41% (95% CI: 31, 51) and 22% (95% CI: 13, 31), respectively. It should also be noted that BV is effective at the time of retreatment.[16] Brentuximab vedotin is currently being developed by Seattle Genetics for the treatment of hematological malignancies.

Nivolumab has demonstrated promising activity as single agent in relapsed HL. [redacted]

[redacted]

Brentuximab vedotin and nivolumab have demonstrated promising single-agent activity in HL. Additionally, both drugs work through distinct mechanisms of action. Given that both agents have demonstrated significant activity in HL, combination therapy could potentially be more effective in the salvage treatment setting than administration of either agent alone. Moreover, both agents are well tolerated, have few overlapping toxicities, and can be infused in the outpatient setting.

3.2.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses[7,18,19]. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[20] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA. [21] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes. [22]These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) 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. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented 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 result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[23]

3.2.2 Brentuximab Vedotin Mechanism of Action

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.[24]

Additionally brentuximab vedotin has shown to induce Immunogenic Cell Death (ICD). [25] 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. Possible immune modulatory properties of BV were demonstrated in a report analyzing its effects in CD30+ Hodgkin Lymphoma cell lines. Brentuximab vedotin was evaluated for its ability to induce endoplasmic reticulum stress. It was shown that BV up-regulated the apoptotic endoplasmic reticulum sensor, C/EBP homologous protein, in a dose-dependent manner, which resulted in cleavage and activation of ATF6, a transcription factor required for induction of ER stress. The net results were induction of endoplasmic reticulum stress and ICD markers. Induction of ICD was associated with activation of immune reaction. It was concluded that exposure of dendritic cells to BV-killed tumor cells evoked an inflammatory phenotype including an increase in co-stimulatory markers CD86 and MHC Class II antigens, and activation of nuclear factor k B (NFkB) an intermediate of the inflammatory signaling pathway. This suggests additional BV anti-tumor effects by activating the innate immune response, although this effect remains to be validated, as the observations are early and ex vivo.

3.3 Benefit/Risk Assessment

Approximately 70% of patients with cHL are cured with conventional chemotherapy, and 30% of patients will either relapse or have primary refractory disease. Salvage multi-agent chemotherapy, followed by ASCT, can only provide long-term disease control in approximately half of the patients with relapsed or refractory disease. Patients with HL who failed ASCT represent an area of substantial unmet medical need. [redacted] However, nivolumab and BV have the potential for clinically relevant adverse events including pulmonary toxicity, hepatotoxicity, diarrhea/colitis, endocrinopathies, nephrotoxicity, peripheral neuropathy and cytopenias. Nevertheless, ongoing trials with the combination have demonstrated that the combination is tolerable. To date, serious AEs with both agents have been manageable with prompt diagnosis and initiation of corticosteroids, dose interruption, and adequate supportive care. [redacted]

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure, and will not be repeated here. Overall, the safety profile of nivolumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few high-grade (Grades 3 to 4) AEs related to study drug. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 5. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

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, toxic epidermal necrolysis, tumor lysis syndrome, 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.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.[26] Similar information on the safety profile of BV is provided in the package insert, summary of product characteristics (SmPC), or equivalent document for brentuximab vedotin

Please see Section 3.1 for an explanation of changes made to the study protocol per Revised Protocol 01 due to Sponsor's decision, communicated to all study sites on 17-Oct-2019 to permanently discontinue enrollment in CheckMate 812.

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4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • To compare progression free survival of nivolumab + BV vs BV per investigator assessment.	• Progression Free Survival (PFS): defined as time from date of randomization to death, or disease progression.
Secondary • To compare the complete response rate of nivolumab + BV vs BV per investigator assessment. • To assess objective response rate and duration of response per investigator assessment. • To assess duration of complete response per investigator assessment. • To assess overall survival of participants treated with nivolumab + BV vs BV.	• Complete Response Rate (CRR): defined as proportion of participants who have achieved complete response (Lugano 2014 classification) • Objective Response Rate (ORR): defined as the proportion of participants who have achieved complete response or partial response (Lugano 2014 classification) • Duration of response or duration of complete response (DOR or DOCR): defined as the time from first response or complete response to the date of initial objectively documented progression as determined using the 2014 Lugano classification or death due to any cause • Overall Survival (OS): defined as the time between the date of randomization and the date of death.
[redacted]	

Table 4-1: Objectives and Endpoints

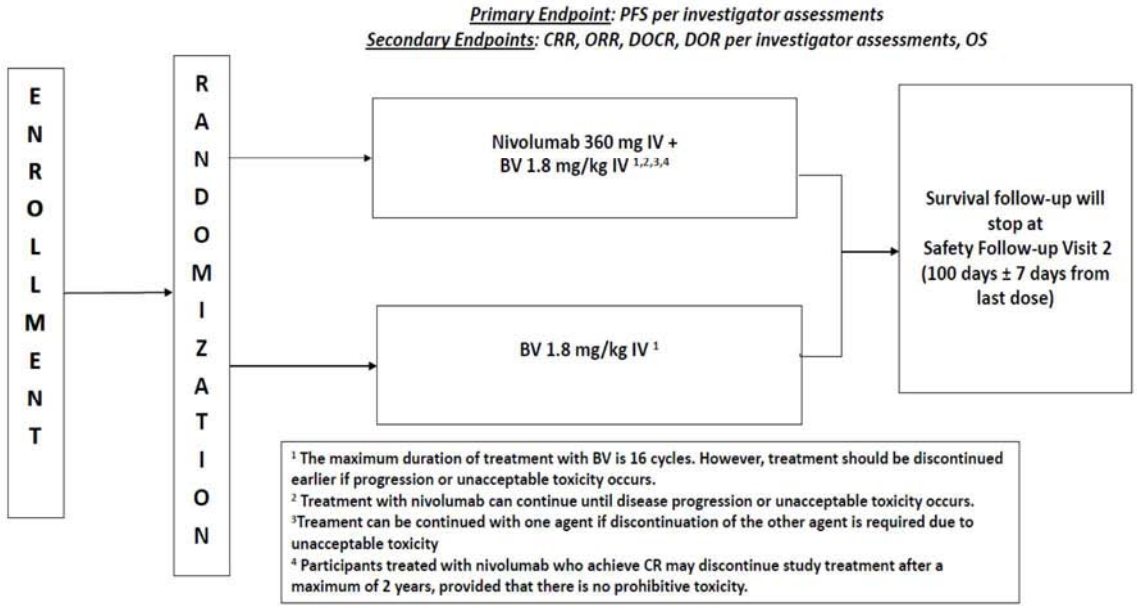
Objectives	Endpoints
[redacted]	

5 STUDY DESIGN

5.1 Overall Design

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Abbreviations: BV = brentuximab vedotin; PFS = progression-free survival; CRR = complete response rate; OS overall survival; ORR = objective response rate; DOCR = duration of complete response; DOR = duration of response.

This is a 1:1 randomized, open-label Phase 3 study in advanced cHL participants ≥ 18 years old who are relapsed refractory or ineligible for ASCT. Patients will be balanced in the 2 groups in regards to prior therapies. Approximately 340 participants will be treated in one of 2 arms. In one arm, participants will receive nivolumab 360 mg IV every 3 weeks until progression or unacceptable toxicity (except for patients in CR who can discontinue at 2 years) plus BV 1.8 mg/kg IV every 3 weeks for up to 16 cycles, or until disease progression or unacceptable toxicity,

whichever occurs first. In the other arm, participants will receive BV alone 1.8 mg/kg every 3 weeks for up to 16 cycles, disease progression, or unacceptable toxicity, whichever occurrs first. Discontinuation of study therapy can also occur if the participant meets other criteria outlined in Section 8.1. Participants receiving nivolumab who achieve CR may discontinue treatment after a maximum of 2 years of therapy, provided that there is no prohibitive toxicity. Participants can be brentuximab vedotin-naïve, or can have prior BV treatment as a single agent or in combination in any line of therapy. Randomization stratification will be performed on the following two factors: 1) Prior ASCT status (YES/NO). 2) Prior BV use (YES/NO). Participants will be balanced based on the stratification factors per arm. The two arms will be balanced in regards to these stratification factors.

Participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 21-day dosing period will constitute a cycle.

Study visits and endpoint measurements will occur as indicated in Table 2-1 though Table 2-3.

Any participant who discontinues the study treatment prior to progression will be followed for progression, then survival, in the follow up phase of the study.

- No dose reductions or escalations of nivolumab are permitted. Skipped doses will not be made up. For dose modifications or reductions of BV, see Section 7.4.2.
- Duration of study participation: Randomization is within 28 days of the screening. The recruitment period is approximately 34 months with a follow up of 4 years after the last patient first visit (LPFV). Participants will receive active treatment of nivolumab until progression or unacceptable toxicity plus BV for 16 cycles or until progression or unacceptable toxicity, whichever comes first, or BV alone up to 16 cycles, or until progression or unacceptable toxicity, whichever occurs first. The treatment period will be followed by a survival follow up period.

As of 17- Oct- 2019, enrollment in this study was stopped at the decision of the Sponsor. For currently enrolled participants, at the investigator's discretion, the same study treatment can be continued if the participant is considered to have clinical benefit. Assessments of efficacy and safety will continue per protocol; however, efficacy assessments will be done by investigator. [redacted] For participants who continue the study treatment, BMS will continue to provide study drugs, per country requirements, until the participant meets the protocol discontinuation criteria. Participants who discontinue all study drugs will continue safety follow-up per protocol requirements. Survival follow-up will stop at safety Follow-up Visit 2 as presented in Table 2-3.

5.1.1 Data Monitoring Committee and Other External Committees

The participants' safety will be monitored on an ongoing basis. The BMS medical monitor is a physician responsible for reviewing, on a systematic and continuous basis, the safety of participants on this study. This includes a review of serious and non-serious adverse events, including all hematological and non-hematological events. In addition, a BMS medical safety team

(MST) routinely reviews safety signals across the entire nivolumab program. The MST is independent from the BMS medical monitor. The MST has the primary responsibility within BMS for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk management plans. The MST is responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

Safety conference calls with investigators and representatives of the sponsor will be held regularly until all participants have entered the FU/observational phase or discontinued the study. BMS clinical and safety team will assess safety in conjunction with the investigators, and will make appropriate modifications of the regimen based on safety assessment, if necessary.

5.2 Number of Participants

Approximately 400 participants were planned to be screened, such that approximately 340 participants were to be randomized to receive either nivolumab + BV or BV in a 1:1 ratio. This targeted number of 400 enrolled participants considered that 15% will be screen failures.

See Section 6.4 for more information on the definition of screen failure and Section 10.1 for a description of the sample size calculation.

As of 17- Oct- 2019, enrollment in this study was stopped at the decision of the Sponsor. The decision to discontinue enrollment is not related to any efficacy or safety concerns in CheckMate 812. At the time enrollment was stopped, 23 participants had been randomized.

5.3 End of Study Definition

The start of the trial is defined as signature of the informed consent form by the first screened participant. End of trial is defined as when all participants have completed safety Follow-up Visit 2. Study completion is defined as the date of the last patient/last visit for safety Follow-up Visit 2.

5.4 Scientific Rationale for Study Design

Harnessing host immune response is an important antitumor strategy. In this context, reversing the effects of exhaustive T cells by checkpoint inhibitors is actively explored as an effective immune therapy in clinical trials. PD-1 inhibitors have demonstrated ability to abolish immunosuppression in the tumors by restoring T cell activation.[6,27,28] Agents with ability to enhance effector cells and up-regulate tumor antigens have the potential to enhance the efficacy of check- point inhibitors such as nivolumab. The MHC class II antigen processing pathway is altered in tumors, thereby precluding efficient presentation of T cell epitopes.[29] One strategy to increase the 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.

Brentuximab vedotin mediates its effects through induction of apoptosis. Furthermore, BV has also shown to induce immunogenic cell death (ICD). [25]

Nivolumab induces robust T-cell activation. This results in augmentation of host anti-tumor immune response.

Collectively, this combination has a high potential of becoming an effective novel therapy due to additive and synergistic effects.

5.5 Justification for Dose

5.5.1 Brentuximab Vedotin

The recommended dose for BV 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 who were treated with BV for a maximum of 16 cycles (approximately 1 year).

5.5.2 Nivolumab

Nivolumab will be administered as a flat dose of 360 mg once every 3 weeks (Q3W). The safety and efficacy of 360 mg Q3W flat dose of nivolumab is expected to be similar to the approved dose of 3 mg/kg Q2W.

The nivolumab dose of 360 mg Q3W 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.

Population PK analyses have shown that the exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks, and no clinically meaningful 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 proportionally with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. Using the PPK model, the overall distributions of nivolumab average steady-state exposures (Cavgss) are comparable after treatment with either nivolumab 3 mg/kg every 2 weeks (Q2W) or 360 mg Q3W. The flat dose regimen of 360 mg Q3W is predicted to result in approximately 23% higher maximum steady state concentrations (Cmaxss) and approximately 6% lower steady state trough concentrations (Cminss) compared to the reference regimen of 3 mg/kg Q2W. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 360 mg Q3W, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. The exposures predicted following administration of nivolumab 360 mg Q3W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 360 mg Q3W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.

5.5.3 Pharmacokinetics Supporting Dosing Rationale

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PPK) analysis using data from patients with various tumor types, including melanoma, NSCLC, and RCC and a time varying CL model, nivolumab clearance was shown to decrease over time, with a median maximal reduction from baseline values of approximately 25% resulting in a geometric mean steady state clearance (CLss) (% coefficient of variation [CV%]) of 8.2 mL/h [53.9%]. The decrease in CLss is not considered to be clinically relevant. The geometric mean [CV%] volume of distribution at steady state (Vss) is 6.8 L (27.3%), and elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-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 clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure (IB).[26]

5.5.4 Rationale for Nivolumab 30-minute Infusion

Long infusion times place a burden on participants and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30-minutes duration in participants 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 participants 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 360 mg doses of nivolumab is not expected to present safety concerns compared to the prior experience at 10-mg/kg nivolumab dose infused over a 60-minute duration.

Note that, in ongoing study CA209436, BV is administered in a 30-minute infusion, followed by a 30-minute pause, and a 30-minute infusion of nivolumab. See Section 7.1 for details concerning conditions of administration of this combination therapy in the present study.

6 STUDY POPULATION

As of 17-Oct-2019, enrollment in this study was stopped at the decision of the Sponsor.

6.1 Inclusion Criteria

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

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board/Independent Ethics Committee (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 participant care.

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

2) Type of Participant and Target Disease Characteristics

a) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1

b) Participants must have a pathologic diagnosis of cHL who are relapsed or refractory with one of the following:

i) ASCT ineligible patients

Chemo-resistant disease (unable to achieve CR or PR to salvage chemotherapy) or any significant coexisting medical condition (cardiac, renal, pulmonary, or hepatic dysfunction) are likely to have a negative impact on tolerability of ASCT. Note: Sponsor review and approval of participants <65 years of age who are not ASCT candidates is required before randomization. Participants must have received at least 2 prior chemotherapy regimens (BV can be included as one regimen).

ii) Patients after failure of ASCT

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

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

Both for i) and ii), participants who are naïve to BV or who were sensitive to the most recent BV treatment are eligible. Participants must demonstrate BV sensitivity as defined as best response of PR or CR per investigator assessment, and by no disease progression during the most recent BV treatment or no early relapse or progression within 3 months after last dose of the most recent BV based on medical record. For ii), prior treatment with BV may have been as a single agent or in combination with chemotherapy and may have occurred during any line of therapy (eg, induction, salvage, or consolidation post-ASCT). Of note, documentation of response following consolidation therapy with BV is not required, as it is assumed that the patients are in remission at the time of consolidation.

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

d) Biopsy confirmation of cHL prior to the initiation of study treatment. cHL should be pathologically confirmed by standard IHC or flow cytometric techniques. Archived tumor block or unstained slides from biopsy are acceptable. Histologically confirmed tissue will be required from the time of relapse or at the time of initial surgery

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

3) Age and Reproductive Status

a) Males and Females, ages ≥ 18 or age of majority

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 treatment.

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for 2 methods of contraception for the duration of treatment with study treatments nivolumab and BV plus 5 half-lives of study treatment plus 30 days (duration of ovulatory cycle) for a total of 6 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for 2 methods of contraception (listed in Appendix 4) for the duration of treatment with study treatment(s) nivolumab and BV, plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

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

Please refer to Appendix 4 for detailed WOCBP definition and contraception guidance.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly (Appendix 4).

4) Physical and Laboratory Test Findings

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

i) Absolute neutrophil count ≥ 1000/μL (no WBC growth factors for prior 14 days)

ii) Platelets ≥ 50 x10^6/mL (no platelet transfusions for prior 14 days)

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

iv) Creatinine clearance (CrCL) ≥ 30 mL/min (measured using the Cockcroft-Gault formula below):

$$\text{Female CrCL} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.8}{72 \times \text{serum creatinine in mg/dL}}$$

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

v) AST/ALT ≤ 2.5 x ULN

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

b) Participants require left ventricular ejection fraction over 50% at rest. (Changed per Administrative Letter 02, 21-Aug-2019).

c) Pulmonary Function Test with diffusing capacity of the lung for carbon monoxide (DLCO) ≥ 60% (hemoglobin-adjusted)

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Known central nervous system lymphoma.

b) Participants with nodular lymphocyte-predominant HL.

2) Medical History and Concurrent Diseases

a) Participants with known history of pancreatitis or progressive multifocal leukoencephalopathy (PML)

b) Participants with active interstitial pneumonitis or CT evidence of ≥ Grade 1 pneumonitis.

i) If the participant has a history of interstitial pneumonitis, they must have CT evidence of resolution.

c) Participants with neuropathy ≥ Grade 2, infection ≥ Grade 3, or documented history of coronary artery disease, cardiovascular accidents, or congestive heart failure (CHF) class III/IV.

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

e) Prior malignancies (other than HL) are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include, but are not limited to, non-melanoma skin cancers; in situ bladder cancer, in situ gastric cancer, or in situ colon cancers; in situ cervical cancers/dysplasia; in situ carcinoma of the prostate; or breast carcinoma in situ).

f) Participants with an active, known or suspected autoimmune disease. Participants 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. For any cases of uncertainty, it is recommended that a BMS medical monitor be consulted prior to signing informed consent.

g) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study treatment administration. Inhaled or topical steroids, and adrenal replacement doses 10mg daily are permitted in the absence of active autoimmune disease.

h) Evidence of active brain metastases on brain imaging (ie, MRI or contrast CT).

3) Prior/Concomitant Therapy

a) ASCT ≤ 30 days prior to first dose of study treatment

b) Prior chemotherapy within 4 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin or major surgery within 2 weeks prior to first dose of study treatment.

c) Carmustine (BCNU) ≥ 600mg/m^2 received as part of the pre-transplant conditioning regimen.

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

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

f) Prior allogeneic transplant

g) BV refractory patients as identified by a failure to achieve a PR or CR, relapse, or progression within 3 months of receiving BV treatment (BV treatment as defined by: patients who previously received BV as a single agent or in combination with chemotherapy in any line of treatment [eg, induction, salvage, or consolidation post-ASCT]).

4) Physical and Laboratory Test Findings

a) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative)

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

i) Testing for HIV must be performed at sites where mandated locally

5) Allergies and Adverse Drug Reaction

a) History of allergy to drug components

History of severe hypersensitivity reaction ≥ Grade 3 to any monoclonal antibody with the following exception: participants who experienced Grade 3 or 4 infusion-related reaction with the first dose of rituximab, but who were able to receive subsequent rituximab without recurrence of Grade 3 or 4 infusion-related reaction are eligible.

6) Other Exclusion Criteria

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

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

c) Females who are pregnant or breastfeeding

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

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

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).

The most current result prior to Enrollment and Randomization (randomized arms) is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in the Screening Procedural Outline, Table 2-1, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Enrollment in this study was stopped on 17-Oct-2019 at the decision of the Sponsor.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study enrollment and randomization.

Study treatment includes 2 Investigational [Medicinal] Products (IPs/IMPs) (Table 7-1). In this study, the IPs/IMPs are nivolumab and BV.

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.

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection) 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[26] and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab. See also the Nivolumab IB (Section 3 of the IB) or prescribing information (eg, USPI[30] [Section 11], SmPC[31] [EMA version, Sections 1, 2, 3 of the SmPC]), or country-specific product label for more information.

For the constituents of brentuximab vedotin (BV)[35,32] see the current version of the associated product labels and SmPCs (respectively footnoted) for more information.

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

Table 7-1: Study treatments for CA209812

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab (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. Carton contains 5 vials of 100mg	2° to 8°C. Protect from light and freezing
Brentuximab Vedotin Powder for Solution for Injection[a]	50 mg	IP	Open-label	White to off-white lyophilized preservative-free cake or powder in a single-use vial for reconstitution	2° to 8°C. Protect from light and freezing

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

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7.1 Treatments Administered

Infusions will be performed over a period of once every 3 weeks. Participants should begin study treatment within 3 calendar days of randomization. Participants will be monitored continuously for AEs while on study. Study treatment modifications (eg, dose delay or discontinuation) will be based on specific laboratory and AE criteria (Section 7.4). Doses of study treatment may be interrupted, withheld, or discontinued depending on how well the participant tolerates the study treatment. Treatment with nivolumab will be continued as described in Section 5.1 until disease progression or unacceptable toxicity. Participants treated with nivolumab who achieve a CR may discontinue treatment after a maximum of 2 years of therapy, provided that there is no prohibitive toxicity. Administration of BV should be discontinued after a maximum of 16 cycles, or until disease progression or unacceptable toxicity, whichever occurs first.

All participants who discontinue therapy will be followed through Safety Follow-up Visit 2.

Nivolumab and Brentuximab vedotin arm

Participants should receive nivolumab at a dose of 360 mg as a 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. No dose escalations or reductions of nivolumab are allowed. Premedications are not recommended for the first dose of nivolumab. For 30-minute infusions, infusion durations are ± 5 minutes. For Q3W dosing cycles, participants may be dosed within a ± 3 day window.

For participants in the nivolumab/BV arm, BV will be administered first as a 30-minute infusion followed by a minimum 30-minute rest prior to the nivolumab infusion. Brentuximab vedotin will be administered as a 1.8 mg/kg dose on Day 1 of each treatment cycle every 3 weeks for 16 cycles. In the absence of infusion-related reactions, the infusion rate for all participants 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. Dosing of BV is based on participant's actual body weight. Doses must be adjusted for participants 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 participants weighing greater than 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

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Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Participants may continue on nivolumab or BV alone if required to discontinue one of the study medications. It is recommended to consult with the medical monitor before discontinuing one of the study medications.

Participants should be carefully monitored for infusion reactions during study treatment administration. If an acute infusion reaction related to nivolumab is noted, participants should be managed according to Section 7.1.5.

Brentuximab Vedotin arm

Brentuximab Vedotin will be administered as a 1.8 mg/kg dose on Day 1 of each treatment cycle every 3 weeks for 16 cycles as a 30-minute infusion. In the absence of infusion-related reactions, the infusion rate for all participants 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. Dosing of BV is based on participant's actual body weight. Doses must be adjusted for participants 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 participants weighing greater than 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

7.1.1 Dose Delay Criteria (Nivolumab)

Dose delays during a given study treatment cycle are permitted in this study. Should withholding the dose be required for a period of time outside the dosing window, study treatment must be omitted and the next study treatment administration performed if and only if criteria in Section 7.1.2 are met. See Section 7.4 for instructions concerning skipped doses.

Participants may be dosed up to ± 3 days before or after the scheduled date if necessary. The target date of subsequent study treatments is based on the actual date of dose #1.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

If toxicity is related to nivolumab then BV can be continued. Similarly, if toxicity is related to BV, then nivolumab can be continued. Nivolumab can be resumed in combination with BV if these criteria for resuming treatment are met. Withholding dose of nivolumab for > 6 weeks during the combination phase is permitted. Under certain circumstances treatment is permitted even if nivolumab was held for > 6 weeks. Medical monitor has to be contacted to discuss the case and to grant permission.

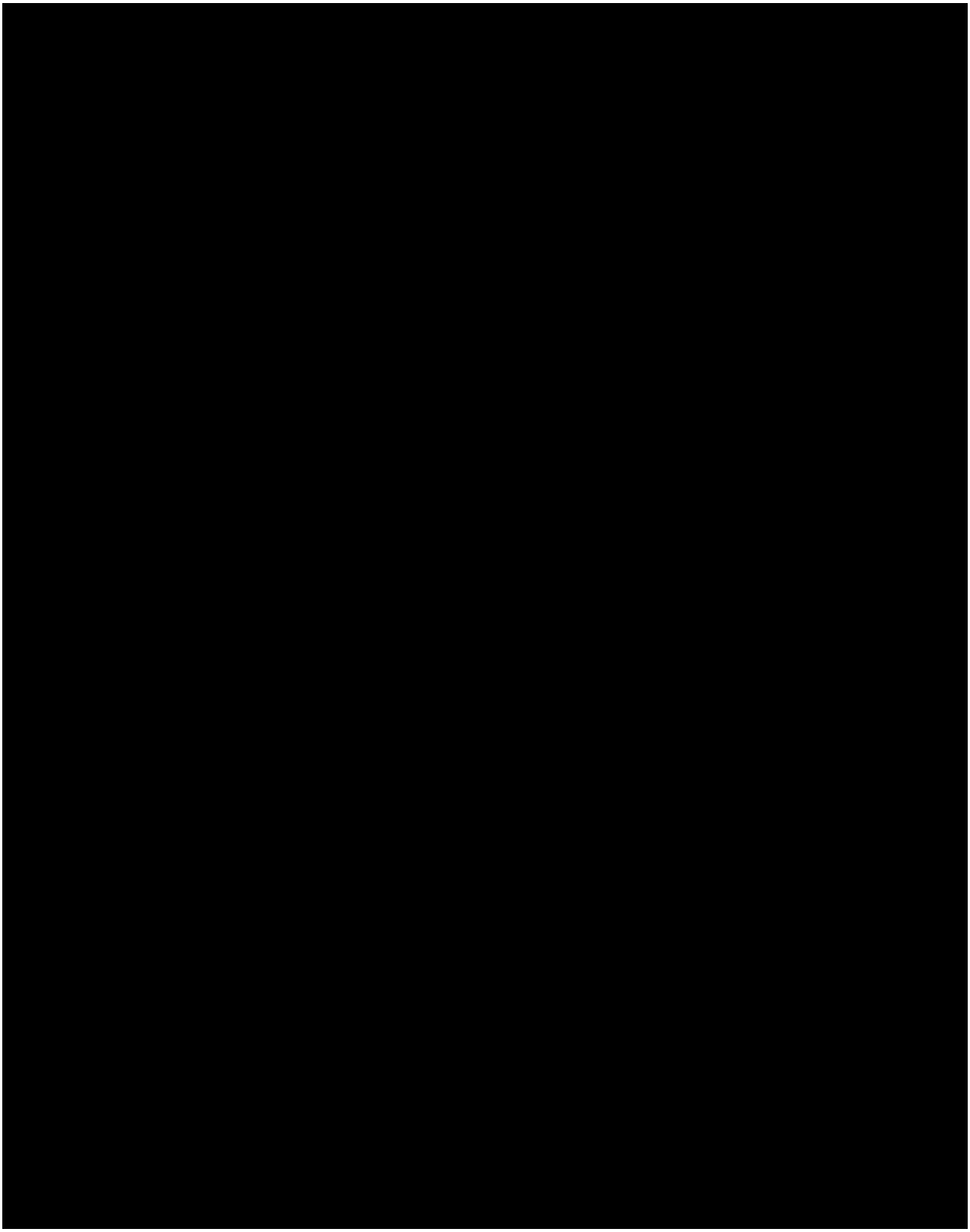
7.1.2 Criteria to Resume Study treatment (Nivolumab)

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

- Participants may resume study treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 study treatment-related skin AE may resume study treatment in the presence of Grade 2 skin toxicity
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 7.1.6) should have study treatment permanently discontinued
- Study treatment-related pulmonary toxicity, diarrhea, colitis, uveitis or neurological toxicity, must have resolved to baseline before study treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete

If the criteria to resume study treatment are met, the participant should restart study treatment at the next scheduled timepoint per protocol. However, if the study treatment is withheld past the window period of the next scheduled timepoint per protocol to ensure adequate recovery from the adverse event or tapering of immunosuppression, the dosing should continue to be withheld until the subsequent scheduled timepoint.

[redacted]



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7.1.4 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 I-O agent in this protocol. Early recognition and management of AEs associated with I-O 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
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

The above algorithms are found in the IB[26] and Appendix 5 of this protocol.

7.1.5 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. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute Common Technology Criteria for Adverse Events (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 to 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. The investigator should begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur.

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).

7.1.6 Dose Discontinuation Criteria (Nivolumab)

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 study treatment-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, study treatment-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, study treatment-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 study treatment-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration require discontinuation
    - Grade 3 study treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
    - Grade 3 study treatment-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 study treatment-related thrombocytopenia > 7 days or associated with clinically significant bleeding requires discontinuation*
        - AST or ALT > 8 x ULN or Total Bilirubin > 5 x ULN requires discontinuation requires discontinuation
        - Concurrent AST or ALT > 3 x ULN and Total Bilirubin > 2 x ULN

  * In most cases of Grade 3 AST or ALT elevation, study treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 study treatment-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or TBili), except for the following events which do not require discontinuation
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. Consult Medical Monitor for Grade 4 amylase and lipase abnormalities
    - 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 study treatment-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.
- If dosing is withheld for > 6 weeks from the previous dose with the following exceptions:
    - Dosing withholdings to allow for prolonged steroid tapers to manage study treatment-related adverse events are allowed. Prior to re-initiating study treatment in a participant with dose omissions lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is withheld.
    - Dosing withholdings > 6 weeks that occur for non-study treatment-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating study treatment in a participant with dose omissions lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is withheld.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued dosing
- Disease progression as determined by investigator assessment following the guidelines given by the Lugano 2014 Classification
- Participant who initiated the preparative regimen for allogeneic stem cell transplant (allogeneic SCT) or ASCT after the first dose of study 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)

7.1.7 Dose Discontinuation Criteria (Brentuximab Vedotin)

Brentuximab vedotin treatment should be permanently discontinued for reasons provided in Table 7.4.2-1. Dose delays of more than 3 weeks may be allowed after discussion with the study medical monitor.

7.1.8 Dose Delay Criteria (Nivolumab and Brentuximab Vedotin)

If the nivolumab dose is delayed, treatment can be continued with BV. Similarly, if the BV dose is delayed, treatment can be continued with nivolumab. See Section 7.4 for instructions concerning dosage modifications.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by calling an IRT and be assigned a participant number. Specific instructions for using IRT will be provided to the investigational site in the IRT manual. The randomization procedures will be carried out via permuted blocks within each stratum. Stratification will be performed on two factors: 1) Prior ASCT status (YES/NO). 2) Prior BV use (YES/NO).

Once registered, participants who have signed the ICF and met all eligibility criteria will be ready to be randomized. The following information is required for participant randomization:

- Participant number
- Date of birth
- Prior therapies and types of therapy (chemotherapy, ASCT)

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

7.3 Blinding

This is an open-label study, blinding procedures are not applicable.

7.4 Dosage Modification

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

7.4.1 Nivolumab

Dose reductions and escalations of nivolumab are not permitted.

7.4.2 Brentuximab vedotin

The recommended dose modifications for BV treatment associated toxicity are provided in Table 7.4.2-1. Doses reduced for BV-related toxicity should not be re escalated without discussion with the sponsor. Dose escalation of BV beyond 1.8 mg/kg is not permitted. Dose reductions below 1.2 mg/kg are not allowed.

If BV treatment is delayed for any reason, other treatments must be continued. Participants who require delay of BV should be re-evaluated frequently and BV dosing resumed when re-treatment criteria are met. Dose delays of more than 3 weeks may be allowed after discussion with the study medical monitor.

Approved v4.0 [redacted]

Recommendations for management of infusion related reactions due to BV are described in Section 7.1.5.

Participants who discontinue nivolumab treatment due to a treatment-related AE may continue treatment with BV for a maximum of 16 cycles, or until disease progression or unacceptable toxicity, whichever occurs first. Participants who discontinue BV due to a treatment-related AE may continue to receive nivolumab treatment until disease progression or unacceptable toxicity.

Approved v1.0 [redacted]

Table 7.4.2-1: Dose Modifications for Brentuximab Vedotin

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral Neuropathy	Continue at same dose level	Hold until peripheral neuropathy resolves to ≤ Grade 1and then resume treatment at 1.2 mg/kg[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
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.	Discontinue treatment

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

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

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

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

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

7.5 Preparation/Handling/Storage/Accountability

The investigational products (nivolumab) 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 Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment (nivolumab) 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 treatment arise, the study treatment should not be dispensed and the site should contact BMS immediately.

Detailed drug preparation, storage, administration, and drug accountability instructions for BV are provided in the Pharmacy Binder, SmPC, country-specific product label, or current prescribing information.[35]

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

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

Further instructions for the storage, handling, and preparation of nivolumab Solution for Infusion will be provided to the clinical sites in the IB[26] and pharmacy manual. Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability as well as the participant's medical records and eCRF.

7.7 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study treatment must be documented in the concomitant therapy section of the CRF.

7.7.1 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 7.7.2)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cHL)

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

The investigator should contact and confirm agreement with the BMS medical monitor (and acknowledgement from the contract research organization medical monitor) prior to the administration of any new concomitant medications.

7.7.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications after enrollment or within 14 days of dosing 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.

7.7.2.1 Permitted Therapy

Participants 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.

7.7.2.2 Imaging Restriction and Precautions

- It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed regarding whether they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to these participants. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.
- The ultimate decision to perform an MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

7.8 Treatment After the End of the Study

At the end of the treatment period, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab is

terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases, BMS will follow local regulations

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue the investigational product(s) for any of the following reasons:

- Disease progression as determined by investigator assessment following the guidelines given in Appendix 6
- Participant's request to stop study treatment. Participants who request to discontinue study treatment 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- 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 participant
- 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 specified reasons for discontinuation.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

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

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Table 2-3. The only exception to this requirement is when a participant 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 treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

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8.1.1 Post Study Treatment Study Follow-up

In this study, PFS is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed in line with Section 2 through Safety Follow-up Visit 2. Study objectives and endpoints are listed in Table 4-1.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants 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 treatment 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 participant 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.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant'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 participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.

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.

For participants who discontinue study therapy by proceeding to allogeneic SCT, documentation of hyper-acute, acute and chronic GVHD will be captured until the first non-CR after SCT is documented through safety Follow-up Visit 2. [Appendix 9]. Investigators will make telephone contact with the participant's hematologist /oncologist /transplant physician to obtain this information if the participant is being followed by another physician.

9.1 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 2.

9.1.1 Imaging Assessment for the Study

Per Revised Protocol 01, images will no longer be submitted to an imaging core lab. .

9.1.2 Disease Response Evaluation

The determination of disease response to study treatment will be made using the Lugano 2014 Classification (Appendix 6).

Surveillance assessments for ongoing study treatment decisions will be completed by the investigator using the Lugano 2014 Classification. Per the Lugano criteria, PET-negative scans are defined on the 5-point scale as scores of 1, 2, or 3 (where 1 = no uptake above background; 2 = uptake ≦ mediastinum; and 3 = uptake > mediastinum but ≦ liver) and PET-positive scans, as scores of 4 or 5 (where 4 = uptake moderately higher than liver; 5 = uptake markedly higher than liver and/or new lesions).[36] Response on PET scans should be reported as CMR, PMR, SMD (stable metabolic disease), or PMD (progressive metabolic disease).

See Section 7.1.1 for information concerning CT findings that indicate progression. Response on CT scans should be reported as complete response (CR), partial response (PR), stable disease, or progressive disease (PD).

In case of equivocal scan results, sites should discuss the case with a BMS medical monitor. Re-imaging will be required 12 weeks of the original scan showing equivocal disease progression. Dosing may continue during the interval of confirming disease progression.

9.1.3 B Symptoms

The presence or absence of B symptoms will be assessed during and after treatment. B symptoms are defined as:

1) Unexplained weight loss of more than 10% during the last 6 months, or
2) Unexplained, persistent, recurrent fever with temperatures above 38 degree Celsius during the previous month, or
3) Recurrent drenching night sweats during the previous month.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of nivolumab. For participants randomized/assigned to treatment and never treated with study treatment, SAEs should be collected for 30 days from the date of randomization.

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

In the present study, AEs, treatment-related AEs, SAEs, and treatment-related SAEs occurring > 100 days after the last study treatment administration during the long-term follow-up periods will be recorded on the eCRF and will be tabulated for AEs of special interest for immuno-oncology agents and for BV. Effects on long-term fertility and evolution of secondary neoplasms will be assessed.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. As an immuno-oncology (I-O) agent, nivolumab is associated with unique AEs, whose mechanism of action is consistent with a potential inflammatory mediated process. These unique immune-related AEs, referred to as "select AEs" in the nivolumab IB and "adverse events of special interest" in this protocol, have not typically been observed with cytotoxic agents. Select AEs have been categorized into 7 areas: pulmonary toxicity, gastrointestinal toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and renal toxicity. Select AEs have occurred with low frequency (< 5%), are manageable, and are reversible with treatment interruption, discontinuation, or with the use of corticosteroid and/or other immunosuppressants. Select AEs, in particular pneumonitis, are considered clinically meaningful as they require greater vigilance and for early recognition and prompt intervention. Therefore, management algorithms have been developed and implemented for each immunologically associated select AE category (refer to IB[26] and Appendix 5 of the protocol). [redacted]

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until [the follow-up contact], at the timepoints specified in the Schedule of Activities (Section 2). 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 participants. All nonserious adverse events (not only those deemed to be treatment related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. [redacted]

Sections 5.6.1 and 5.6.2 in the IB[26] represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

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 treatment or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious.
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment 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). [redacted]

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives and 30 days 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 Appendix 3.

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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 Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant 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).

9.2.7 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 9.2 and Appendix 3 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.

9.2.8 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.

9.3 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 9.2).

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For this study, any dose of nivolumab greater than 10 mg/kg within a 24-hour time period will be considered an overdose. Also, any dose of BV exceeding 180 mg in a 24-hr period will be considered an overdose.

In the event of an overdose the [investigator/treating physician] should:

1) Contact the Medical Monitor immediately
2) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

All screening assessments should be performed as indicated in Section 2 and within a maximum of 28 days prior to randomization.

Baseline disease assessments should be performed within 28 days prior to randomization.

At Screening:

- Medical history will be obtained to capture relevant underlying conditions
- Physical examinations should include weight, height, ECOG Performance Status, BP), heart rate, and temperature
- Screening laboratory assessments will be conducted locally

During the Treatment Period:

- Participants will perform assessments as outlined in Section 2 and detailed in the Notes column
- The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented
- Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page
- Participants will be evaluated for safety if they have received any study treatment. Laboratory testing will be performed locally
- Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations
- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used for safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations

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At Follow-Up:

- Toxicity assessments will be continuous during the first two safety follow-up visits.
- 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 treatment related toxicities resolve, return to baseline, or are deemed irreversible

9.4.1 Physical Examinations

Refer to Schedule of Activities, Section 2.

9.4.2 Vital signs

Refer to Schedule of Activities, Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities, Section 2.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report
- All protocol specified laboratory tests are to be completed within 3 calendar days prior to dosing, analyzed and reported by the local lab
  Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations
- Results of safety laboratory collections (ie, Chemistry and Hematology) must be obtained and reviewed in advance of study treatment dosing
- Laboratory parameters assessed in this study are identified in Table 9.4.4-1.

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Table 9.4.4-1: Clinical Safety Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST)	Sodium
Alanine aminotransferase (ALT)	Potassium
Total bilirubin (TBili)	Chloride
Direct bilirubin	Calcium
Alkaline phosphatase	Phosphorus
Lactate dehydrogenase (LDH)	Magnesium
Serum Creatinine	Amylase
Blood Urea Nitrogen (BUN) or serum urea level	C-reactive protein
Albumin	
Uric acid	
Fasting glucose	
Creatinine clearance	
Thyroid Function Testing	
TSH	
Free T4	
Free T3	
Urinalysis	
Total Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Serology	
Hep B/C (HBV sAG, HCV antibody or HCV RNA)	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose, discharge)	

Approved v4.0 [redacted]

9.4.5 Imaging Safety Assessment

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.

[redacted]

Approved v1.0 [redacted]

[redacted]

10 STATISTICAL CONSIDERATIONS

As of 17-Oct-2019, enrollment in this study was stopped at the decision of the Sponsor. At the time enrollment was stopped, 23 participants had been randomized. No formal statistical testing or inferential analyses will be performed. The statistical analyses as previously planned will only be conducted if appropriate in the final analysis. Further details are presented in the SAP.

10.1 Sample Size Determination

The planned sample size for this study was to be approximately 340 randomized participantsThe sample size of the study accounts for the primary efficacy endpoint, PFS. PFS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided), with 90% power. As of 17 October 2019, enrollment was stopped. At total of 23 participants were randomized.

[redacted]

[redacted]

Table 10.1-1: Schedule of Statistical Analyses

	Interim Analysis	Final Analysis
Conditions	At least 131 PFS events and 6 months follow-up	At least 187 events
Expected timing	40 months (34 months + 6 months of follow-up)	45 months (34 months+ 11 months of follow-up)
Alpha level	Interim PFS analysis projected at 0.0148 level[a]	Final PFS analysis projected at 0.0455 level

[a] Using O'Brien and Fleming alpha spending function in case exact 131 PFS events are observed at the interim PFS analysis.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Randomized	Participants who had no post-randomization efficacy measure for the parameter being analyzed will be excluded.
Safety	All treated participants who received at least 1 dose of study treatment. Participants will be included in the treatment group that they actually received

10.3 Statistical Analyses

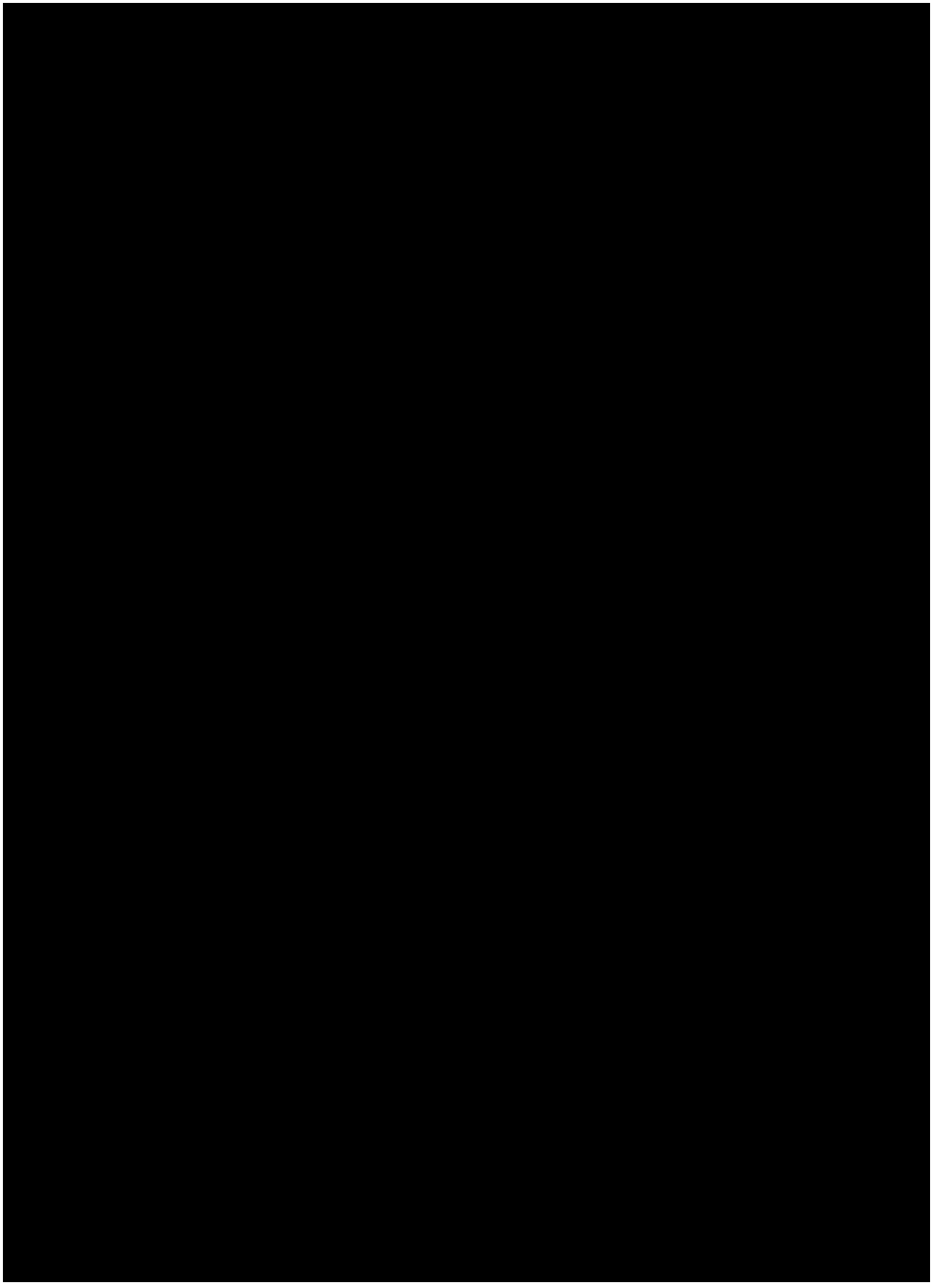
The SAP will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint, PFS based on investigator assessment, will be compared in two randomized armsvia a two-sided, log-rank test stratified by the same factors used in randomization. Participants who die without a reported progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last tumor assessment. Participants who did not have any on study assessments and did not die will be censored on the randomization date. A participant who initiates a subsequent anti-cancer therapy will be censored on the date of last tumor assessment prior or on the start date of their subsequent anti-cancer therapy. Sensitivity analyses will be performed using different PFS definitions to assess the robustness of the primary analysis. The PFS curve, median and PFS rate at 6, 12, 18, and 24 months for each randomized arm will be estimated using the Kaplan-Meier product-limit method. Two sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method. A two-sided, 95% confidence interval for the PFS rates will be computed by Greenwood method. The hazard ratio (HR) and corresponding two-sided 100 * (1-α)% (α adjusted for the interim analysis) confidence interval will be estimated in a Cox proportional hazards model using randomized arm as a single covariate, stratified by the same factors used in randomization.
Secondary	CRR/CMR based on investigator assessment will be compared in two randomized armsvia a two-sided, Cochran-Mantel-Haenszel test stratified by the same factors used in randomization. An estimate of the treatment odds ratio between the nivolumab + BV and BV arm along with corresponding two-sided 95% CIs and p-value will be presented. The estimate of the CRR/CMR and associated exact two-sided 95% CIs (by Clopper - Pearson method) will be presented for both arms. ORR as defined as proportion of participants who achieved CR/CMR or PR/PMR before taking any subsequent anti-cancer therapy, will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. Duration of response (or complete response) in each treatment group will be estimated using KM product-limit method for participants who achieve PR or CR /CMR (or CR/CMR only). Median values along with two-sided 95% CI will be calculated. The OS curves for each treatment group will be estimated using the Kaplan-Meier product-limit method. Two-sided, 95% confidence intervals for median OS will be provided. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive.When the primary endpoint, PFS, is statistically significant, the secondary endpoint CRR/CMR will be tested. The hierarchical testing procedure that ensures the study-wise type I error is controlled at 5% levels will be described in the SAP.
[redacted]	

10.3.2 Safety Analyses

Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE version 4.03. All on-study AEs, treatment-related, AEs, SAEs and treatment-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.



[redacted]

10.3.4 Interim Analyses

As described in Section 10.1, an interim analysis of PFS assessed by BICR was to be performed after at least 131 PFS events (70% of total PFS events needed for final analysis) had occurred. It also required a minimum follow up of 6 months from the last patient first visit. This analysis was to be reviewed by the DMC while the Sponsor remained blinded. The estimated timing of this analysis was to be around 40 months after the start of randomization. The SAP will further describe the planned interim analyses.

[redacted]

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Approved v4.0 [redacted]

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12 APPENDICES

Approved v4.0 [redacted]

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
[redacted]	
ADC	anti-drug conjugate
AE	adverse event
AIDS	Acquired Immuno-Deficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
BV	Brentuximab Vedotin
C	Celsius
Ca	calcium
Cavgss	average steady state concentration
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CI	confidence interval
Cl	chloride
CL	clearance
CLss	steady state clearance
Cmaxss	maximum concentration at steady state
Cminss	minimum concentration at steady state
CMR	complete metabolic response
CMV	cytomegalovirus
CR	complete response (remission)
CRF	case report form, paper or electronic

Term	Definition
CrCL	creatinine clearance
CRR	complete response rate
CT	computed tomography
[redacted]	
CTLA	cytotoxic T-lymphocyte associated (protein)
CV	coefficient of variation
DILI	drug-induced liver injury
dL	deci-liter
DLCO	Diffusing capacity of the lung for carbon monoxide
DSMC	Data Safety Monitoring Committee
[redacted]	
DOCR	duration of complete response
DOR	duration of response
[redacted]	
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eg	exempli gratia (for example)
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EOT	end of treatment
[redacted]	
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FSH	follicle stimulating hormone
FU	Follow-up
g	gram
G-CSF	granulocyte colony stimulating factor

Term	Definition
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage colony stimulating factor
h	hour
HBV	hepatitis B virus
HBV sAG	hepatitis B virus surface antigen
HCV	hepatitis C virus
Hep B^-	hepatitis B
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
[redacted]	
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	immunogenic cell death
ICH	International Council on Harmonisation
ICOS	Inducible T-cell Costimulator
[redacted]	
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IMP/IP	investigational medicinal product / investigational product
I-O	Immuno-oncology
IPS	International Prognostic Score
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IUD	intrauterine device
IV	intravenous

Term	Definition
[redacted]	
K	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LDi	longest diameter
[redacted]	
mg	milligram
Mg	magnesium
min	minute
mL	milliliter
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MST	medical safety team
MTD	Maximum Tolerated Dose
N	number of subjects or observations
Na	sodium
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed death 1 (receptor)
PD-L1/PD-L2	programmed death ligand 1/2
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PK	pharmacokinetics
PMD	progressive metabolic disease
PML	progressive multifocal leukoencephalopathy

Term	Definition
PMR	partial metabolic response
PPD	perpendicular diameter
PPK	population pharmacokinetics
PR	partial response (remission)
Q2W	once every 2 weeks
Q3W	once every 3 weeks
QoL	Quality of Life
RBC	red blood cell
RCC	renal cell carcinoma
RNA	ribonucleic acid
[redacted]	
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	stem cell transplant
SD	standard deviation
SDi	shortest diameter
SMD	stable metabolic disease
SmPC	Summary of Product Characteristics
t1/2	Half life
T3	triiodothyronine
T4	thyroxine
TBili	total bilirubin
TIL	tumor-infiltrating lymphocyte
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USPI	United States Package Insert
V	visit
[redacted]	
Vss	volume of distribution at steady state
W	week

Term	Definition
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
[redacted]	

Approved v4.0 [redacted]

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP)
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee 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).

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, participant 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, Sponsor or designee 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.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) 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 relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC for
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (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).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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 participant volunteers to participate.

Sponsor or designee 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.

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Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion
- 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

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

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 participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant 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.

SOURCE DOCUMENTS

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.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	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 participant, including unique participant 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

If	Then
	• dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

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 Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. 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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee 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. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor or designee 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 Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) 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, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

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

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If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

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

- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant 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)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. 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 Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

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APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant 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.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant 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) 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)
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 participant 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 9.2.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study treatment 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 9.2.5 for reporting pregnancies).

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

EVALUATING AES AND SAES

Assessment of Causality
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.

Follow-up of AEs and SAEs
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.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- 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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state 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 > 40 mIU/mL to confirm menopause.

Note: 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.

- 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. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

Approved v4.0 [redacted]

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Two of the highly effective methods of contraception listed below are required during study duration and until the end of relevant systemic exposure, defined as approximately 6 months after the end of study treatment.

Local laws and regulations may require use of alternative and/or additional contraception methods. See the current prescribing information/country-specific label/SmPC for brentuximab vedotin pregnancy/contraception information.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected.

• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of nivolumab or brentuximab vedotin treatment.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of nivolumab or brentuximab vedotin treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of nivolumab or brentuximab vedotin treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of nivolumab or brentuximab vedotin treatment.

See the current prescribing information/country-specific label/SmPC for brentuximab vedotin pregnancy/contraception information.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

Approved v4.0 [redacted]

APPENDIX 5 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.

Approved v4.0 [redacted]

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

27-Jun-2019

Approved v4.0 [redacted]

Renal Adverse Event Management Algorithm

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

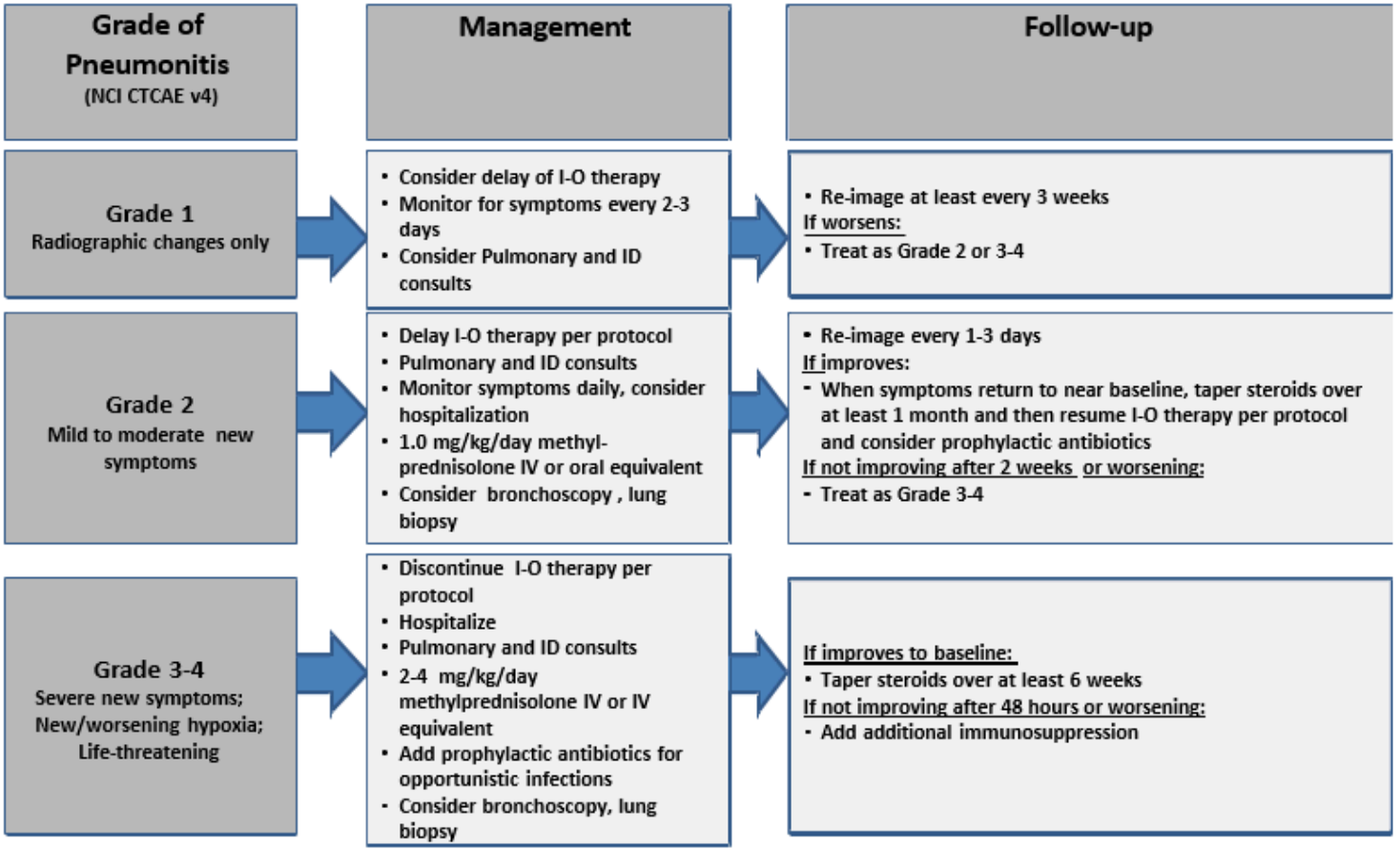
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



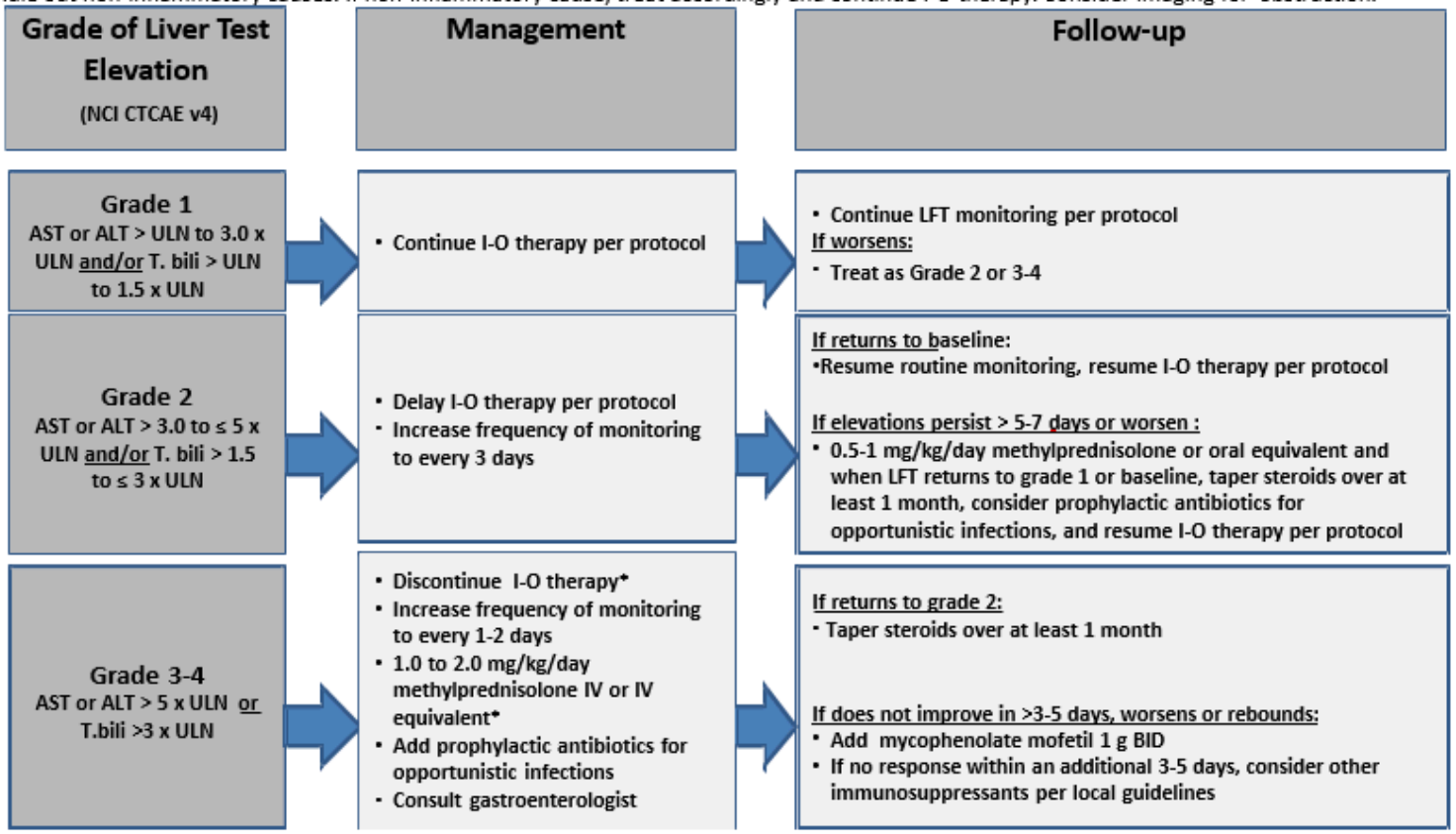
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Approved v4.0 [redacted]

Hepatic Adverse Event Management Algorithm

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



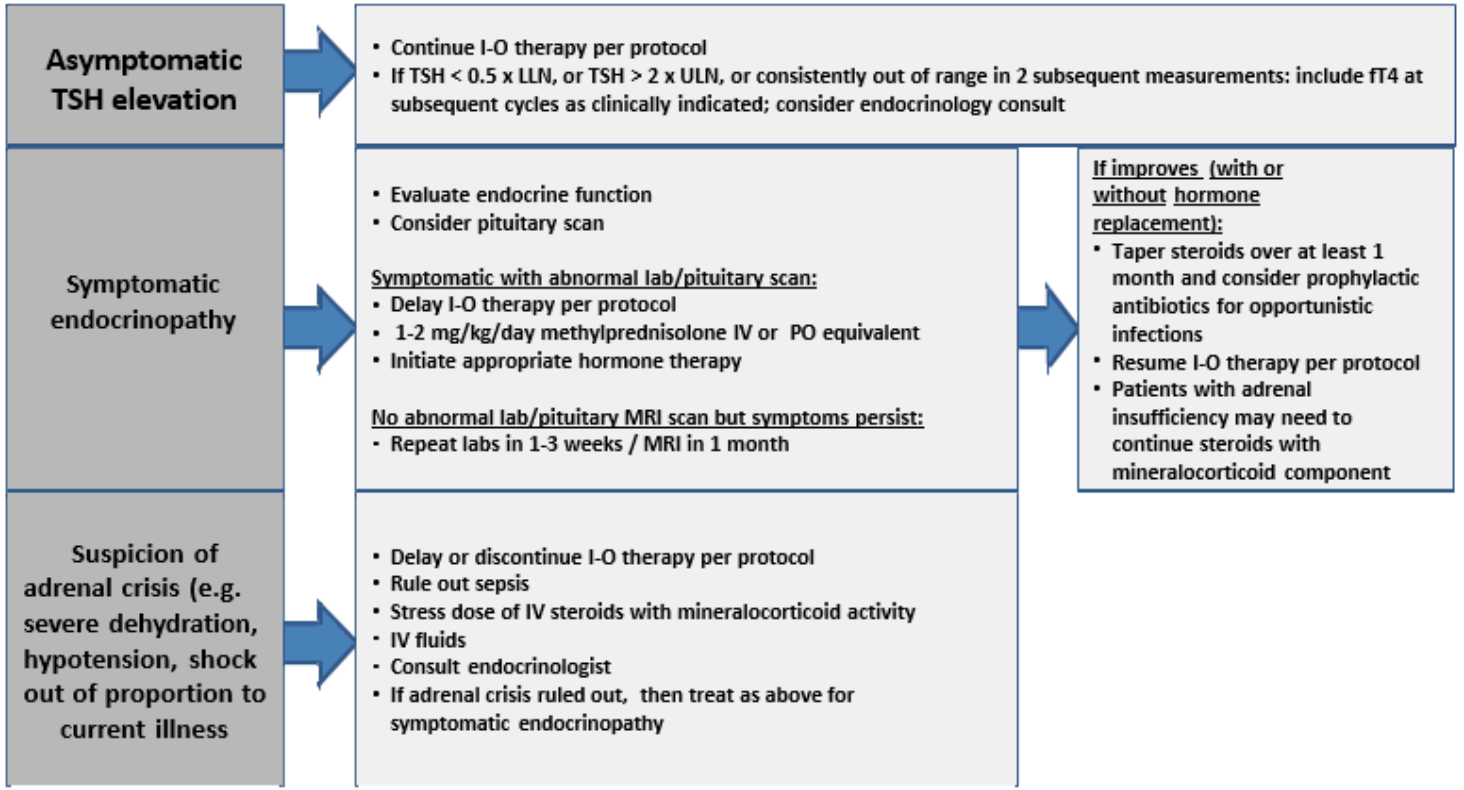
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

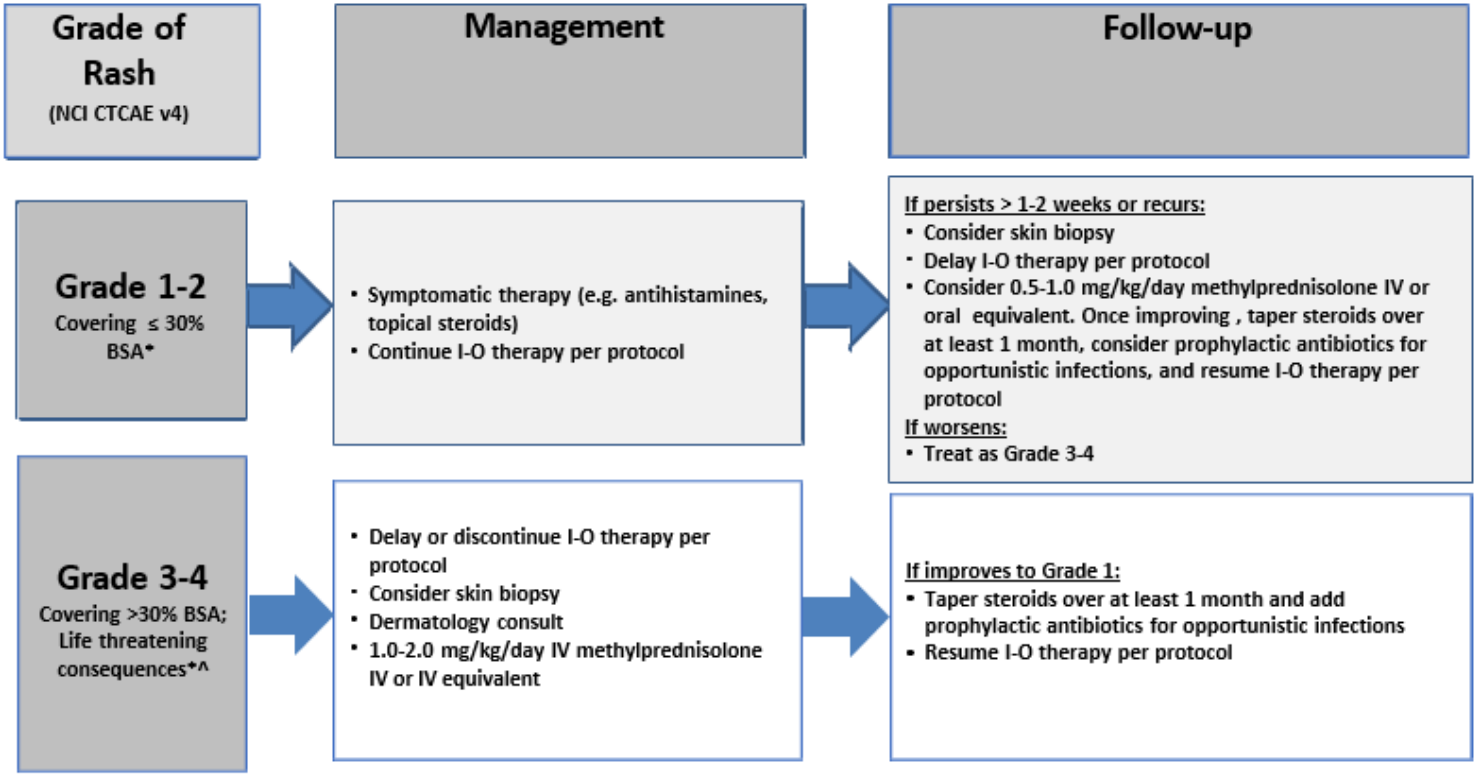


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Skin Adverse Event Management Algorithm

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



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

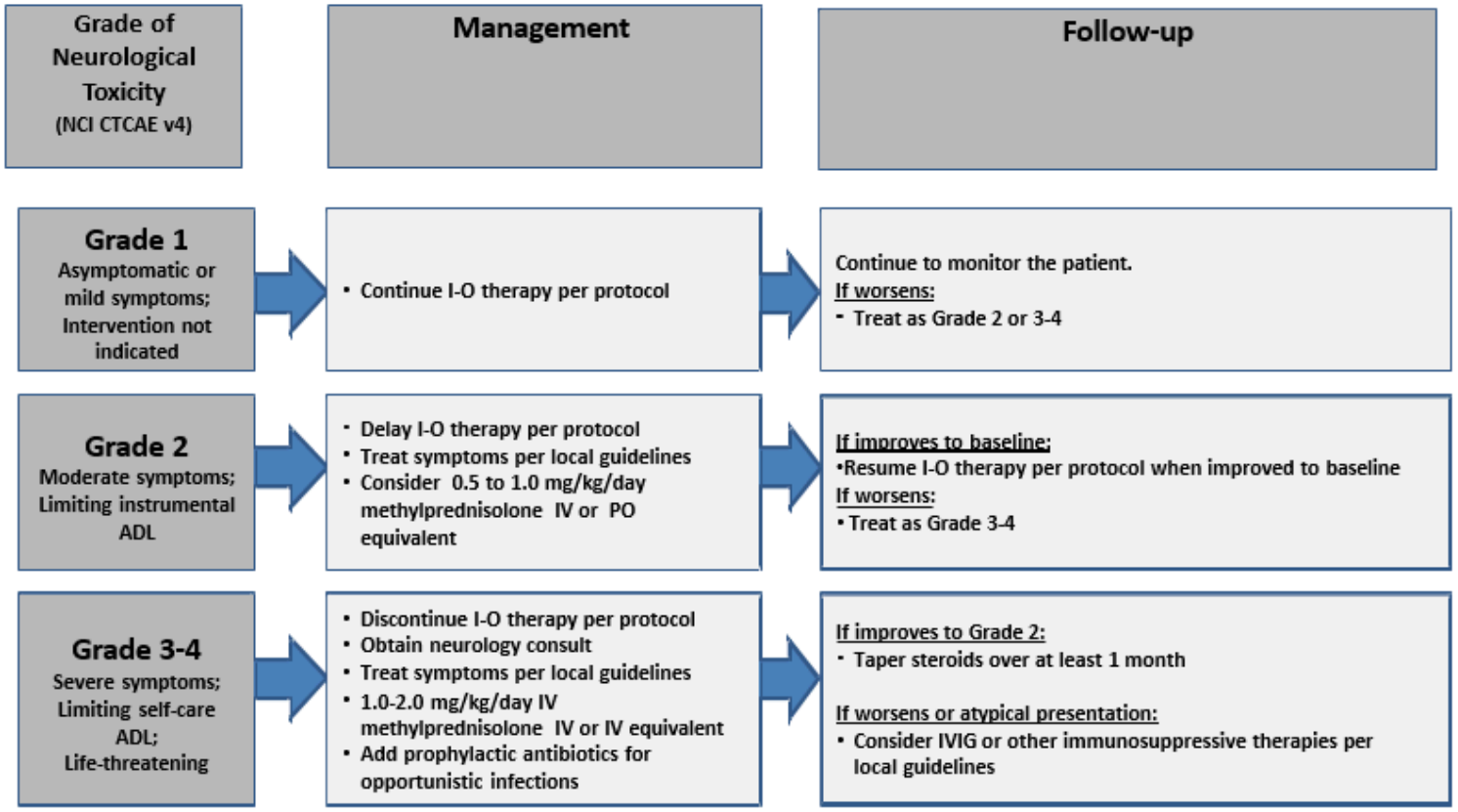
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

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



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

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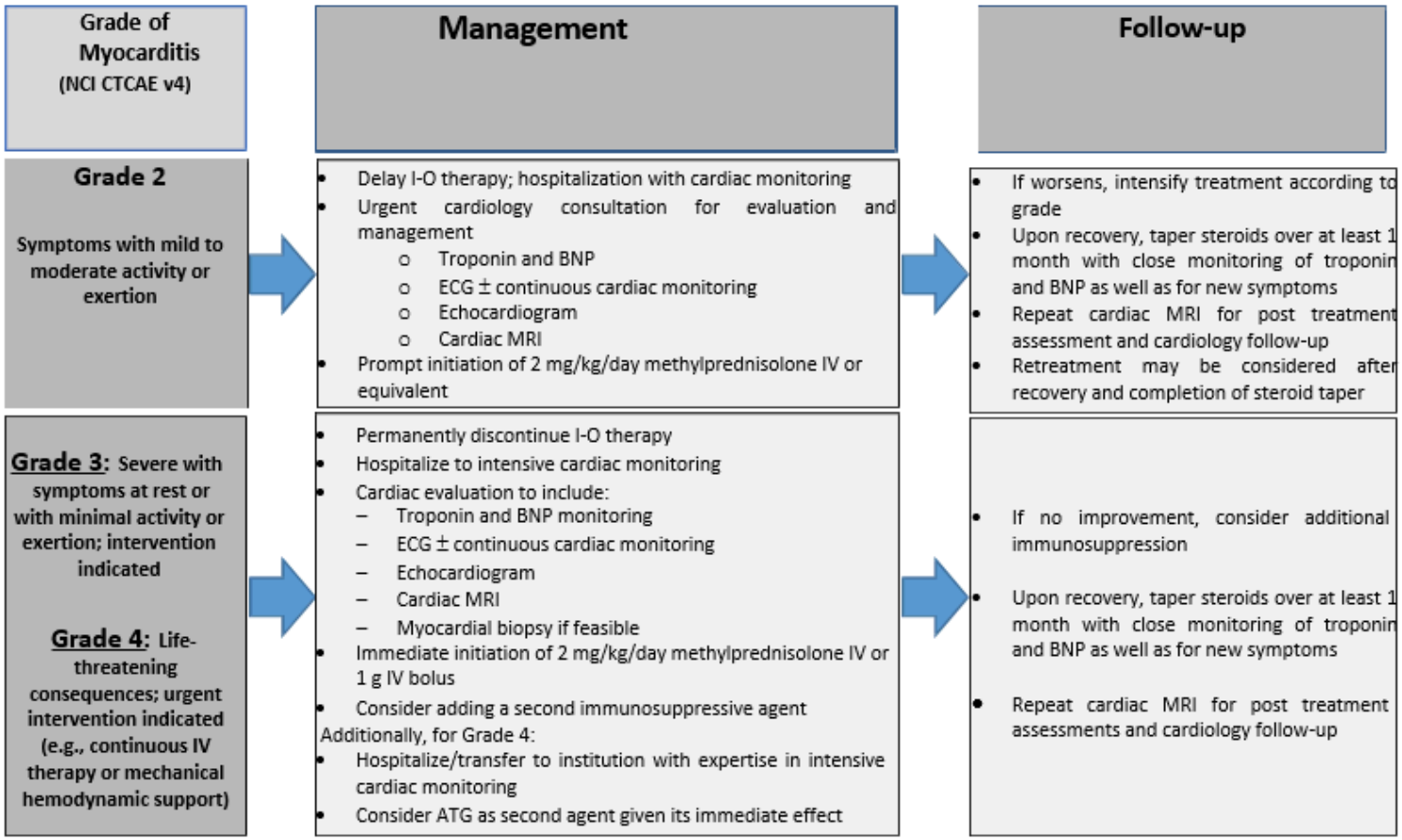
Myocarditis Adverse Event Management Algorithm



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

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 6 LUGANO 2014 CLASSIFICATION FOR INITIAL EVALUATION, STAGING, AND RESPONSE FOR HODGKIN 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
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.

Reference: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 2014;32:3059-3067.

APPENDIX 7 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

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

Approved v4.0 [redacted]

APPENDIX 8 HASENCLEVER SCORE (INTERNATIONAL PROGNOSIS SCORE)

Composite score determined by assigning 1 point for each of the following factors;

- Age ≥ 45 yrs
- Serum albumin < 40 g/L
- Disease Stage 4
- Gender is male
- Hemoglobin level < 105 g/L
- White Blood Cells ≥ 15G/L
- Lymphocytes < 0.6 G/L or < 8% of White Blood Cells

Reference: Hasenclever D and Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998;339:1506-14.

APPENDIX 9 ACUTE GVHD GRADING AND STAGING

Table 1: Extent of Organ Involvement

Stage	Skin	Liver	Gut
1	Rash on < 25% of skin[a]	Bilirubin 2 - 3 mg/dL[b]	Diarrhea > 500 mL/day[c] or persistent nausea[d]
2	Rash on 25 - 50% of skin	Bilirubin 3 - 6 mg/dL	Diarrhea > 1000 mL/day
3	Rash on > 50% of skin	Bilirubin 6 - 15 mg/dL	Diarrhea > 1500 mL/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1 - 2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	--	Stage 2 - 3 or	Stages 2 - 4
IV[f]	Stage 4	Stage 4	--

[a] Use "Rules of Nines" (Table 2) or burn chart to determine extent of rash.

[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[c] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

[d] Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.

[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[f] Grade IV may also include lesser organ involvement with an extreme decrease in performance status.

Table 2: Percent Body Surfaces

Body Area	Percent	Total Percentage
Each Arm	9%	18%
Each Leg	18%	36%
Chest & Abdomen	18%	18%
Back	18%	18%
Head	9%	9%
Pubis	1%	1%

Ref.: Przepiorka et al. Bone Marrow Transplant 1995;15(6):825.

Stage of Chronic GVHD

Limited: Localized skin involvement resembling localized scleroderma with or without liver involvement; no other organ involvement.
Extensive: Generalized skin and/or multiple organ involvement.

Ref. Sullivan KM, Blood 1981;57:267.

Approved v4.0 [redacted]