Official Title of Study:

Risk-based, Response-adapted, Phase II Open-label Trial of Nivolumab + Brentuximab Vedotin (N + Bv) for Children, Adolescents, and Young Adults With Relapsed/Refractory (R/R) CD30 + Classic Hodgkin Lymphoma (cHL) After Failure of First-line Therapy, Followed by Brentuximab + Bendamustine (Bv + B) for Participants With a Suboptimal Response (CheckMate 744: CHECKpoint Pathway and Nivolumab Clinical Trial Evaluation)

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CLINICAL PROTOCOL CA209744

Risk-based, response-adapted, Phase II open-label trial of nivolumab + brentuximab vedotin (N + Bv) for children, adolescents, and young adults with relapsed/refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by brentuximab + bendamustine (Bv + B) for participants with a suboptimal response.

CheckMate 744: CHECKpoint pathway and nivolumab clinical Trial Evaluation

Protocol Amendment Number: 04

Clinical Trial Physician - Medical Monitor
[redacted]
86 Morris Avenue
Summit, NJ 07901
Phone: [redacted]
email: [redacted]

Clinical Scientist
[redacted]
Celgene, a BMS Company
Route de Perreux 1, Boudry - Switzerland
Phone [redacted]
email: [redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]
Japan: [redacted]

Bristol-Myers Squibb Research and Development

3401 Princeton Pike
Lawrence, NJ 08648 USA

Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

6-5-1 Nishi-Shinjuku, Shinjuku-ku,
Tokyo, 163-1328, Japan

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	26-Mar-2021	Closed recruitment of R1 cohort [redacted]. Total cohort size for R1 was reduced. Added clarifying statements to planning of sample size for each cohort. Corrected a typo in the Description for Response-evaluable Participants in Section 10.2, Populations for Analyses. Added BMS standard for COVID-19 protocol language. Other minor edits were made, as described in the Summary of Key Changes
Revised Protocol 03	26-Mar-2018	The response assessment by investigators using Lugano 2014 response criteria was added as a secondary endpoint to allow for a comprehensive interpretation of the study data. Guidance for collection and submission of tumor assessments was added to support the evaluation of this new secondary endpoint. Contraception requirements for female participants of child bearing potential were modified to properly align with Nivolumab clinical research standard guidelines and brentuximab label. Other minor edits were made, as described in the Summary of Key Changes.
Revised Protocol 02	01-Jun-2017	[redacted] the co-primary endpoint CMR rate has been added. [redacted] Clarification about contraception guidelines was needed in order to avoid confusion and to harmonize differences between the protocol and global product labels (Brentuximab and Bendamustine). A common approach for all IMPs requires 6 months of contraception after last IMP dose for WOCBP and 7 months for males with partners of WOCBP. Additionally, clarification was provided about the requirement for 2 contraception methods or complete abstinence. Other minor edits were made, as described in the Summary of Key Changes. Incorporates changes from Administrative Letter 03
Administrative Letter 03	14-Apr-2017	Created to clarify an inconsistency in the protocol table between the X in the Table 2.-2 columns for pregnancy testing at D15 visits and the notes.
Revised Protocol 01	01-Mar-2017	Incorporates changes from Amendment 02, Administrative Letter 01 and Administrative Letter 02
Amendment 02	01-Mar-2017	[redacted] Additionally, clarifying: R1 Consolidation Therapy may be inclusive of all types of Radiation Therapy (RT) per institutional guidelines, adds up to 2 additional cycles of Bv+B with BMS MM approval for R2 cohort consolidation therapy delays (to be consistent with the approach taken for

Document	Date of Issue	Summary of Change
		Induction Phase, N+Bv), deletes wording "for biomarker analysis" as the biopsy is required per Standard of Care and provided to BMS for histologic confirmation of disease and biomarker testing, modification of requirements for FDG-PET at screening and during treatment in alignment with Standard of Care practices, and LYRIC 2016 criteria will be added as an exploratory endpoint for future data analysis according to refinement of LUGANO classification in the era of immunomodulatory therapy. Other minor clarifications were made [redacted]
Administrative letter 02	14-Jan-2017	To clarify equivalent H1/H2 blocker pre-medications are permitted and sites should follow institutional practice for stem cell collections to rule out bone marrow disease involvement. To correct a fragment sentence, per bendamustine package insert.
Administrative letter 01	17-Nov-2016	Change In Medical Monitor Contact Information. To clarify: Bv PK collections are plasma and serum. To correct error in language that conflicts with other existing language: NSAE/SAE collected until FU2 (Day100), and treatment Beyond Progression is permitted, per the study design.
Original Protocol	23-Sep-2016	Not Applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

The primary reason for this amendment is the closing of recruitment into the R1 cohort. The cohort is being modified [redacted]. The original R1 cohort size was estimated to approximately 40 participants. [redacted] It was considered to reduce number of accrued R1 participants from 40 to 28 and closing recruitment in cohort R1. Importantly, closing recruitment today will still allow the planned analyses of the R1 cohort to be conducted with acceptable precision based on n = 28. [redacted] the total number of study participants (see Section 5.2) and study completion date (May-2024) of the study CA209744 were revised. Lastly, BMS standard for COVID-19 protocol language has been added to the protocol. Additional revisions, including to sections of the Synopsis, have been made to align the protocol with respect to these changes.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added Clinical Scientist Updated for Medical Monitor.	Medical Monitor has changed. Updated key study contacts.
Section 5.1.1 Data Monitoring Committee and Other External Committees	Added clarity to planning of sample size for each cohort.	Updated to give actual number of participants in each cohort.
Section 5.2 Number of Participants	Added actual numbers of participants to each cohort. Revised sample size of R1 cohort.	Updated to give actual number of participants in each cohort. [redacted]
Section 6.1 Inclusion Criteria	Revised section for Age and Reproductive status for males who are sexually active with WOCBP.	The duration of contraception requirement post-treatment completion for male participants who are sexually active with WOCBP was revised from 7 months to 6 months based on the

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
		information in the product labels of brentuximab vedotin and bendamustine. Such requirement for nivolumab was removed.
Section 7.6.1 Prohibited and/or Restricted Treatments	Updated text to include details on how to handle live COVID-19 vaccines.	Added BMS standard for COVID-19 protocol language.
Section 7.6.3 Permitted Therapy	Updated text to include details how to handle not live COVID-19 vaccines.	Added BMS standard for COVID-19 protocol language.
Section 9.2.8 Other Safety Considerations	Updated text to include details for CRF to capture COVID-19 related AEs/SAEs as per normal reporting procedure.	Added BMS standard for COVID-19 protocol language.
Section 10.1 Sample Size Determination	Added clarity to planning of sample size for each cohort.	Updated to give actual number of participants in each cohort.
Section 10.2 Populations for Analyses	In the Description column for Response-evaluable Participants, corrected sentences from PMD (Progressive Metabolic Disease) to PMR (Partial Metabolic Response).	Corrected due to typo.
Appendix 2 Study Governance Considerations	Updated monitoring details.	Updated language to allow for remote monitoring.

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1 SYNOPSIS

Protocol Title:

Risk-based, response-adapted, Phase II open-label trial of nivolumab + brentuximab vedotin (N + Bv) for children, adolescents, and young adults with relapsed/refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by brentuximab + bendamustine (Bv + B) for participants with a suboptimal response. CheckMate 744: CHECKpoint pathway and nivolumab clinical Trial Evaluation.

Study Phase: II

Rationale:

Classical Hodgkin lymphoma (cHL) is characterized by rare malignant Reed Sternberg cells surrounded by an extensive but ineffective inflammatory immune cell infiltrate. Recent work has demonstrated that chromosome 9p24.1/CD274 (PD-L1) PDCD1LG2 (PD-L2) genetic alterations increase the PD-1 ligands expression, and are described as a defining feature of cHL. The 9p24 amplicon also contains JAK2, and copy number-dependent JAK2-signal transducers and activators of transcription which can further increase PD-1 ligand expression.

These genetic alterations commonly found in cHL indicate that PD-1 blockade is a reasonable target in this disease. In addition, Epstein-Barr virus (EBV) infection can increase expression of PD-1 ligands in EBV-positive Hodgkin lymphomas (HLs). This study will align with the current strategy to integrate checkpoint blockade (nivolumab) into the treatment of cHL.

Study Population:

Males and females, 5 through 30 years of age, with confirmed cHL, excluding nodular lymphocyte-predominant cHL, after failure of or non-response to first-line therapy. Participants > 16 years of age must have a Karnofsky performance level ≥ 50%, and participants ≤ 16 years of age must have a Lansky performance level ≥ 50. Participants who previously received an allogeneic and/or ASCT for cHL are excluded, as are participants with prior exposure to anti-PD1, anti-PDL1, anti-PD-L2, anti CD137, or anti-CTLA-4 antibodies, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
R1 (Low Risk) Cohort: To describe the complete metabolic response (CMR) rate prior to RT and event-free survival (EFS) rate at 3 years, as assessed by blinded independent central review (BICR), using Lugano 2014 response criteria.	**R1 Cohort: CMR rate at any time prior to RT and EFS rate at 3 years** • The CMR rate is defined as the proportion of all response-evaluable participants who, assessed by the BICR, achieve best response of CMR using Lugano 2014 criteria. • EFS is the time from the date of first treatment to the earliest occurrence of composite events including the following: – High-dose chemotherapy followed by autologous stem cell transplant (HDCT/ASCT) – Disease progression per Lugano (2014) – Failure to achieve CMR after 4 cycles of N+Bv and 2 cycles of Bv+B – Secondary malignancy – Death due to any cause • Participants who did not have an "event" will be censored at the last adequate tumor assessment. Participants who start subsequent anticancer therapy (that is not part of HDCT/ASCT) without a prior reported "event" will be censored at the last tumor assessment prior to or on the day of the subsequent anticancer therapy. • Other definitions of EFS, employing somewhat different censoring rules, may be added as sensitivity analyses.
R2 (Standard Risk) Cohort: To describe the complete metabolic response (CMR) rate prior to HDCT/ASCT by BICR, using Lugano 2014 response criteria	**R2 Cohort: CMR rate at any time prior to HDCT/ASCT** • The CMR rate is defined as the proportion of all response-evaluable participants who, assessed by the BICR, achieve best response of CMR using Lugano 2014 criteria.
Secondary in Both R1 and R2 Cohorts:	
To assess overall response rate (ORR) (CMR + partial metabolic response [PMR]) using Lugano 2014 criteria of the low risk and standard risk cohorts following 4 cycles of nivolumab and brentuximab vedotin by BICR.	**ORR following 4 cycles of nivolumab + brentuximab vedotin treatment** • ORR is defined as the proportion of all response-evaluable participants who, assessed by the BICR, achieve a best response of CMR or PMR using Lugano 2014 criteria.

Objectives	Endpoints
To assess PFS rate at 3 years by BICR using Lugano 2014 criteria	**PFS rate at 3 years** • The analysis is performed when participants have been followed for 3 years. PFS is the time from the date of first treatment to the date of first documented disease progression by BICR or death. Participants who neither progress nor die will be censored at the last adequate tumor assessment. Participants who start subsequent anticancer therapy (that is not part of HDCT/ASCT Consolidation Therapy for R2 Cohort) without a prior reported progression or death will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy. • Other definitions of PFS, employing somewhat different censoring rules, may be added as sensitivity analyses.
Duration of Response (DOR) will be evaluated for those participants who achieved PMR or CMR by BICR as well as for those participants who achieved CMR by BICR prior to RT in the low risk cohort and for those participants who achieved CMR prior to HDCT/ASCT in the standard risk cohort.	**DOR** • DOR is defined as the time from first response (CMR or PMR) to the date of EFS (R1)/PFS (R2) event. For participants who did not have an event, the DOR will be censored on the date of their last tumor assessment. Participants who start subsequent anticancer therapy (that is not part of HDCT/ASCT) without a prior reported EFS/PFS event will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy.
To evaluate efficacy as assessed by investigators using LUGANO (2014) response criteria.	**All efficacy endpoints above, per investigator assessments** R1 cohort: CMR rate prior to RT and EFS at 3 years R2 cohort: CMR rate prior to HDCT/ASCT Both R1 and R2 cohorts: ORR following 4 cycles of N+Bv treatment, PFS rate at 3 years, and DOR.
To describe the toxicity of nivolumab + brentuximab in combination in pediatric and young adult participants with relapsed or refractory classical Hodgkin's lymphoma (cHL) after failure of first-line treatment.	**Toxicity/Safety** Endpoints are serious and non-serious AEs, clinical laboratory tests (hematology, chemistry, urinalysis), vital sign measurements, etc.

Objectives	Endpoints
Exploratory	
• To assess overall survival (OS) in all treated participants in the SR and LR cohorts, respectively. • Association of biomarker levels with response including ORR, PFS, and OS.	• OS is defined as the time from the date of first dose of study drug until the date of death for any reason. If the participant is alive or the vital status is unknown, the participant will be censored at the date the participant was last known to be alive.
• To assess changes in biomarkers in the peripheral blood, such as soluble factors, immune cells, and vaccinated antibody concentrations.	• To assess biomarkers in the tumor tissue, such as PD-L1 expression, 9p24.1 copy number alteration, and tumor infiltrating lymphocytes and their association with response. • To summarize changes in biomarker levels over time (see protocol Section 9.8).
• To characterize pharmacokinetics (PK) of nivolumab and brentuximab following combination therapy.	• Serum samples will be collected to characterize PK of nivolumab and brentuximab.
• To characterize the immunogenicity of nivolumab and brentuximab following combination therapy.	• Samples will be evaluated for the presence of anti-drug antibody.
• To evaluate participant-reported general health status and cancer-specific quality of life (QoL).	• General health status as assessed by the EQ-5D-3L, and cancer-specific QoL as assessed by the FACT-Lym
• To investigate the effect of 4 potential risk factors on EFS and ORR.	• See definition of EFS and ORR above (see risk factors in protocol Section 3.1)
• Implementation of LYRIC 2016 for efficacy assessments.	• The same efficacy variables detailed above and measured for LUGANO 2014 will be explored for LYRIC 2016.

Overall Design:

Risk Stratification Algorithm			
Stage at Initial Diagnosis	**Time to Relapse (from end of therapy)**	**B symptoms or extranodal disease at relapse, extensive disease where radiation therapy was contraindicated at relapse, or relapse in a prior radiation field**	**Relapse Risk Category**
IA, IIA	≥ 12 months	No	**R1 Cohort: Low Risk**
	3-12 months (≤ 3 cycles and no RT)		
IB, IIB, IIIA	> 12 months	No	
All Others			**R2 Cohort: Standard Risk**

CA209744 is a Phase 2, open-label study of N+Bv for children and young adults with relapsed/refractory cHL. Participants who do not achieve CMR after 4 cycles of N+Bv will receive Bv+B to help achieve CMR. There are 2 treatment cohorts: one with participants at low risk relapse (R1 cohort), and one with participants at standard risk relapse (R2 cohort) (Table 5.1-1 and Figure 5.1-1).

- R1 cohort will receive N+Bv for 2 cycles (6 weeks) followed by Tumor Assessments (TA). Participants with radiographic progression, as assessed by Investigator (per Appendix 6) at Cycle 2 N+Bv, will be taken off study treatment and enter follow-up (unless treatment beyond progression is approved by the Bristol-Myers Squibb (BMS) Medical Monitor, per Section 8.1.2). All other participants will receive 2 additional cycles of N+Bv study therapy (total 4 cycles = 12 weeks).
  - Participants who have a CMR, as assessed by BICR, after a total of 4 cycles (12 weeks) of N+Bv will receive an additional 2 cycles of treatment of N+Bv (for a total of 6 cycles [18 weeks]), followed by Radiation Therapy (RT), per institutional guidelines (See Appendix 8: Radiotherapy Guidelines for R1 Cohort further recommendations).
  - Participants without a CMR after 4 cycles of N+Bv, as assessed by BICR, will receive 2 cycles of Bv+B; participants who achieve CMR after these 2 cycles will proceed with RT, per institutional guidelines (See Appendix 8: Radiotherapy Guidelines for R1 Cohort further recommendations).
  - Participants who have radiographic progression after cycle 4 N+Bv, as assessed by BICR, (unless Treatment Beyond Progression is approved by BMS Medical Monitor, per Section 8.1.2 of the protocol) or those who do not achieve CMR, as assessed by BICR, after 2 cycles of Bv+B will be taken off study treatment and enter follow-up.
- R2 cohort will receive N+Bv for 2 cycles (6 weeks), followed by TA. Participants with radiographic progression, as assessed by Investigator (per Appendix 6) at Cycle 2 N+Bv, will be taken off study treatment and enter follow-up (unless Treatment Beyond Progression is

approved by BMS Medical Monitor, per Section 8.1.2). All other participants will receive 2 additional cycles of N+Bv study therapy (total 4 cycles = 12 weeks).

- Participants who have CMR, as assessed by BICR, after a total of 4 cycles of N+Bv will proceed with HDCT/ASCT (performed per institutional guidelines).
  - Participants with CMR will have the option to receive up to two additional cycles of N+Bv if their HDCT/ASCT has to be postponed for any reason (this requires prior BMS Medical Monitor approval).
- Participants without a CMR, as assessed by BICR, after 4 cycles of N+Bv will receive 2 cycles of Bv+B.
  - Participants in CMR, as assessed by BICR, after 2 cycles of Bv+B will receive HDCT/ASCT (performed per institutional guidelines).
  - Participants without CMR as assessed by BICR will have an option to receive 2 additional cycles of Bv+B (this requires prior BMS Medical Monitor approval). If these participants attain CMR, as assessed by BICR, they will proceed with HDCT/ASCT (performed per institutional guidelines).
  - Participants with CMR will have the option to receive up to two additional cycles of B+Bv if their HDCT/ASCT has to be postponed for any reason (this requires prior BMS Medical Monitor approval).
- Participants who have radiographic progression after cycle 4 N+Bv, as assessed by BICR, during study treatment (unless Treatment Beyond Progression is approved by BMS Medical Monitor, per Section 8.1.2 of the protocol) or those who do not achieve CMR, as assessed by BICR, after final cycle of Bv+B will be taken off study treatment and enter follow-up.

R1 and R2 Cohort Follow-up Visits will occur Day 30, and then synched up with tumor assessments Day 100 and then 6, 12, 18, 24, and 36 months Post-Consolidation Therapy/Treatment Discontinuation. Once participants reach the survival follow-up phase, either in-person visits or documented telephone calls/email correspondence to assess the participant's status are acceptable. Tumor assessments are required for participants who have not radiographically progressed, per BICR, as per Table 2-3 and Section 9.1 of the protocol. If Investigator tumor assessment = CMR for a treatment related-decisions time point (Cycle 4 Induction, or Cycle 2 or 4 Intensification, as applicable) but BICR assessment differs, and as a result study treatment is discontinued and HDCT/ASCT (for R2 Cohort) and RT (for R1 Cohort) is performed in follow-up, tumor assessments should continue to be provided until radiographic progression per Investigator Assessment, per LUGANO 2014. For these cases, it is recommended to follow the same scan frequency and modality as when BICR assessment = CMR (per table 2.-4: 100 days and then 6, 12, 18, 24, and 36 months post-Consolidation Therapy/Treatment Discontinuation), but at a minimum the Month 36 tumor assessment is required.

Number of Participants:

Approximately 100 participants were planned to be enrolled, with approximately 80 treated (40 in each cohort), in consideration of potential screening failures or those who are treated but not response-evaluable. A minimum of 25 treated participants (R1: 5, R2: 20) will be pediatric (5 to < 18 years old), unless BMS Study Team instructs otherwise.

The protocol reflected a proposal to include a total of 100 enrolled participants to obtain 80 treated participants (age 5 to < 30), with 40 participants per cohort, and a minimum of 25 pediatric participants (age 5 to < 18). [redacted] Although the proposed sample size in the protocol was not intended to support statistical hypothesis testing, 90% confidence intervals (CI), corresponding to a range of observed response rates, were provided to illustrate the precision of estimation (See Table 10.3.1-1).

Study CA209744 is being conducted in 11 countries worldwide (although only 10 of them have been able to recruit participants) with 75 activated sites in total; however, only 20% of the totality of the sites recruited R1 participants. [redacted]

In light of above, the protocol is being modified to reduce the total number of participants from 80 to 72 (total number of treated participants enrolled R1 = 28 and R2 = 44) [redacted] with an overall sizeable population that can support a future assessment of benefit/risk. Assuming 24 responders out of 28 R1 participants, the exact 2-sided 90% confidence interval would be 70.23% to 94.97%.

See Section 10 for details on statistical considerations and sample size determination.

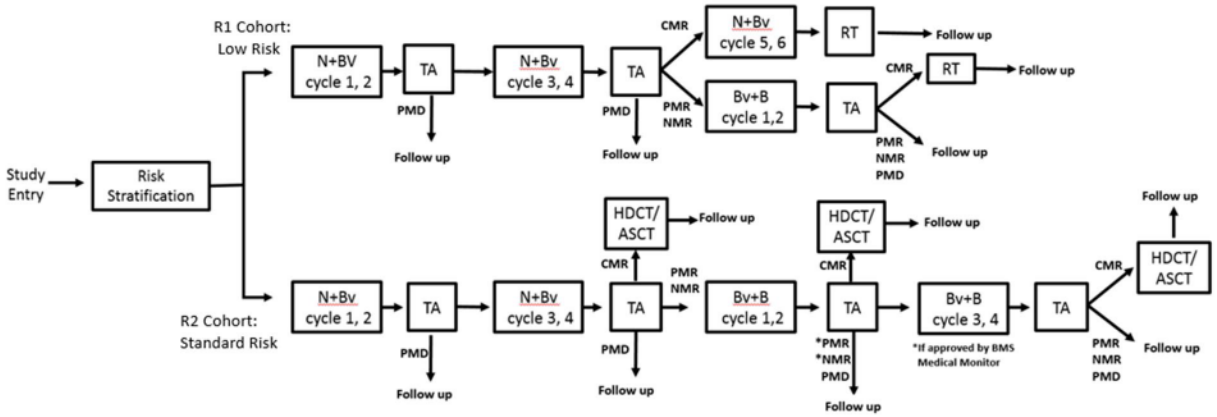
Treatment Arms and Duration:

Study Treatment:

Study Treatments for CA209744					
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[a]	100 mg (10 mg/mL)	IMP	Open label	10 mL Vial/ Clear to opalescent colorless to pale yellow liquid. May contain particles.	2 to 8°C. Protect from light and freezing
Brentuximab Vedotin powder for solution for Injection[b]	50 mg	IMP	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
Bendamustine powder for solution for Injection[b] OR Bendamustine Solution for Injection[b]	25 mg or 100 mg OR 100 mg/4 ml (25 mg/ml)	IMP	Open label	White to off-white lyophilized powder in a single-dose vial for reconstitution OR Clear and colorless to yellow ready-to-dilute solution	15 to 25°C (powder) OR 2 to 8C (solution). Protect from light

[a] May be labeled as either "BMS-936558-01" or "Nivolumab."

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC)



TA= Tumor Assessments
CMR= Complete Metabolic Response
PMR= Partial Metabolic Response
NMR= No Metabolic Response
PMD= Progressive Metabolic Disease

Note: R2 patients who attain a CMR anytime after Cycle 4, N+BV will proceed with HDCT/ASCT.

2. SCHEDULE OF ACTIVITIES

Screening assessments for this study are summarized in Table 2-1, induction IMP treatment and post-IMP therapy procedures in Table 2-2, intensification IMP treatment and post-IMP therapy procedures in Table 2-3, follow-up assessments in Table 2-4, biomarker sampling schedule in Table 2-5, and pharmacokinetic (PK) and immunogenicity sampling schedule in Table 2-6.

Table 2-1: Screening Assessments (CA209744)

Visit	Screening (Day -28 to -1)	Screening (Day -14 to -1)	Screening (Day -1)	Screening Notes
Eligibility Assessments				
Informed Consent	X			
Inclusion / Exclusion Criteria	X			
Medical History	X			
Prior Systemic Therapy	X			
Karnofsky / Lansky Performance Status (PS)		X		Karnofsky ≥ 50 for participants > 16 years of age or Lansky ≥ 50 for participants ≤ 16 years of age (Appendix 5)
IRT Participant Assignment / Cohort Assignment	X			Contact IRT for participant number assignment (and cohort assignment, per Table 5.1-1- Risk Stratification Algorithm), when informed consent is obtained. Triggers drug shipment.
Safety Assessments				
Complete Physical Examination (PE)		X		Skin & mucus membranes, Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen, liver), and neurological examination
Physical Measurements		X		Height, weight, RR (respiration rate), and BSA (body surface area)
Vital Signs		X		Temperature, BP, HR
Pregnancy Test (serum or urine)			X	Serum or urine results within 24 hours prior to first dose, for WOCBP only.
Concomitant Medications		X		
Assessment of Signs and Symptoms		X		
Monitor for Serious Adverse Events	X			
CBC with Differential and Platelets		X		

Table 2-1: Screening Assessments (CA209744)

Visit	Screening (Day -28 to -1)	Screening (Day -14 to -1)	Screening (Day -1)	Screening Notes
Chemistry (excluding LFTs)		X		Uric acid, BUN or serum urea level, creatinine, Ca, Mg, K, Cl, Na, phosphate, amylase, lipase, glucose, and LDH
LFT assessments		X		AST, ALT, total bilirubin, alkaline phosphatase
Thyroid Function Tests		X		Thyroid Stimulating Hormone (TSH) (reflex to free T3, free T4 for abnormal TSH result),
Urinalysis		X		Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH
Serology	X			Hepatitis B surface antigen, and hepatitis C antibody or HCV ribonucleic acid. Testing for HIV must be performed at sites, where mandated locally.
Efficacy				
Tumor Assessments FDG PET-CT or PET-MRI, or FDG-PET with CT/MRI	X			To be performed within 28 days prior to first dose. FDG-PET whole-body (top-of-head to mid-thighs) and all known/suspected sites of disease will be used for metabolic response assessment. If the CT performed as part of a FDG PET-CT is of comparable quality to a diagnostic CT (with IV contrast preferred) then the adequate-dose CT of FDG PET-CT can be used for tumor measurements. If low dose CT is used for PET-CT, perform contrast enhanced CT neck, chest, abdomen-pelvis and other known or suspected sites of disease with IV contrast. Gadolinium enhanced MRI is acceptable if CT contrast is contraindicated. Non-contrast MRI/CT is acceptable if CT and MR contrasts are contraindicated. If CNS involvement is suspected, perform Brain MRI without and with Gadolinium contrast at baseline to exclude subjects with brain involvement. See Section 9.1 for further details.
Biomarker Sampling	See Note			See Inclusion Criteria 2c and Table 2-5 for details

Table 2-2: Induction IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Induction Phase (N+Bv)											Consolidation Phase	
Visit	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5D1, C6D1[c]**	**C5D15, C6D15[c]**	**Post-IMP Therapy**	**Notes**
Event					**Day 15[a]**				**Day15[b]**				**+/- 7 day window for C2D15 Induction Phase, per footnote a** **+/- 3 day window for all other visits**
Safety Assessments													
Karnofsky/ Lansky Performance Status	X	X	X	X	X	X	X	X	X	X	X	X[d]	Karnofsky PS for participants > 16 years and Lansky PS for participants ≤ 16 years of age (Appendix 5)
Targeted Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X[d]	Skin & mucus membranes, Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen, liver), and neurological examination
Physical Measurements	X	X	X	X	X	X	X	X	X	X	X	X[d]	Weight
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X[d]	Temperature, BP, HR
CBC with Differential and Platelets		X	X	X	X	X	X	X	X	X	X	X[d]	Collected within 3 days prior to each dose

Table 2-2: Induction IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Induction Phase (N+Bv)											Consolidation Phase	
Visit	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5D1, C6D1[c]**	**C5D15, C6D15[c]**	**Post-IMP Therapy**	**Notes**
Event					**Day 15[a]**				**Day15[b]**				**+/- 7 day window for C2D15 Induction Phase, per footnote a** **+/- 3 day window for all other visits**
Chemistry (excluding LFTs)		X	X	X	X	X	X	X	X	X	X	X[d]	Uric acid, BUN or serum urea level, creatinine, Ca, Mg, K, Cl, Na, phosphate, amylase, lipase, glucose, and LDH Collected within 3 days prior to each dose
LFT assessments		X	X	X	X	X	X	X	X	X	X	X[d]	AST, ALT, and total bilirubin Collected within 3 days prior to each dose
Thyroid Function Tests (TFTs)				X				X		X		X[d]	TSH (reflex to free T3 and free T4 if abnormal result) to be performed at every other cycle
Urinalysis		X	X	X	X	X	X	X	X	X	X	X[d]	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH
Pregnancy Test (serum or urine)	X	X		X		X		X		X		X[d]	Serum or urine within 24 hours prior to first dose and then D1 of every cycle (and D8 for Cycle 1 N+Bv), for WOCBP.

Table 2-2: Induction IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Induction Phase (N+Bv)											Consolidation Phase	
Visit	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5D1, C6D1[c]**	**C5D15, C6D15[c]**	**Post-IMP Therapy**	**Notes**
Event					**Day 15[a]**				**Day15[b]**				**+/- 7 day window for C2D15 Induction Phase, per footnote a** **+/- 3 day window for all other visits**
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Monitor for Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[d]	

Table 2-2: Induction IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Induction Phase (N+Bv)											Consolidation Phase	
Visit	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5D1, C6D1[c]**	**C5D15, C6D15[c]**	**Post-IMP Therapy**	**Notes**
Event					**Day 15[a]**				**Day15[b]**				**+/- 7 day window for C2D15 Induction Phase, per footnote a** **+/- 3 day window for all other visits**
Efficacy													
Tumor Assessments FDG PET-CT or PET-MRI, or FDG-PET with CT/MRI					X				X				FDG-PET whole-body (top-of-head to mid-thighs) and all known/suspected sites of disease will be used for metabolic response assessment, until the participant is in BICR assessed CMR, post-4 cycles of N+Bv. CT/MRI for N/C/A/P and other known or suspected sites of disease. See guidelines from Table 2.-1 and Section 9.1 Participants who experience PD/PMD per BICR, will come off treatment and enter follow-up, unless treatment beyond progression is approved per Section 5.1 and Section 8.1.2
Biomarker Sampling													See Table 2-5 for details
PK and Immunogenicity Sampling													See Table 2-6 for details

Table 2-2: Induction IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Induction Phase (N+Bv)											Consolidation Phase	
Visit	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5D1, C6D1[c]**	**C5D15, C6D15[c]**	**Post-IMP Therapy**	**Notes**
Event					**Day 15[a]**				**Day15[b]**				**+/- 7 day window for C2D15 Induction Phase, per footnote a** **+/- 3 day window for all other visits**
Outcomes Research Assessments													
EQ-5D-3L and FACT-Lym	X-pre-dose				X				X				Complete for participants ≥ 12 years old. (See Section 9.9.1)
Medical Resource Utilization	X	X	X	X	X	X	X	X	X	X	X	X[d]	See Section 9.9
Pre-medications				X		X		X		X			See Section 7.1.1 for prophylactic premedication requirements for combination therapy
Study Drug Administration													
IRT Treatment Assignment	X	X		X		X		X		X			Contact IRT to assign IMP treatment
Nivolumab[e]		X		X		X		X		X			See Section 7
Brentuximab Vedotin[e]	X			X		X		X		X			See Section 7

Table 2-2: Induction IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Induction Phase (N+Bv)											Consolidation Phase	
Visit	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5D1, C6D1[c]**	**C5D15, C6D15[c]**	**Post-IMP Therapy**	**Notes**
Event					**Day 15[a]**				**Day15[b]**				**+/- 7 day window for C2D15 Induction Phase, per footnote a** **+/- 3 day window for all other visits**
Radiation Therapy (RT)												X	For R1 Cohort, with BICR assessed CMR and Completion of Induction, Cycle 6.
HDCT/ASCT												X	For R2 Cohort with BICR assessed CMR, after Cycle 4. If additional treatment is required prior HDCT/ASCT for BICR assessed CMR post 4 cycles of N+Bv; it should be a cycle of N+Bv. Follow same procedures as C5D1,C6D1 (N+Bv) Induction Phase. See Section 5.1.

[a] Participants who experience progressive metabolic disease (PMD), per Appendix 6 as assessed by Investigator at Cycle 2, will come off treatment and enter follow-up, unless MM approves Treatment Beyond Progression (TBP). Cycle 3, N+Bv does not require treatment delay while awaiting results, therefore C2 Induction Tumor Assessment has +/- 7 day window.

[b] R1 participants with Complete Metabolic Response (CMR), assessed by BICR ,will have 2 additional cycles of N+Bv prior to RT and then enter Follow-up. R2 participants with CMR, assessed by BICR,will proceed to have HDCT/ASCT and then enter Follow-up. Participants with Progressive Metabolic Disease (PMD), assessed by BICR, will come off treatment and enter Follow-Up, unless MM approves TBP. R1 or R2 participants with Partial Metabolic Response/No Metabolic Response (PMR/NMR) assessed by BICR, or BMS MM approved TBP (Section 8.1.2), will enter Intensification Phase (Table 2-3).

[c] If applicable: R1 cohort- N+Bv Induction Phase (Cycles 5 and 6) required post-CMR (assessed by BICR) at Cycle 4 Radiographic Assessment. R2 Cohort- If Cycle 4 Induction Tumor Assessment is CMR (assessed by BICR) and Cycles 5 and 6 are approved by BMS Medical Monitor, due to delay in HDCT/ASCT.

[d] Safety Assessments and Medical Resource Utilization should be collected, within 3 days, prior to Consolidation Therapy.

[e] Brentuximab vedotin will be administered at C1D1 and nivolumab will be administered on C1D8. At all subsequent cycles, both study drugs will be administered on the same day. Brentuximab vedotin will be administered first followed by a minimum 30-minute rest. Nivolumab will be administered second. IRT should be contacted within 3 days prior to study drug administration to receive vial assignment.

Table 2-3: Intensification IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Intensification Phase (Bv+B)				Consolidation Phase	
Visit	**C1D1, C2D1**	**C2 D15**	***C3D1, C4D1, C5D1, C6D1**	***C4D15**	**Post-IMP Therapy**	**Notes**
Event	**R1/R2 w/o CMR[a]**	**Day 15**	***R2, ONLY w/ MM approval[b]**	***R2, ONLY if applicable**		**+/- 3 day window for all visits**
Safety Assessments						
Karnofsky/ Lansky Performance Status	X		X		X[c]	Karnofsky PS for participants > 16 years and Lansky PS for participants ≤ 16 years of age (Appendix 5)
Targeted Physical Examination	X		X		X[c]	Skin & mucus membranes, Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen, liver), and neurological examination
Physical Measurements	X		X		X[c]	Weight
Vital Signs	X		X		X[c]	Temperature, BP, HR
CBC with Differential and Platelets	X		X		X[c]	Collected within 3 days prior to each dose
Chemistry (excluding LFTs)	X		X		X[c]	Uric acid, BUN or serum urea level, creatinine, Ca, Mg, K, Cl, Na, phosphate, amylase, lipase, glucose, and LDH Collected within 3 days prior to each dose
LFT assessments	X		X		X[c]	AST, ALT, and total bilirubin Collected within 3 days prior to each dose

Table 2-3: Intensification IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Intensification Phase (Bv+B)				Consolidation Phase	
Visit	**C1D1, C2D1**	**C2 D15**	***C3D1, C4D1, C5D1, C6D1**	***C4D15**	**Post-IMP Therapy**	**Notes**
Event	**R1/R2 w/o CMR[a]**	**Day 15**	***R2, ONLY w/ MM approval[b]**	***R2, ONLY if applicable**		**+/- 3 day window for all visits**
Thyroid Function Tests (TFTs)	X		X		X[c]	TSH (reflex to free T3 and free T4 if abnormal result) to be performed at every other cycle
Urinalysis	X		X		X[c]	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH
Pregnancy Test (serum or urine)	X		X		X[c]	Serum or urine within 24 hours prior to first dose and then D1 of every cycle (and D8 for Cycle 1 N+Bv), for WOCBP.
Concomitant Medications	X		X		X[c]	
Monitor for Adverse Events	X		X		X[c]	
Efficacy						
Tumor Assessments FDG PET-CT or PET-MRI, or FDG-PET with CT/MRI		X		X		FDG-PET whole-body (top-of-head to mid-thighs) and all known/suspected sites of disease will be used for metabolic response assessment, until the participant is in BICR assessed CMR. CT/MRI for N/C/A/P and other known or suspected sites of disease. See guidelines from Table 2-1 and Section 9.1 Participants who experience PD/PMD, per BICR, will come off treatment and enter follow-up, unless treatment

Table 2-3: Intensification IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Intensification Phase (Bv+B)				Consolidation Phase	
Visit	**C1D1, C2D1**	**C2 D15**	***C3D1, C4D1, C5D1, C6D1**	***C4D15**	**Post-IMP Therapy**	**Notes**
Event	**R1/R2 w/o CMR[a]**	**Day 15**	***R2, ONLY w/ MM approval[b]**	***R2, ONLY if applicable**		**+/- 3 day window for all visits**
						beyond progression is approved per Section 5.1 and 8.1.2.
Biomarker Sampling	See Table 2-5 for details					
PK and Immunogenicity Sampling	See Table 2-6 for details					
Outcomes Research Assessments						
EQ-5D-3L and FACT-Lym		X		X		Complete for participants ≥ 12 years old. (See Section 9.9.1)
Medical Resource Utilization	X		X		X[c]	See Section 9.9
Pre-medications	X		X			See Section 7.1.1 for prophylactic premedication requirements for combination therapy
Study Drug Administration						
IRT Treatment Assignment	X		X			Contact IRT to assign IMP treatment
Brentuximab Vedotin	X		X			See Section 7
Bendamustine	X		X			Delivered on Days 1 and 2 of 21-day cycle (See Section 7)
Radiation Therapy (RT)					X	For R1 Cohort, with CMR, assessed by BICR, upon completion of Intensification Phase.

Table 2-3: Intensification IMP Treatment and Post-IMP Therapy (RT, HDCT/ASCT) Procedures (CA209744)

	Intensification Phase (Bv+B)				Consolidation Phase	
Visit	**C1D1, C2D1**	**C2 D15**	***C3D1, C4D1, C5D1, C6D1**	***C4D15**	**Post-IMP Therapy**	**Notes**
Event	**R1/R2 w/o CMR[a]**	**Day 15**	***R2, ONLY w/ MM approval[b]**	***R2, ONLY if applicable**		**+/- 3 day window for all visits**
HDCT/ASCT					X	For R2 Cohort with CMR, assessed by BICR, upon completion of Intensification Phase. If additional treatment is required prior HDCT/ASCT for BICR assessed CMR post 2-4 cycles of B+Bv; it should be a cycle of B+Bv.

[a] Bv+B Intensification Phase (Cycles 1 and 2) applicable for participants with PMR/NMR (assessed by BICR) or MM approved TBP per Section 8.1.2 at Cycle 4 Induction Period Radiographic Assessment.

[b] R2 participants who do not have CMR (assessed by BICR) after 2 cycles of Bv+B may receive 2 additional cycles (Cycles 3 and 4), upon approval from BMS Medical Monitor. R2 Participants who achieve CMR after Cycle 2 or 4 Tumor Assessment, per BICR but have a delay in Consolidation Therapy may receive up to 2 additional cycles of Bv+B with approval from BMS MM. (See Section 5.1)

[c] Safety Assessments and Medical Resource Utilization should be collected, within 3 days, prior to Consolidation Therapy.

Table 2-4: Follow-Up Assessments (CA209744)

Visit	Day 30	Day 100	Response / Survival / FU	Follow-up Notes
Event	**FU 1**	**FU 2**		
Visit Window	**+/- 7 days**	**+/- 7 days**	**+/-14 days**	
Safety Assessments				
Karnofsky/Lansky Performance Status	X			Karnofsky PS for participants > 16 years and Lansky PS for participants ≤ 16 years of age (Appendix 5)
Targeted Physical Examination	X	X		Skin & mucus membranes, Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen, liver), and neurological examination
Monitor for Adverse Events	X	X		Adverse event assessments will continue until all related AEs have resolved, returned to baseline, or are deemed irreversible. (See Section 9.2)
CBC with Differential and Platelets	X	X if FU1 results abnormal		
Chemistry (excluding LFTs)	X	X if FU1 results abnormal		Ca, Mg, K, Cl, Na, amylase, lipase, glucose, and LDH
LFT assessments	X	X if FU1 results abnormal		AST, ALT, and total bilirubin
Thyroid Function Tests (TFTs)	X	X if FU1 results abnormal		TSH (reflex to free T3 and free T4 if abnormal result) to be performed at every other cycle
Urinalysis	X	X if FU1 results abnormal		Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH
Pregnancy Test (serum or urine)	X	X		For WOCBP Only
Efficacy Assessments				
Subsequent Anti-Cancer Therapy	X	X	X	

Table 2-4: Follow-Up Assessments (CA209744)

Visit	Day 30	Day 100	Response / Survival / FU	Follow-up Notes
Event	**FU 1**	**FU 2**		
Visit Window	**+/- 7 days**	**+/- 7 days**	**+/-14 days**	
Other Primary Malignancies	X	X	X	
Tumor Assessments	See Note			After the subjects achieve BICR assessed CMR: CT/MRI of neck, chest, abdomen, pelvis, and other known or suspected sites of disease; performed at 100 days and then 6, 12, 18, 24, and 36 months post-Consolidation Therapy/Treatment Discontinuation or if progression is suspected based on clinical signs and symptoms. If the results of the CT or MRI is equivocal, follow-up FDG PET may be obtained for clarification. Subjects with BICR assessed PMR/NMR upon completion of study treatment will provide tumor assessments during follow-up at the same time intervals specified (or at a minimum, per Standard of Care). See Section 5.1 and 9.1 for further details.
Biomarker Sampling	See Note			See Table 2-5 for details
PK and Immunogenicity Sampling	See Note			See Table 2-6 for details
Outcomes Research Assessments				
EQ-5D-3L	See Note			Collected at first follow-up tumor assessment, then every 6 months for 2 years
Medical Resource Utilization	X	X		See Section 9.9
Survival Status	X	X	X	

Follow-up Visits will occur Day 30, Day 100, and then 6, 12, 18, 24, and 36 months Post-Consolidation Therapy/Treatment Discontinuation; then Survival FU Visits continue yearly thereafter, until study completion. Once participants complete FU1 and 2, either in-person visits or documented telephone calls/email correspondence to assess the participant's status are acceptable.

Table 2-5: Biomarker Sampling Schedule (CA209744)

Visit	Event	Visit Window	Tumor Biopsy[a]	Soluble Biomarker, Serum	Soluble Biomarker, Plasma	Peripheral Blood Immune Cell Subsets	SNP	Visit Notes
Screening (Day -28 to -1)			X					Formalin-fixed paraffin-embedded (FFPE) tumor block or a minimum of 20 slides.
Cycle 1 Day 1	Predose (Bv)	within 3 days prior		X	X	X	X	
Cycle 2 Day 1	Predose (N+Bv)	within 3 days prior		X	X	X		
Cycle 3 Day 1	Predose (N+Bv)	within 3 days prior		X	X[b]	X		
Cycle 4 Day 1	Predose (N+Bv)	within 3 days prior		X	X	X		
Cycle 4 Day 15		+/- 3 days		X	X	X		For Cycle 4/Day 15, Induction Phase Tumor Assessment Only
When Clinically Indicated			X optional					All participants may volunteer to undergo tumor biopsies at any time during therapy if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy is encouraged.

Table 2-5: Biomarker Sampling Schedule (CA209744)

Visit	Event	Visit Window	Tumor Biopsy[a]	Soluble Biomarker, Serum	Soluble Biomarker, Plasma	Peripheral Blood Immune Cell Subsets	SNP	Visit Notes
Upon Progression			X optional	X optional	X optional	X optional		Samples from participants that have confirmed progression are optional.
FU 1 - Day 30	Post Last Treatment (+/- 7 days)	within 3 days prior		X	X	X		Participants will enter Follow-up Post-Consolidation Therapy/Treatment Discontinuation, as applicable.

[a] Participants may undergo tumor biopsy during screening or submit archival tumor tissue collected prior to obtaining informed consent. Relapsed participants must have a recent biopsy sample within 90 days from collection of informed consent or obtained during screening. Rare cases may allow samples > 90 days from collection of the informed consent. Refer to Section 9.8.1 for further details. In order to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period. Note: Under special circumstances, if tumor tissue provided is deemed inadequate, contact the Medical Monitor for approval to begin treatment.

[b] If the participant is < 18Kg, Cycle 3 Day 1 Soluble Biomarker, Plasma Sample is not required. Investigators should follow their blood volume institutional guidelines for blood volume collection.

Table 2-6: PK and Immunogenicity Sampling Schedule (CA209744)

Visit	Time Relative to Dosing	Event	Visit Window	Bv PK Blood Sample Collection (serum and plasma/MMAE)	Bv Immunogenicity (ADA) Blood Sample Collection	Nivolumab PK Blood Sample Collection	Nivolumab Immunogenicity (ADA) Blood Sample Collection
Cycle 1 Day 1	0:00	Predose (Bv) [a]		X	X		
Cycle 1 Day 8	0:00	Predose (N) [a]				X	X
Cycle 2 Day 1	0:00	Predose (N+Bv) [a, b]		X	X	X	X
Cycle 3 Day 1	0:00	Predose (N+Bv) [a, b]		X	X	X	X
Cycle 4 Day 1	0:00	Predose (N+Bv) [a, b]		X	X	X	X
FU 2 - Day 100		Post Last Treatment (+/- 7 days) [c]	+/- 7 days	X	X	X	X

[a] Pre-dose samples should be taken just prior to the administration (preferably within 30 min, but not sooner than 24 hours day of dosing). If study medication dose should be delayed, PK/ADA collection should be done pre-dose the day dosing resumes. However, if study medication dose is delayed and a pre-dose sample was already collected, there is no need to collect an additional pre-dose sample.

[b] It is acceptable to collect the pre-dose sample for nivolumab and brentuximab vedotin at the same time, as long as it is collected prior to the start of the infusion.

[c] Participants will enter follow-up Post-Consolidation Therapy/Treatment Discontinuation, as applicable.

3. INTRODUCTION

3.1 Study Rationale

Classical Hodgkin lymphoma (cHL) is characterized by rare malignant Reed Sternberg cells surrounded by an extensive but ineffective inflammatory immune cell infiltrate.[1,2,3] Recent work has demonstrated that chromosome 9p24.1/CD274 (PD-L1) PDCD1LG2 (PD-L2) genetic alterations increase the PD-1 ligands expression, and are described as a defining feature of cHL.[4] The 9p24 amplicon also contains JAK2, and copy number-dependent JAK2-signal transducers and activators of transcription which can further increase PD-1 ligand expression.[2]

These genetic alterations commonly found in cHL indicate that PD-1 blockade is a reasonable target in this disease. In addition, Epstein-Barr virus (EBV) infection can increase expression of PD-1 ligands in EBV-positive Hodgkin lymphomas (HLs).[5] This study will align with the current strategy to integrate checkpoint blockade (nivolumab) into the treatment of cHL.

Hodgkin lymphoma is divided into 2 broad pathological categories: classical cHL (including lymphocyte-rich classical, nodular sclerosing, mixed cellularity, and lymphocyte depleted subtypes) and nodular lymphocyte predominant cHL. Hodgkin lymphoma has a bimodal age distribution in highly industrialized societies and around the world, with peak incidence at 15-34 years of age and again at 50-60 years. A significant proportion of cases occur in the pediatric age group, the majority of which present in adolescents, and a minority of the cases are seen in patients younger than 10 years of age.[6]

The treatment for both children and adults with cHL is the same: chemotherapy ± radiation therapy. The focus of pediatric cHL treatment regimens is the reduction of late toxicity while maintaining excellent outcomes. Therefore, treatment is risk based and response adapted. Treatment decisions for pediatric cHL are based on stratification into two risk groups (cohorts).

The standard chemotherapeutic regimens for first-line treatment in newly-diagnosed pediatric cHL vary between the US and Europe, making the direct comparison of outcomes from different studies difficult. The most common multi-agent regimens in the United States (US) are ABVE/ABVE-PC (adriamycin, bleomycin, vincristine, etoposide ± prednisone, cyclophosphamide) and BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisone, procarbazine). The most common multi-agent regimens in Europe are OPPA (vincristine, prednisone, procarbazine, adriamycin); OEPA (vincristine, etoposide, prednisone, adriamycin); and COPDAC (cyclophosphamide, vincristine, prednisone, dacarbazine). Several adverse risk factors have been identified to have prognostic significance in patients with recurrent or refractory cHL after failure of first-line therapy.[7] Time to initial treatment failure is a strong predictor of survival for patients.[8,9] Response to therapy prior to high-dose chemotherapy followed by autologous stem cell transplant (HDCT/ASCT) has also been recognized as an important prognostic factor.[10] The most predictive prognostic factors identified for pediatric patients with relapsing or refractory (R/R) cHL include primary progression or early relapse, chemotherapy-resistant disease at relapse, and the presence of disease prior to ASCT. Following a retrospective analysis of the CIBMTR database, consisting of participants median age 21 (3-29) years, 50% of whom were Stage I-II or

Stage III-IV at diagnosis, and received an ASCT between 1995-2010, 4 risk factors, all easily available at the time of ASCT, have been identified and can be used to predict outcome in children, adolescent, and young adult R/R cHL patients post ASCT.[11] These 4 risk factors (performance status < 90 vs. ≥ 90, time from diagnosis to relapse/refractory disease < 1 yr vs. ≥ 1 year, extranodal disease at the time of ASCT, and chemosensitivity), were identified as impacting PFS in this population.[11]

In pediatric adolescent and young adult studies, while prognostic factors are commonly used to stratify therapy, there has been variability in the risk stratification used by cooperative groups.[12] The EuroNet-PHL-C1 protocol stratified patients, depending on time of relapse. [13] Children's Oncology Group (COG) has proposed a comprehensive risk-stratified, response-based algorithm for treating children with relapsed and refractory cHL.[7] An aligned risk-stratified algorithm will be used to separate participants into the R1 vs R2 risk cohorts in the present protocol (Table 5.1-1). Participants with late relapse of low-stage disease will be stratified into the low-risk cohort and are predicted to have excellent outcomes with conventional chemotherapy or chemoradiotherapy.[14,15,16,17,18] Similarly, participants with early stage disease, who have early relapse after limited therapy (< 4 cycles of chemotherapy and no radiation) are also expected to have good outcomes with conventional chemotherapy. [19] Participants with early relapse, or extranodal disease, or B symptoms at relapse have worse prognosis and will be classified as standard risk participants.[20,21,22] For the standard risk cohort in this study, only participants who attain a complete metabolic response (CMR) to salvage therapy, previously identified as one of the strongest predictors of long-term outcome,[23,24] will proceed to HDCT/ASCT.

Disease status following salvage therapy is the most important prognostic factor for long-term outcome.[25,26,27] Functional imaging (FI) with fluorodeoxyglucose positron emission tomography (FDG-PET) scans has become important in measuring response to therapy and can serve as a marker of chemosensitive disease. Patients achieving a CMR after salvage chemotherapy have a long-term relapse-free survival of ~75% post-ASCT. In contrast, patients with evidence of residual disease prior to HDCT/ASCT have a long-term relapse-free survival that is only ~25%.[24]

Because results from salvage therapy influence long-term event-free survival (EFS) post-ASCT, it is important to develop well-tolerated regimens that increase complete response (CR) rates pre-ASCT.[28] There is currently no consensus or identified best salvage chemotherapy regimen in pediatric and adolescent patients with R/R HL. Several regimens have been used. These include the use of ifosfamide, carboplatin, and etoposide (ICE).[29] In Europe the current standard approach for retrieval regimen for pediatric patients is alternating IEP-ABVD. In order to reduce the long-term treatment-related events reported with ICE, COG has also explored other retrieval regimens, such as ifosfamide with vinorelbine (IV) on their AHOD00P1 protocol, or gemcitabine + vinorelbine (GV). More recently, AHOD0521 evaluated the addition of bortezomib, a proteasome inhibitor, to ifosfamide/vinorelbine IV.[30] Because of this variability, the comparison of outcomes between studies is difficult. The United Kingdom HD 3 trial reported the outcome of 80 children and adolescents aged < 18 years who had either primary refractory HL or relapsed after achieving

a first remission. All but 1 patient had chemotherapy alone as their primary treatment. Treatment at relapse was predominantly a combination chemotherapy plus involved field radiation therapy (IFRT) (N = 50; 63%). Salvage treatment amongst the remaining 30 patients consisted of chemotherapy alone (N = 19, 24%), IFRT (N = 6; 8%) or excision biopsy in the lymphocyte predominant subtypes (N = 3; 4%). Twenty-three patients (70%) achieved a CR following salvage. Forty-three patients (55%) underwent stem cell transplant. A total of 17/23 patients (74%) who were in CR at the end of salvage therapy and who did not receive ASCT are alive without relapse (median follow up time 105 months; range 53-128 months).[31] These results demonstrated that children can be cured with salvage therapy alone, reserving HDCT/ASCT for patients with either early relapse/primary resistant disease or poor response to salvage chemotherapy.[32,33,34,35]

Given that brentuximab vedotin and nivolumab both have documented high single-agent response rates in cHL and also work through distinct mechanisms of action, it is expected that 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. This study will evaluate the safety and antitumor activity of combination therapy with nivolumab + brentuximab vedotin (N+Bv) in a population of patients after failure of standard frontline chemotherapy. Participants not achieving an adequate response (CMR) following N+Bv will be further treated with brentuximab vedotin + bendamustine (Bv+B) before consolidation.

Rationale for Nivolumab + Brentuximab Vedotin

Most H/RS cells strongly express CD30, a member of the TNF cell receptor superfamily that has highly restricted expression in normal cells. Brentuximab vedotin has been shown to kill H/RS cells through the intracellular release of MMAE, disrupting the microtubule network and leading to G2/M cell cycle arrest and apoptosis. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved brentuximab vedotin for adult patients with cHL after failure of ASCT or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT. Post-ASCT maintenance therapy with brentuximab vedotin has recently been found to prolong PFS in adults with recurrent cHL.[36] The combination of N+Bv is currently being studied in a Phase 1/2 trial of adults with R/R cHL after failure of first-line therapy. This study is actively enrolling (ClinicalTrials.gov identifier: NCT02572167). In addition a Phase 1/2 trial of this combination in adults with CD30+ R/R NHL is also underway (ClinicalTrials.gov identifier: NCT02581631). In that study, the study team reviewed all available safety data of the 6 treated subjects that were enrolled in Cohort A during the DLT period. Based on the safety data available from these subjects and study NCT02572167 with similar combination in Hodgkin lymphoma, the study team recommended and endorsed the expansion of the study to Cohort B.

Rationale for Brentuximab Vedotin + Bendamustine

Brentuximab vedotin and bendamustine are highly active when administered as single agents to patients with R/R cHL (34% and 33% CR rates, respectively) and have manageable safety profiles.[37,38] As reported at the 2015 ASH meeting, in an ongoing Phase 1/2, single-arm, 2-stage,

open-label study evaluating the safety and efficacy of brentuximab vedotin in combination with bendamustine for the treatment of patients with primary refractory disease or in first relapse,[39] 55 patients with a median age of 36 years (range 19-79) were enrolled. Fifty-one percent of patients had relapsed disease and 49% of patients had primary refractory disease after frontline therapy. No dose-limiting toxicities were observed. The recommended dose of bendamustine in combination with brentuximab vedotin (1.8 mg/kg q3 wks) was 90 mg/m^2. The CR rate of the combination was 74% (39/53 patients evaluable for response) and the overall response rate (ORR) (CR and partial remission) was 93% (49/53 patients). The CR rate was 64% and 84% for refractory and relapsed patients, respectively. This regimen is well tolerated in the patient population from this study.[39]

3.2 Background

While the treatment of cHL has improved dramatically over the past 2 decades, with reported 5-year EFS rates between 80%-90%, there is still a subset of patients who either relapse or in whom first-line treatment fails. Ten percent to 15% of patients with localized disease and 25% of patients with advanced cHL have recurrent disease after first-line treatment.[40,41,42] Patients with cHL who are refractory to initial therapy, or relapse after primary initial chemotherapy, have poor outcome.[43,44]

There is currently no consensus or identified best salvage chemotherapy regimen in pediatric and adolescent participants with relapsed/refractory cHL. Given that brentuximab vedotin and nivolumab both have documented high single-agent response rates in cHL and also work through distinct mechanisms of action, it is expected that combination therapy could potentially be more effective in the salvage treatment setting than administration of either agent alone.

Background information on nivolumab can be found in the nivolumab Investigator Brochure (IB).[45]

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. Additional information regarding brentuximab vedotin can be found in the product prescribing information.[46]

Bendamustine hydrochloride is a novel alkylating agent[47,48] approved for use in the treatment of chronic lymphocytic leukemia, and for indolent non-cHL. Bendamustine consists of a mechlorethamine group, a benzimidazole ring, and a butyric acid side chain, crosslinks between deoxyribonucleic acid (DNA) bases, and produces direct cytotoxic damage.[49,50,51]

There are no published retrieval trials that risk stratify using a strategy identical to the one in this study (Table 5.1-1) to serve as an historical control. We have identified multiple published pediatric[9] and adult retrieval trials that have enrolled similar patients to our study population.[37,52,53]

For the low risk / R1 cohort, the aim is to demonstrate 3-year EFS in participants treated without autologous stem cell rescue. The ST-HD-86 clinical trial for patients with progressive and relapsed Hodgkin disease after primary treatment in the pediatric DAL/GPOH studies is the only pediatric cooperative group trial reporting long-term survival in patients who did not receive autologous stem cell rescue. In this trial, 10 year disease-free survival for 57 participants with early relapse treated without stem cell rescue was 55%.

In the standard risk / R2 cohort, the primary endpoint is the CMR rate at any time prior to ASCT. Historical CMR rates attained by either brentuximab or bendamustine monotherapy are approximately 35% (Table 3.2-1).

Table 3.2-1: Response Rates for Brentuximab Vedotin or Bendamustine Monotherapy

Trial	N	Salvage Regimen	Response time point (median cycles delivered)	Response modality	CR rate
Younes, 2012[37]	102	Brentuximab	Best response (9)	PET & CT	35%
Moskowitz, 2013[53]	34	Bendamustine	Best response (4)	PET & CT	35%
Corazzelli[52]	41	Bendamustine	Best response (2-8)	PET & CT	31%

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.[54,55,56] 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.[57] 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. [58] PD-1 signaling has been shown to inhibit CD-28-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.[59] 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) restimulation assay with human peripheral blood mononuclear cells, 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).[60]

3.2.2 Clinical Pharmacology Summary

Single-dose PK of nivolumab was evaluated in participants with multiple tumor types in CA209001, whereas multiple-dose PK is being evaluated in participants in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from 350 participants from CA209001, CA209002, and CA209003.

Single-dose PK of nivolumab was evaluated in 39 participants with multiple tumor types in study CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. Geometric mean Cmax and AUC(INF) of nivolumab administered at dosages of 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg demonstrated approximate dose proportionality. Geometric mean clearance (CL), after a single intravenous (IV) dose, ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution during the terminal phase (Vz) varied between 83 to 113 mL/kg across doses. There was moderate variability in PK parameters among participants, with coefficient of variation (CV) of 20% to 32% in Cmax, 39% to 47% in AUC(INF), 17% to 43% in clearance, and 23% to 40% in Vz. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the nivolumab IB.[45]

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 participants from CA209001, CA209002, and CA209003. Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. The body weight-normalized

dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

In a study of nivolumab including pediatric participants (CA209070), preliminary analysis indicates participants 6 to 12 years old had a similar exposure to nivolumab as adults. After the first dose (3 mg/kg every 2 weeks), the geometric mean of observed Cmin was 20.8 µg/mL compared to ~18 µg/mL in adults with multiple solid tumors.

3.2.3 Safety Summary

Nivolumab has been studied in approximately 12,300 participants and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the IB,[45] and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose reached at any dose tested up to 10 mg/kg. Most adverse events (AEs) were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 7. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. For additional material, see the nivolumab IB.[45]

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.[45]

3.3 Benefit/Risk Assessment

Nivolumab

Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of nivolumab may be found in the IB.[45] A recent report from a Phase 1 study of nivolumab in participants with advanced hematological malignancies demonstrated a high response rate in participants with relapsed or refractory cHL, with an ORR of 87% (20/23 participants) and a CR rate of 17% (4/23 participants). The responses obtained were durable with a 6-month progression-free survival (PFS) of 86% and no significant difference in the ORR in the subset of 18 participants in whom brentuximab vedotin treatment had previously failed.[61] This was demonstrated further in a Phase 2 registrational study in heavily pretreated cHL patients with failure of prior ASCT and brentuximab vedotin treatment: nivolumab demonstrated high IRRC-assessed ORR of 66%, investigator-assessed ORR of 73%, the potential to produce durable responses including durable partial responses, with ongoing responses in 62% of patients at data cut-off and an acceptable safety profile, consistent with previous reports.[62] FDA recently approved single-agent nivolumab for the treatment of adults with R/R cHL following failure of ASCT and brentuximab vedotin.

Brentuximab Vedotin

Brentuximab vedotin is generally well tolerated in pediatric patients at a dose of up to 1.8 mg/kg every 3 weeks. Five participants aged 12-17 with cHL were enrolled in the pivotal Phase 2 trial[63] that led to the FDA approval and there were no common severe toxicities or premature discontinuation of therapy related to an AE. Ten participants aged 2 to 18 years with relapsed or refractory cHL received single-agent brentuximab vedotin in an international pediatric Phase 1 study. A Phase 2 study is in progress (NCT 01492088). The combination of brentuximab vedotin with gemcitabine is being investigated in a COG Phase 1/2 trial for relapsed/refractory cHL up to age 30 years (NCT01780662). Results from the Phase 1 part also confirm that the combination is generally well tolerated, and the Phase 2 part is recruiting participants. In addition, brentuximab vedotin combined with chemotherapy in the frontline setting in high-risk pediatric cHL is currently being investigated in 2 active trials. A Phase 2 study is investigating the early response rate and PFS of brentuximab vedotin as a substitute for vincristine in the European OEPA/COPDac regimen (NCT01920932). In a 600-patient randomized Phase 3 trial, COG is evaluating the efficacy of brentuximab vedotin as a replacement for bleomycin in the ABVE-PC regimen (NCT02166463). This trial is ongoing with data monitored continuously by the independent Data Safety and Monitoring Board. None of the stopping rules have been triggered.

Bendamustine

Bendamustine is a bifunctional mechlorethamine derivative with a benzimidazole heterocyclic ring. Data from 2 randomized trials have resulted in approval of bendamustine as second-line therapy for indolent relapsed and refractory indolent non-Hodgkin lymphoma.[64,65] In patients with Hodgkin lymphoma, bendamustine has been shown to be highly active and has induced complete remission in 25%-35% of very heavily pretreated adults,[52,53,66,67] including those who have received prior autologous hematopoietic stem cell rescue.[68] Bendamustine has been studied as a single agent in pediatrics.[69] Combining bendamustine with other agents may improve both the rate and duration of response.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
R1 (Low Risk) Cohort: To describe the complete metabolic response (CMR) rate prior to RT and event-free survival (EFS) rate at 3 years, as assessed by blinded independent central review (BICR), using Lugano 2014 response criteria .	**R1 Cohort: CMR rate at any time prior to RT and EFS rate at 3 years** • The CMR rate is defined as the proportion of all response-evaluable participants who, assessed by the BICR, achieve best response of CMR using Lugano 2014 criteria. • EFS is the time from the date of first treatment to the earliest occurrence of composite events including the following: – High-dose chemotherapy followed by autologous stem cell transplant (HDCT/ASCT) – Disease progression per Lugano (2014) – Failure to achieve CMR after 4 cycles of N+Bv and 2 cycles of Bv+B – Secondary malignancy – Death due to any cause • Participants who did not have an "event" will be censored at the last adequate tumor assessment. Participants who start subsequent anticancer therapy (that is not part of HDCT/ASCT) without a prior reported "event" will be censored at the last tumor assessment prior to or on the day of the subsequent anticancer therapy. • Other definitions of EFS, employing somewhat different censoring rules, may be added as sensitivity analyses. •
R2 (Standard Risk) Cohort: To describe the complete metabolic response (CMR) rate prior to HDCT/ASCT by BICR, using Lugano 2014 response criteria	**R2 Cohort: CMR rate at any time prior to HDCT/ASCT** • The CMR rate is defined as the proportion of all response-evaluable participants who, assessed by the BICR, achieve best response of CMR using Lugano 2014 criteria.
Secondary in Both R1 and R2 Cohorts:	
To assess overall response rate (ORR) (CMR + partial metabolic response [PMR]) using Lugano 2014 criteria of the low risk and standard risk cohorts following 4 cycles of nivolumab and brentuximab vedotin by BICR.	**ORR following 4 cycles of nivolumab + brentuximab vedotin treatment** • ORR is defined as the proportion of all response-evaluable participants who, assessed by the BICR, achieve a best response of CMR or PMR using Lugano 2014 criteria.

Objectives	Endpoints
To assess PFS rate at 3 years by BICR using Lugano 2014 criteria	**PFS rate at 3 years** • The analysis is performed when participants have been followed for 3 years. PFS is the time from the date of first treatment to the date of first documented disease progression by BICR or death. Participants who neither progress nor die will be censored at the last adequate tumor assessment. Participants who start subsequent anticancer therapy (that is not part of HDCT/ASCT Consolidation Therapy for R2 Cohort) without a prior reported progression or death will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy. • Other definitions of PFS, employing somewhat different censoring rules, may be added as sensitivity analyses.
Duration of Response (DOR) will be evaluated for those participants who achieved PMR or CMR by BICR as well as for those participants who achieved CMR by BICR prior to RT in the low risk cohort and for those participants who achieved CMR prior to HDCT/ASCT in the standard risk cohort.	**DOR** • DOR is defined as the time from first response (CMR or PMR) to the date of EFS (R1)/PFS (R2) event. For participants who did not have an event, the DOR will be censored on the date of their last tumor assessment. Participants who start subsequent anticancer therapy (that is not part of HDCT/ASCT) without a prior reported EFS/PFS event will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy.
To evaluate efficacy as assessed by investigators using LUGANO (2014) response criteria.	**All efficacy endpoints above, per investigator assessments** R1 cohort: CMR rate prior to RT and EFS at 3 years R2 cohort: CMR rate prior to HDCT/ASCT Both R1 and R2 cohorts: ORR following 4 cycles of N+Bv treatment, PFS rate at 3 years, and DOR.
To describe the toxicity of nivolumab + brentuximab in combination in pediatric and young adult participants with relapsed or refractory classical Hodgkin's lymphoma (cHL) after failure of first-line treatment.	**Toxicity/Safety** Endpoints are serious and non-serious AEs, clinical laboratory tests (hematology, chemistry, urinalysis), vital sign measurements, etc.

Objectives	Endpoints
Exploratory	
• To assess overall survival (OS) in all treated participants in the SR and LR cohorts, respectively. • Association of biomarker levels with response including ORR, PFS, and OS.	• OS is defined as the time from the date of first dose of study drug until the date of death for any reason. If the participant is alive or the vital status is unknown, the participant will be censored at the date the participant was last known to be alive.
• To assess changes in biomarkers in the peripheral blood, such as soluble factors, immune cells, and vaccinated antibody concentrations.	• To assess biomarkers in the tumor tissue, such as PD-L1 expression, 9p24.1 copy number alteration, and tumor infiltrating lymphocytes and their association with response. • To summarize changes in biomarker levels over time (see protocol Section 9.8).
• To characterize pharmacokinetics (PK) of nivolumab and brentuximab following combination therapy.	• Serum samples will be collected to characterize PK of nivolumab and brentuximab.
• To characterize the immunogenicity of nivolumab and brentuximab following combination therapy.	• Samples will be evaluated for the presence of anti-drug antibody.
• To evaluate participant-reported general health status and cancer-specific quality of life (QoL).	• General health status as assessed by the EQ-5D-3L, and cancer-specific QoL as assessed by the FACT-Lym
• To investigate the effect of 4 potential risk factors on EFS and ORR.	• See definition of EFS and ORR above (see risk factors in protocol Section 3.1)
• Implementation of LYRIC 2016 for efficacy assessments.	• The same efficacy variables detailed above and measured for LUGANO 2014 will be explored for LYRIC 2016.

5. STUDY DESIGN

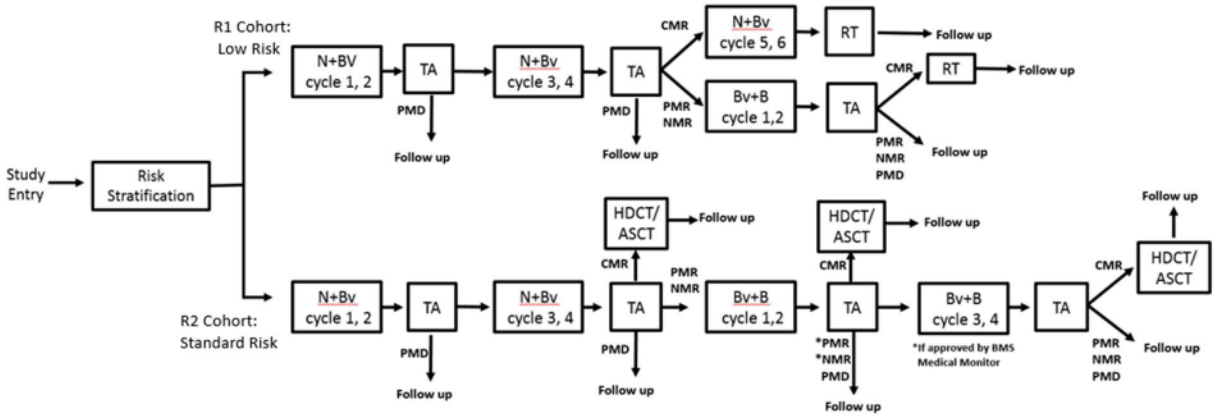
5.1 Overall Design

CA209744 is a Phase 2, open-label study of N+Bv for children and young adults with relapsed/refractory cHL. Participants who do not achieve CMR after 4 cycles of N+Bv will receive Bv+B to help achieve CMR. There are 2 treatment cohorts: one with participants at low risk relapse (R1 cohort), and one with participants at standard risk relapse (R2 cohort) (Table 5.1-1 and Figure 5.1-1).

Table 5.1-1: Risk Stratification Algorithm

Stage at Initial Diagnosis	Time to Relapse (from end of therapy)	B symptoms or extranodal disease at relapse, extensive disease where radiation therapy was contraindicated at relapse, or relapse in a prior radiation field	Relapse Risk Category
IA, IIA	≥ 12 months	No	**R1 Cohort: Low Risk**
	3-12 months (≤ 3 cycles and no RT)		
IB, IIB, IIIA	> 12 months	No	
All Others			**R2 Cohort: Standard Risk**

Figure 5.1-1: Study Design Schematic



- R1 cohort will receive N+Bv for 2 cycles (6 weeks) followed by Tumor Assessments (TA). Participants with radiographic progression, as assessed by Investigator (per Appendix 6) at

Cycle 2 N+Bv, will be taken off study treatment and enter follow-up (unless treatment beyond progression is approved by the Bristol-Myers Squibb (BMS) Medical Monitor, per Section 8.1.2). All other participants will receive 2 additional cycles of N+Bv study therapy (total 4 cycles = 12 weeks).

- Participants who have a CMR, as assessed by BICR, after a total of 4 cycles (12 weeks) of N+Bv will receive an additional 2 cycles of treatment of N+Bv (for a total of 6 cycles [18 weeks]), followed by Radiation Therapy (RT), per institutional guidelines (See Appendix 8: Radiotherapy Guidelines for R1 Cohort further recommendations).
- Participants without a CMR after 4 cycles of N+Bv, as assessed by BICR, will receive 2 cycles of Bv+B; participants who achieve CMR after these 2 cycles will proceed with RT, per institutional guidelines (See Appendix 8: Radiotherapy Guidelines for R1 Cohort further recommendations).
- Participants who have radiographic progression after Cycle 4 N+Bv, as assessed by BICR, (unless Treatment Beyond Progression is approved by BMS Medical Monitor, per Section 8.1.2) or those who do not achieve CMR, as assessed by BICR, after 2 cycles of Bv+B will be taken off study treatment and enter follow-up.

- R2 cohort will receive N+Bv for 2 cycles (6 weeks), followed by TA. Participants with radiographic progression, as assessed by Investigator (per Appendix 6) at Cycle 2 N+Bv, will be taken off study treatment and enter follow-up (unless Treatment Beyond Progression is approved by BMS Medical Monitor, per Section 8.1.2). All other participants will receive 2 additional cycles of N+Bv study therapy (total 4 cycles = 12 weeks).
  - Participants who have CMR, as assessed by BICR, after a total of 4 cycles of N+Bv will proceed with HDCT/ASCT (performed per institutional guidelines). Participants with CMR will have the option to receive up to two additional cycles of N+Bv if their HDCT/ASCT has to be postponed for any reason (this requires prior BMS Medical Monitor approval).
- Participants without a CMR, as assessed by BICR, after 4 cycles of N+Bv will receive 2 cycles of Bv+B.
  - Participants in CMR, as assessed by BICR, after 2 cycles of Bv+B will receive HDCT/ASCT (performed per institutional guidelines).
  - Participants without CMR as assessed by BICR will have an option to receive 2 additional cycles of Bv+B (this requires prior BMS Medical Monitor approval). If these participants attain CMR, as assessed by BICR, they will proceed with HDCT/ASCT (performed per institutional guidelines).
  - Participants with CMR will have the option to receive up to two additional cycles of B+Bv if their HDCT/ASCT has to be postponed for any reason (this requires prior BMS Medical Monitor approval).
- Participants who have radiographic progression after Cycle 4 N+Bv, as assessed by BICR, during study treatment (unless Treatment Beyond Progression is approved by BMS Medical Monitor, per Section 8.1.2) or those who do not achieve CMR, as assessed by BICR, after final cycle of Bv+B will be taken off study treatment and enter follow-up.

- R1 and R2 Cohort Follow-up Visits will occur Day 30, and then synched up with tumor assessments on Day 100 and then 6, 12, 18, 24, and 36 months Post-Consolidation Therapy/Treatment Discontinuation. Once participants reach the survival follow-up phase,

either in-person visits or documented telephone calls/email correspondence to assess the participant's status are acceptable. Tumor assessments are required for participants who have not radiographically progressed, per BICR, as per Table 2-4 and Section 9.1. If Investigator tumor assessment = CMR for a treatment related-decisions time point (Cycle 4 Induction, or Cycle 2 or 4 Intensification, as applicable) but BICR assessment differs, and as a result study treatment is discontinued and HDCT/ASCT (for R2 Cohort) and RT (for R1 Cohort) is performed in follow-up, tumor assessments should continue to be provided until radiographic progression per Investigator Assessment, per LUGANO 2014. For these cases, it is recommended to follow the same scan frequency and modality as when BICR assessment = CMR (per table 2.-4: 100 days and then 6, 12, 18, 24, and 36 months post-Consolidation Therapy/Treatment Discontinuation), **but at a minimum the Month 36 tumor assessment is required.**

5.1.1 Data Monitoring Committee and Other External Committees

Two independent committees will be utilized, a Study Steering Committee (SSC) and a Data Monitoring Committee (DMC).

The SSC will be comprised of country-level subject matter experts, with chairman representation from each of the Cooperative Groups (eg, COG and Euronet). They will provide guidance for study design and input as needed throughout the course of the study. The SSC will assist with day-to-day management/oversight of the study and with implementing the monitoring rules for toxicity.

A DMC will be established to provide oversight and safety and efficacy considerations and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for combination therapy of N+Bv in combination with therapy of Bv+B delivered sequentially in a subset of participants who have suboptimal response to N+Bv. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

The incidence of nivolumab, brentuximab vedotin, or bendamustine-related toxicity will be monitored in all participants treated with at least one dose of study drug at the combination doses defined in the protocol. The prescribing information for brentuximab vedotin, nivolumab, and bendamustine individually describe adverse events commonly observed relative to the agents (i.e., neutropenia or peripheral neuropathy with brentuximab vedotin; immune-mediated adverse events with nivolumab), as well as less common serious findings. If an ad hoc meeting is established based on the incidence of events exceeding that expected with the agents as reported with single-agent administration, the DMC will review safety data and provide recommendations. In the event that the DMC recommends terminating the study or making significant changes to study design, BMS will inform Health Authorities of the DMC recommendation. In addition, BMS may consult with Health Authorities before making the final decision.

Additionally, rules that will trigger an ad-hoc DMC meeting will be established to evaluate benefit-risk and need to amend or stop the study for the following:

Rash ≥ Grade 3, pulmonary toxicity, and peripheral neuropathy as recognized toxicities associated with these agents when delivered as monotherapy, will be closely monitored for potential stopping of the study if the AE rates are deemed unacceptably high. Rash ≥ Grade 3 will be classified as erythema multiforme, Stevens-Johnson Syndrome, or toxic epidermal necrolisis (TEN) per CTC 4.0 criteria. Pulmonary toxicity will be defined by dyspnea ≥ Grade 3, hypoxia ≥ Grade 3, or pneumonitis ≥ Grade 2. There must be no evidence of other etiologies, including left atrial hypertension, congestive heart failure, infection, metabolic abnormalities, or cancer related causes (eg, malignant pericarditis). Peripheral neuropathy events include both sensory and motor neuropathy ≥ Grade 3.

A Bayesian rule is adopted for this monitoring. Each cohort in this study will be monitored separately.

For rash ≥ Grade 3 and pulmonary toxicity, the prior distribution for each toxicity p is a Beta distribution with parameters $\alpha = 1$ and $\beta = 19$. This Beta distribution has a mean of 5%; the support for $p \leq 10\%$ is 86%. If given the observed data at ad-hoc monitoring, the posterior probability of $p \geq 5\%$ is 0.8 or higher, it will be considered compelling evidence that the toxicity rate of each is unacceptable and the study will be referred to the DMC for review and consideration for early closure.

This monitoring will be performed for every DMC meeting. Operationally the monitoring will require, for example, ≥ 2/6, ≥ 3/20, or ≥ 4/40 participants with the toxicity in question for the rule to be met. The exact rule will depend on the number of participants in the denominator at the time of the interim monitoring. The study will tolerate at most 3 participants with respect to each toxicity in each cohort at the end.

With an initial planned sample size of N = 40, if the true rate of the toxicity is 5%, 10%, or 15%, respectively, the chance of observing 4 or more participants with the toxicity in question are 14%, 58%, and 87%, respectively.

For peripheral neuropathy toxicity, the prior distribution for each toxicity p is a Beta distribution with parameters $\alpha = 4$ and $\beta = 16$. This Beta distribution has a mean of 20%; the support for $p \leq 30\%$ is 87%. If given the observed data at interim monitoring, the posterior probability of $p \geq 20\%$ is 0.8 or higher, it will be considered compelling evidence that the toxicity rate of each is unacceptable and the study will be referred to DMC for review and consideration for early closure. Operationally this will require, for example, ≥ 4/6, ≥ 7/20, or ≥ 11/40 participants with peripheral neuropathy toxicity for the rule to be met. The exact rule will depend on the number of participants in the denominator at the time of the interim monitoring. The study will tolerate at most 10 participants with peripheral neuropathy in each cohort at the end.

With an initial planned sample size of N = 40, if the true rate of the peripheral neuropathy is 20%, 25% or 30% respectively, the chance of observing 11 or more participants with toxicities are 16%, 42%, and 69% respectively.

If the number of patients achieving CMR per blinded independent central review (BICR) at cycle 4 assessment is 5 or fewer among the first 20 treated R2 patients, then further accrual for additional

patients in the R2 cohort will be halted. The Sponsor will thoroughly review all efficacy and safety data, and early termination of the R2 cohort may be considered if the conclusion does not warrant success of the study for this cohort.

Additional study governance considerations are detailed in Appendix 2.

5.2 Number of Participants

Approximately 100 participants were planned to be enrolled, with approximately 80 treated (40 in each cohort), in consideration of potential screening failures or those who are treated but not response-evaluable. A minimum of 25 treated participants (R1: 5, R2: 20) will be pediatric (5 to < 18 years old), unless BMS Study Team instructs otherwise.

The protocol reflected a proposal to include a total of 100 enrolled participants to obtain 80 treated participants (age 5 to < 30), with 40 participants per cohort, and a minimum of 25 pediatric participants (age 5 to < 18).[redacted] Although the proposed sample size in the protocol was not intended to support statistical hypothesis testing, 90% confidence intervals (CI), corresponding to a range of observed response rates, were provided to illustrate the precision of estimation (See Table 10.3.1-1)

Study CA209744 is being conducted in 11 countries worldwide (although only 10 of them have been able to recruit participants) with 75 activated sites in total; however, only 20% of the totality of the sites recruited R1 participants.[redacted]

In light of above, the protocol is being modified to reduce the total number of participants from 80 to 72 (total number of treated participants enrolled R1 = 28 and R2 = 44)[redacted] with an overall sizeable population that can support a future assessment of benefit/risk. Assuming 24 responders out of 28 R1 participants, the exact 2-sided 90% confidence interval would be 70.23% to 94.97%.

See Section 10 for details on statistical considerations and sample size determination.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first screened participant. The end of the trial is defined as the last scheduled procedure shown in the Schedule of Activities in Section 2 for the last participant. Study completion is defined as the final date on which data for the primary endpoint is expected to be collected.

5.4 Scientific Rationale for Study Design

See Section 3.1.

5.5 Justification for Dose

Nivolumab

Participants should receive nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

In a study of nivolumab including pediatric participants (CA209070), preliminary analysis has shown the pediatric participants (6 – 12 yrs) have a similar exposure to adults. Post the first dose (3 mg/kg Q2W), the geometric mean of observed Cmin is 20.8 ug/mL compared to ~18 ug/mL in adults with multiple solid tumors.

Brentuximab Vedotin

Brentuximab vedotin is generally well tolerated in pediatric patients at a dose of up to 1.8 mg/kg every 3 weeks. Five participants aged 12-17 with cHL were enrolled in the pivotal Phase 2 trial[63] that led to the FDA approval and there were no common severe toxicities or premature discontinuation of therapy related to an AE.

Bendamustine

After 4 cycles of N+Bv, participants with response assessment of PMR/NMR will receive intensification therapy with brentuximab vedotin + bendamustine (90 mg/m^2), to help achieve CMR prior to HDCT/ASCT (or RT).

In a Phase 1/2 study of brentuximab vedotin + bendamustine in R/R cHL (median age of 36 years [range 19-79]), the reported recommended doses of brentuximab vedotin (1.8 mg/kg) on Day 1 and bendamustine (90 mg/m^2) were delivered on Days 1 and 2 in 3-week cycles, respectively. The safety profile was manageable. The main toxicity observed with the combination was infusion-related reactions (56% overall). The most common symptoms (≥ 10%) were pyrexia (26%), chills (20%), dyspnea and nausea (15% each), flushing (13%), and hypotension (11%). Premedication

with corticosteroids and antihistamines was instituted with a protocol amendment and appeared effective.

6. STUDY POPULATION

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

6.1 Inclusion Criteria

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

c) For participants unable to give their written consent, in accordance with local regulations, one or both parents, a guardian, or a legally acceptable representative must be informed of the study procedures and must document permission by signing the informed consent form approved for the study prior to clinical study participation

d) Each participant must be informed about the nature of the study to the extent compatible with his or her understanding. Should a participant become capable or reach the age of majority, his or her consent should be obtained as soon as possible. The explicit wish of a participant who is a minor or unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

2) Type of Participant and Target Disease Characteristics

a) Participants must have measurable disease, documented by pathological and radiographic criteria

i) Participants with pathologically confirmed cHL, excluding nodular lymphocyte-predominant HL, after failure or non-response to first-line therapy.

(1) Relapsed disease is defined as achieving a CR to previous therapy but then progressing 3 months or more after completion of that therapy.

(2) Refractory disease is defined as never achieving a CR to previous therapy or achieving a CR but then progressing within 3 months of completion of that therapy.

ii) At least 1 measureable site of disease according to the Lugano 2014 criteria (International Working Group criteria). [70,71]

iii) Participants must have FDG-PET-avid and bidimensional measureable disease of at least 1.5 cm in longest axis as documented by radiographic technique (CT preferred).

b) Performance Level: Karnofsky ≥ 50 for participants > 16 years of age or Lansky ≥ 50 for participants ≤ 16 years of age (Appendix 5). Participants who are unable to walk because

of paralysis, but who are in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

c) Evaluable tumor tissue (archived or new biopsy) must be provided to the central laboratory as formalin-fixed paraffin-embedded (FFPE) tumor block or slides. In order to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period. Note: Under special circumstances, if tumor tissue provided is deemed inadequate, contact the Medical Monitor for approval to begin treatment.

3) Age and Reproductive Status

a) Males and Females, ages 5 to 30 years, inclusive

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) WOCBP must agree to follow instructions for 2 methods of contraception or complete abstinence (listed in Appendix 4) for the duration of treatment with investigational drugs (all IMPs) and for an additional 6 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for 2 methods of contraception or complete abstinence (listed in Appendix 4) for the duration of treatment with investigational drugs (all IMPs) and for an additional 6 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.

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. Additional details are provided in Appendix 4.

4) Physical and Laboratory Test Findings

a) Screening laboratory values must meet the following criteria:

i) Adequate bone marrow function defined as the following:

(1) For participants without known bone marrow involvement:

(a) Peripheral absolute neutrophil count (ANC) $\geq 750/mm^3$

(b) Platelet count $\geq 75{,}000/mm^3$ (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment). Participants with known bone marrow metastatic disease will be eligible for study provided they meet the platelet counts following transfusion, however they will not be eligible for assessment of hematologic toxicity

(2) For participants with known bone marrow involvement:

(a) Participants with cytopenias secondary to known bone marrow involvement are eligible regardless of ANC or platelet counts

(b) Participants may be enrolled and receive transfusions provided they are not known to be refractory to red cell or platelet transfusions. Participants with bone marrow involvement will not be evaluated for hematologic toxicity regardless of ANC or platelet counts at the time of diagnosis.

ii) Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m^2 or a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

Note: the threshold values in this table were derived from the Schwartz formula for estimating GFR,[72] utilizing child length and stature data published by the US Centers for Disease Control and Prevention

iii) Adequate hepatic function as evidenced by the following:

(1) Total bilirubin ≤ 1.5 x upper limit of normal (ULN)

(2) SGPT (alanine aminotransferase [ALT]) ≤ 3 x ULN. For the purpose of this study, the ULN for SGPT is 45 U/L

5) Prior Anti-tumor Therapy

a) Participants must have received first-line anti-cancer therapy that failed

b) Participants must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy prior to signing consent.

c) Myelosuppressive chemotherapy: At least 14 days after the last dose of myelosuppressive chemotherapy.

d) Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for short-acting growth factor. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the BMS Medical Monitor.

e) Biologic (anti-neoplastic agent): At least 3 half-lives after the last dose of a biologic agent.

f) Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody.

g) Bleomycin: At least 28 days must have elapsed since the most recent dose of bleomycin, to allow adequate time to detect evidence of bleomycin-related pulmonary toxicity

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants with an immunodeficiency that existed prior to diagnosis, such as primary immunodeficiency syndromes, organ transplant recipients, and participants on current systemic immunosuppressive agents are not eligible

b) Active cerebral/meningeal disease related to the underlying malignancy

c) History of progressive multifocal leukoencephalopathy (PML)

d) Pre-existing neuropathy of ≥ Grade 2

e) Any active Grade 3 or higher (per Common Terminology Criteria for Adverse Events [CTCAE] version 4) viral, bacterial or fungal infection prior to the first dose of brentuximab vedotin; routine antimicrobial prophylaxis is permitted

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

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

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

i) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

2) Prior/Concomitant Therapy

a) Participants who received more than one line of anti-cancer therapy or are treatment naive are not eligible

b) Previously received an allogeneic and/or autologous SCT for HL

c) Participants who have received a prior solid organ transplantation are not eligible

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

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

f) Prior radiation therapy within 3 weeks, or chest radiation ≤ 12 weeks prior to first dose of study drug(s)

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

h) Prior exposure to bendamustine

i) Live vaccine (< 4 weeks prior to the start of study treatment)

3) Physical and Laboratory Test Findings

a) Any positive test for hepatitis B or C virus indicating acute or chronic infection, and/or detectable virus

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

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

5) 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 BMS approval is required).

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

Eligibility criteria for this study have been carefully considered to ensure the safety of the study 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/entered in the study/included in the analysis population. 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.

The most current result prior to treatment assignment is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

7. TREATMENT

Study drug includes both Investigational (Medicinal) Product (IP/IMP) and Non-investigational (Medicinal) Product (Non-IP/Non-IMP). Study drugs for this study are summarized in Table 7-1.

Table 7-1: Study Treatments for CA209744

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[a]	100 mg (10 mg/mL)	IMP	Open label	10 mL Vial/ Clear to opalescent colorless to pale yellow liquid. May contain particles.	2 to 8°C. Protect from light and freezing
Brentuximab Vedotin powder for solution for Injection[b]	50 mg	IMP	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
Bendamustine powder for solution for Injection[b] OR Bendamustine Solution for Injection[b]	25 mg or 100 mg OR 100 mg/4 ml (25 mg/ml)	IMP	Open label	White to off-white lyophilized powder in a single-dose vial for reconstitution OR Clear and colorless to yellow ready-to-dilute solution	15 to 25°C (powder) OR 2 to 8C (solution). Protect from light.

[a] May be labeled as either "BMS-936558-01" or "Nivolumab."

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC)

7.1 Treatments Administered

The selection and timing of dose for each participant is described in Table 7.1-1. The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	3 mg/kg	21-day cycles	IV
Brentuximab Vedotin	1.8 mg/kg[a]	21-day cycles	IV
Bendamustine	90 mg/m^2/day	21-day cycles (on Days 1 and 2)	IV

[a] If the participant weighs more than 100 kg, the dose calculation for Bv should be 100 Kg. See local package insert or PIL for further guidance.

Nivolumab + Brentuximab Vedotin Administration

Eligible participants will receive treatment with brentuximab vedotin at 1.8mg/kg IV as a 30 minute infusion on Day 1 of every 21-day cycle.

For Cycle 1 only, nivolumab will be administered alone on Day 8 of Cycle 1. Nivolumab injection at 3 mg/kg is to be administered as an IV infusion over 30 minutes. Detailed instructions for dilution and infusion of nivolumab injection will be provided in the pharmacy manual or reference sheets. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

By delivering brentuximab vedotin, a directly cytotoxic agent, 1 week prior to nivolumab in Cycle 1, it is anticipated that tumor-associated antigens will be released and available for presentation to resident cytotoxic T-cells at the same time that these cells become activated through PD-1 blockade. However, because of the long half-life of nivolumab there is no rationale to continue staggered dosing beyond Cycle 1.

For Cycle 2 and beyond, nivolumab should be administered at least 30 minutes after the completion of brentuximab vedotin infusion. Participants should begin study treatment within 3 calendar days of treatment assignment.

Dosing calculations should be based on the body weight assessed at baseline (Cycle 1, Day1). It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

The recommended dose for brentuximab vedotin per its prescribing information is 1.8 mg/kg via IV infusion administered every 3 weeks.[46] This dose and schedule was evaluated in two pivotal Phase 2 studies (SG035-0003 and SG035-0004) in patients with CD30-positive hematologic malignancies.

Brentuximab + Bendamustine Dosing

After 4 cycles of N+Bv, R1 (or R2) cohort with tumor assessment of PMR/NMR will receive augment therapy with Bv+B, with objective to achieve CMR prior to RT (or HDCT/ASCT).

Eligible participants will receive brentuximab vedotin (1.8 mg/kg) on Day 1 and bendamustine (90 mg/m^2) on Days 1 and 2 of a 21-day cycle, respectively. Bendamustine should be administered at least 30 minutes after the completion of brentuximab vedotin infusion on Day 1 of each cycle.

Administration of brentuximab vedotin and bendamustine should performed in accordance with their respective prescribing information.[46,49] See local package insert or PIL for further information.

7.1.1 Treatment of Infusion Reactions

Infusion-related reactions have been reported and may occur during the infusion of study treatment(s) N+ Bv and Bv + B cycles of therapy. 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, bendamustine, or nivolumab. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE (version 4) guidelines.

Required Premedications for Nivolumab + Brentuximab Vedotin

All participants receiving combination therapy with N+Bv will receive prophylactic premedication at least 30 minutes prior to dosing study drug(s) with famotidine 40 mg IV (adult) or 0.5 mg/kg (pediatric) and diphenhydramine 50 mg IV (adult) or 1 mg/kg (pediatric) [or equivalent H2/H1 blockers] prior to every cycle from Cycle 2. For participants in Cycle 5 and beyond who have had no infusion reactions, H1/H2 blockers (eg,: diphenhrdramine) dose may be lowered to 25 mg (or equivalent) or omitted per investigator discretion. Acetaminophen 650 mg (adult) or 15 mg/kg (pediatric) may be included as a premedication per investigator discretion. Participants who experience a Grade 1 or Grade 2 infusion-related reaction while receiving premedication should be premedicated adding methylprednisolone 40 mg IV (adult) or 0.3 mg/kg (pediatric) or equivalent. 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. Participants 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 and participant would enter follow-up.

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).

For additional treatment guidance of immune mediated adverse events see Appendix 7.

Required Premedications for Brentuximab Vedotin + Bendamustine

Prophylactic premedication with corticosteroids and antihistamines will be administered to all subjects approximately 30 to 60 minutes prior to infusion of brentuximab vedotin (on days when brentuximab vedotin and bendamustine are administered). Recommended doses for premedication are the following:

- Methylprednisolone 100 mg IV or equivalent (eg, dexamethasone 20 mg IV) for adults and 0.8 mg/kg for pediatric participants.
- Diphenhydramine 50 mg IV or equivalent (1 mg/kg for pediatric participants).

Premedication with acetaminophen may also be given at the discretion of the treating investigator.

For individual participants who discontinue bendamustine and continue on brentuximab vedotin, premedication (corticosteroids and antihistamines) for single-agent brentuximab vedotin may be reduced or discontinued at the discretion of the investigator.

Participants who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the discretion of the investigator after discussion with the Sponsor.

7.1.1.1 Method of Treatment Assignment

This is an open-label study. An aligned risk-stratified algorithm will be used (Table 5.1-1). Participants with late relapse of low-stage disease will be stratified into the low-risk cohort, and participants with early relapse, extranodal disease or B symptoms at relapse, extensive disease where radiation therapy was contraindicated at relapse, or relapse in a prior radiation field will be stratified into the standard-risk cohort. All participants will be assigned to treatment 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.

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

7.2 Blinding

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

7.3 Dosage Modification

Participants may be dosed within a +/- 3-day window at the start of each cycle.

Nivolumab Dose Delays

There will be no dose escalations or reductions of nivolumab allowed. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.1.1.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. 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 (see section 8)
- Any AE, 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.

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT, or TBILI elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT AND TBILI values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before 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.

If nivolumab treatment is delayed for any reason, brentuximab vedotin must also be delayed until the participant has appropriately recovered and is able to resume the combination treatment on the first day of the subsequent cycle.

Recommended Dose Modification for Brentuximab-related Events

Table 7.3-1 describes the recommended dose modifications for brentuximab vedotin treatment associated toxicity. Doses reduced for brentuximab vedotin-related toxicity should not be re-escalated without discussion with the sponsor. Dose escalation of brentuximab vedotin beyond 1.8 mg/kg is not permitted.

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

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

Table 7.3-1: Dose Modifications for Brentuximab Vedotin

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

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

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

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

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

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

Recommended Dose Modification for Bendamustine-related Events

Bendamustine administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved (Absolute Neutrophil Count [ANC] ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L) bendamustine can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. See local package insert or PIL for further information.

Dose modifications for non-hematologic toxicity: for ≥ Grade 3 non hematologic toxicity that recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. See local package insert or PIL for further information.

7.4 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study 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 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 BMS should be contacted immediately.

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

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

Nivolumab vials must be stored at a temperature of 2-8 degrees Celsius and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab Investigator Brochure[45] section for "Recommended Storage and Use Conditions" and/or pharmacy manual.

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

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

7.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as by the participant's medical record and Case Report Form (CRF).

7.6 Concomitant Therapy

7.6.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cHL)
- Live vaccines
  - Live coronavirus disease 2019 (COVID-19) vaccines should generally not be administered to a subject during the study, including the treatment and safety follow-up period. Live vaccines are defined as those that are capable of transmitting infectious severe acute respiratory syndrome coronavirus (SARS-CoV-2) or other viruses. If it cannot be determined whether or not the vaccine is live, it is recommended that the vaccine not be administered until it is confirmed that there is no risk of viral infectivity within the subject. If a patient has received a live COVID-19 vaccine prior to screening, enrollment should be delayed until the impact of the vaccine is stabilized, unless a delay would compromise patient health.
- No data are available on the response to COVID-19 vaccines. The efficacy and safety of vaccination in subjects who are receiving nivolumab, brentuximab vedotin, and bendamustine are unknown. Please contact the Medical Monitor with any questions related to COVID-19 vaccines.
- Refer to the brentuximab vedotin and bendamustine prescribing information for additional prohibited medications.[46,49] See local package insert or PIL for further information.

7.6.2 Other Restrictions and Precautions

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

Additionally, please follow local prophylaxis guideline recommendation for opportunistic infections in this patient population

7.6.2.1 Mobilization and Collection of Peripheral Blood Stem Cells

Autologous peripheral blood stem cells (PBSCs) may be collected from consenting participants after any cycle of therapy. Participants who had bone marrow involvement at the time of study enrollment must undergo repeat bone marrow biopsies (at least two sites) prior to stem cell collection or follow institutional practices to rule out bone marrow disease involvement. Stem cells will not be collected until the bone marrow biopsies are negative for disease involvement or bone marrow disease is ruled out, as per institutional practice. Stem cells may be collected following ANY cycle of therapy, subsequent to the demonstration of negative bone marrow biopsies or bone marrow disease ruled out, per institutional practice.

Institutional standard operating procedures should be used for the collection procedure.

7.6.2.2 Imaging Restriction and Precautions

If a participant has a known allergy to contrast material, local prophylaxis standards may be used to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a participant have a contraindication for CT IV contrast, a non-contrast CT chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained.

Study-related MRI imaging will be performed per the frequency specified in the protocol. Investigators may obtain additional follow-up MRI scans as medically indicated. For other locally performed imaging, 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 as to whether or not 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 < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population, who should be excluded from the study. In addition, participants with surgically implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for participants with tattoos, body piercings, or other body art.

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

7.6.3 Permitted Therapy

In cycles with nivolumab, 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.

COVID-19 vaccines that are NOT live can be administered during the study, including during nivolumab, brentuximab vedotin, and bendamustine treatment and after the last administration of respective treatments. COVID-19 vaccines that are NOT live should be handled in the same manner as other vaccines.

The following are NOT considered live vaccines and the decision to vaccinate should be made by the investigator and participant: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines, toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (Pfizer/BioNTech and Moderna COVID-19 vaccines) and replication-incompetent recombinant vector vaccines.

For COVID-19 vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment when feasible, and when a delay in enrollment would not put the patient at risk. If a patient has received a specific COVID-19 vaccination during the course of the study, the type of vaccine and date(s) received should be recorded on the concomitant medications CRF page.

No data are available on the response to COVID-19 vaccines. The efficacy and safety of vaccination in subjects who are receiving nivolumab, brentuximab vedotin, and bendamustine are unknown. Please contact the Clinical Trial Physician or Medical Monitor with any questions related to COVID-19 vaccines.

7.7 Treatment After the End of the Study

At the end of the study, 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.

8. DISCONTINUATION CRITERIA

Nivolumab treatment should be permanently discontinued for the following:

- Disease progression as determined by Investigator Assessment at Cycle 2, N+Bv or by BICR thereafter during treatment period with the exception as per Section 8.1.2 (treatment beyond progression).
- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation

  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT, or TBILI requires discontinuation*
    - Concurrent AST or ALT > 3xULN and TBILI > 2xULN

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

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - 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 drug-related endocrinopathy AEs, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants (or their parents, guardians, or legally acceptable representatives on their behalf, as applicable) 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 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 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

Refer to the Schedule of Activities in Section 2 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 Section 2. 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 CRF page.

8.1.1 Post Study Treatment Study Follow-up

In this study, EFS 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 for collection of outcome and/or survival follow-up data as required and in line with Section 9 until death or the conclusion of the study.

8.1.2 Treatment Beyond Progression

Evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD, [73] eg, due to inflammatory reaction simulating progression ("tumor flare" or pseudoprogression). Pseudoprogression is well described in neuro-oncology, and refers to radiographic enlargement of tumor lesions that would be interpreted as disease progression by conventional response criteria, but upon histologic examination reveals necrosis and/or inflammation (treatment effect) and not disease progression.[73] A similar phenomenon has been observed in various tumors when treated with immunotherapeutic agents, in which transient enlargement of lesions or appearance of new lesions is attributable to the influx of immune cells. These potential immune treatment effects complicate the evaluation of response and may lead to premature discontinuation of therapy. Furthermore, the time period to pseudoprogression or tumor flare with different immune therapies varies in different malignancies.

Treatment beyond progression will be permitted, per the study design. Participants meeting progression defined by relapsed disease (after CMR) or progressive disease (after PMR, NMR) per Lugano criteria may continue receiving study medication beyond investigator-assessed or BICR assessed, progression (per Section 5.1) as long as they meet the following criteria:

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

The decision to continue treatment beyond investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records. The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment.

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. Withdrawal of consent may be requested by participants, parents, guardians, or legally acceptable representatives, in accordance with local regulations. The wishes of minor participants to withdraw their assent should also be respected.

- 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 (Section 2).
- 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.

9.1 Efficacy Assessments

9.1.1 Tumor Assessments

Imaging and response criteria are based on the International Lymphoma Working Group's revised recommendations for malignant lymphoma.[70,71] Primary response assessment will be evaluated using Lugano 2014 Classification (Appendix 6). In addition, LYRIC 2016 will be used for exploratory response assessment internally.[74]

For PET-based assessments, a response of progressive metabolic disease (PMD), no metabolic response (NMR), partial metabolic response (PMR), or complete metabolic response (CMR) will be determined. The PET scan metabolic uptake will be graded using the Deauville 5-point scale[75,76] with a score of < 4 considered to represent a CMR (see Appendix 6).

Assessment will be performed by PET with CT/MRI of diagnostic quality, with disease involvement determined by focal FDG uptake in nodal and extranodal (including spleen, liver, bone marrow, and thyroid) sites that is consistent with lymphoma, according to the pattern of FDG uptake. In addition to PET-based assessment, up to six of the largest nodes, nodal masses, or other involved lesions that are measurable in two diameters should be identified as target lesions using CT/MRI images performed along with PET; if possible they should be from disparate regions of the body and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

After the subjects achieve BICR assessed CMR, MRI/CT-based assessments will be performed. The PET-CT or PET-MRI that is CMR (per BICR assessment) will be used as baseline for MRI/CT-based assessment. Response will be categorized as progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR).

Subjects with BICR assessed PMR/NMR upon completion of study treatment will provide tumor assessments at the same time intervals specified in follow-up (or at a minimum, per SOC). Modality should be per Standard of Care.

PMD/PD includes radiological evidence of progression per Lugano Classification Revised Staging System for malignant lymphoma. If clinical progression is determined by the investigator, radiographic staging should also be performed to determine response assessment per Lugano Classification Revised Staging System for malignant lymphoma.

9.1.2 Imaging Assessment for the Study

Participants will be evaluated for tumor response by FDG PET-CT or PET-MRI, or FDG-PET with CT/MRI, per the Schedule of Activities (Section 2) at specified time points. BICR is required for treatment related-decisions at N+Bv, Cycle 4 and Bv+B, Cycle 2 and 4 (as applicable).

Therefore, treatment would be withheld, until the results are obtained, unless clinically indicated to treat sooner. Refer to Section 5.1 for additional study design details, including requirements for tumor assessments when a patient is discontinued from treatment, due to Investigator disagreement with BICR assessment.

Imaging modality should remain the same for each participants during this phase of the study. After the patient is in CMR by PET per BICR, progression of disease will be followed by MRI/CT scans of diagnostic quality. To reduce radiation exposure, participants will be allowed to switch modality to MRI during follow-up. If the results of the CT or MRI is equivocal, follow-up FDG-PET may be obtained for clarification (see Table 2-4).

Images will be submitted to an imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the BMS CA209744 Imaging Manual to be provided by the core lab.

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.

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 FU 2 (Day 100) 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.

Sections 5.6.1 and 5.6.2 in the nivolumab IB[45] represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent (or the parent/guardian/legally appointed representative's permission) to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and until FU2 (Day 100).

- 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.
- 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.)

For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's CRF.

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 (see Appendix 3).
- 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). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up.

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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting AEs 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 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 Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

AT (ALT or AST) elevation > 3xULN

AND

Total bilirubin > 2xULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

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.

The CRF will capture COVID-19-related AEs/SAEs as per normal reporting procedure (eg, changes in study visit schedules, missing study visits, study drug modification/discontinuation, study discontinuation, etc.).

9.2.9 Management Algorithms for Immuno-Oncology Agents

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

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab IB[45] and Appendix 7 of this protocol.

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 and Appendix 3).

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

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
- 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 timepoints for all safety assessments are listed in the Schedule of Activities (Section 2).

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, Karnofsky / Lansky Performance Status, blood pressure (BP), heart rate (HR), and temperature. Screening assessments should be performed within 28 days prior to treatment assignment.

Screening local laboratory assessments should be done within 14 days prior to treatment assignment; see Table 2-1 for a list of assessments.

Screening pregnancy tests for WOCBP must be performed within 24 hours prior to the initial administration of study drug.

The following screening local laboratory assessments should be done within 28 days prior to treatment assignment: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

On-study local laboratory assessments should be done within 3 calendar days prior to each dose: see Table 2-1 for a list of assessments.

Thyroid function testing (reflex to free T3, and free T4 if abnormal result) is to be done every other cycle.

On treatment pregnancy tests should be performed as per the Schedule of Activities (Section 2).

Participants will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase as well as during the first two safety follow-up visits. Once participants reach the survival follow-up phase, either in-person visits or documented telephone calls/email correspondence to assess the participant's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

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 SAE page.

On treatment local laboratory assessments are to be completed within 3 calendar days prior to dosing.

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 nivolumab IB.[45]

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.

9.4.1 Physical Examinations

Refer to Schedule of Activities in Section 2.

9.4.2 Vital Signs

Refer to Schedule of Activities in Section 2.

9.4.3 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. See Section 2 for additional details on the assessments to be conducted.

9.4.4 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.

9.5 Pharmacokinetic

Samples for PK and immunogenicity assessments will be collected for all participants receiving nivolumab and brentuximab vedotin as described in Table 2-5. All timepoints are relative to the start of the previous study drug administration. After cycle 1 (once both study drugs of the combination are administered on the same day), predose samples are to be collected relative to the star of brentuximab vedotin. All on-treatment time points are intended to align with days on which study drugs is administered, if dosing occurs on a different day, the PK and immunogenicity sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

A detailed schedule of PK and immunogenicity evaluations for nivolumab and brentuximab vedotin is provided in Table 2-5. PK samples will be analyzed for nivolumab and brentuximab vedotin by validated ligand binding assays. Immunogenicity samples will be analyzed for anti-nivolumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AE).

9.6 Pharmacodynamics

See Section 9.8.2 and 10.3.3.3.

9.7 Pharmacogenomics

See Section 9.8.2.

9.8 Biomarkers

Peripheral blood and tumor tissue will be collected prior to therapy and at selected timepoints on treatment as outlined in Section 2, unless restricted by local requirements. A variety of factors that could potentially predict clinical response to nivolumab will be investigated in peripheral blood and in tumor specimens taken from all participants prior to treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (AE) data. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with nivolumab treatment. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate procedure manual at the time of study initiation.

9.8.1 Biomarkers in the Tumor

Tumor Biopsy

Tumor biopsy specimens will be obtained to characterize immune cell populations and expression of selected tumor markers. Biopsy samples should be excisional, incisional or core needle. Fine needle biopsies are not allowed because the architecture of the tumor in its microenvironment cannot be assessed. Tumor tissue (obtained during the screening phase or collected prior to obtaining informed consent) must be provided for biomarker analysis. Participants with relapsed disease must provide a recent biopsy sample within 90 days prior to obtaining informed consent or obtain it during the screening period. In rare cases where a recent tumor tissue cannot be provided due to increased risk of complications, biopsies older than 90 days from the date of consent may be submitted. The reason must be clearly documented in the medical record and the BMS Medical Monitor must be contacted. In order for participants to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period. Minimum of 1 FFPE tumor tissue block (preferred) OR a minimum of 20 FFPE unstained sections are required for assessment of PD-L1 status and other biomarker evaluations. Note: Under special circumstances, if tumor tissue provided is deemed inadequate, contact the

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

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

Characterization of Tumor Infiltrating Lymphocytes (TILs) and Tumor Antigens

Immunohistochemistry (IHC) may be used to assess the number, composition, and function of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin embedded (FFPE) tumor tissue before and after exposure to therapy. These IHC analyses may include, but not necessarily be limited to, the following markers: CD30, CD3, CD4, CD8, FOXp3, PD-1, PD-L1, PD-L2, HLA-DR, CD56, CD68, CD163, PAX5, pSTAT3, and MHC class I/II.

Characterization of Tumor Genotype and Phenotype

Gene mutations, chromosomal translocations, copy number alterations, mRNA and miRNA gene expression, and epigenetic modifications within tumors may be characterized and explored by technologies including but not limited to IHC, FISH, RNAseq, and whole exome sequencing. Associations of altered tumor cell genetic structure, gene expression, disease heterogeneity and subtypes with nivolumab efficacy will be performed. EBV status using EBER test may be examined if not previously known.

9.8.2 Biomarkers in the Blood

Soluble Biomarkers in Serum

Soluble factors, such as cytokines, chemokines, and soluble receptors may be characterized and quantified by immunoassays in serum. Collected serum samples may also be used for the assessment of vaccinated antibody concentrations.

Soluble Biomarker in Plasma

Plasma samples will be collected and assessed for additional cytokines and soluble factors, including soluble PD-L1 as well as circulating free DNA to determine Minimal Residual Disease (MRD) by high-throughput sequencing.

Peripheral Blood Immune Cells Subset Analysis

Peripheral blood samples will be collected prior to initiation of study therapy and at designated timepoints on-treatment for immune cell subset analysis (Table 2-5). Collection of peripheral blood is mandatory at all timepoints. Blood samples may be used for immunophenotyping or characterization of the immune cell subsets in the circulation, including, but not limited to, T-cells, B-cells, NK cells, myeloid-derived suppressor cells, or subpopulations of the aforementioned immune cell types. These samples may also be used to assess immune cell function or antigen

specific T-cell proliferation or activation pending emerging information from other nivolumab studies.

Single Nucleotide Polymorphism (SNP) Analysis

In order to identify potential polymorphisms associated with safety and efficacy of nivolumab, selected genes may be evaluated for single nucleotide polymorphisms (SNP). Analysis may include but not limited to genes associated with CD30 and TNF receptors and apoptosis, PD-1/PD-L1 pathway and activated T cell phenotype, including PD-1, PD-L1, PD-L2, and CTLA-4. The genetic information in this blood sample may also be used to examine germline (predisposing) characteristics as well as to identify genetic information specific to your tumor. A blood sample will be obtained at Day 1, unless restricted by local requirements.

9.8.3 Additional Research Collection

Retention of sample collection for additional research is mandatory for all participants, except where prohibited by local laws or regulations.

This protocol will include residual sample storage for additional research.

This retention for additional research is intended to expand the translational research and development (R&D) capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in R&D to ensure the research supports appropriate and well-defined scientific research activities.

- Residual tumor and blood samples from biomarker collections (see Table 9.8.3-1) will be retained for additional research purposes

Samples will be securely stored by the BMS Biorepository [redacted] or at a BMS approved third party storage management facility.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 9.8.3-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK	All
Tumor Biopsy	All archived and fresh pre-treatment tumor samples as well as all on-treatment tumor biopsies
Serum	All
Plasma	All
Whole blood	C1D1

9.8.4 Other Assessments

Not applicable.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include the following:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

9.9.1 Outcomes Research Assessments

9.9.1.1 EQ-5D-3L

The EQ-5D-3L[77] is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems. Responses to these 5 dimensions are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to severe/extreme problems on all 5 dimensions (33333). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. In addition, the EQ-5D includes a visual

analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0–100 with 0 being the worst health state imaginable and 100 being the best health state imaginable.

The EQ-5D-3L will be administered to all treated participants that are of the age 12 or older at the time of first treatment (C1D1). Assessments will be collected on-treatment during the induction and intensification phase and during follow-up phases as outlined in Study Assessments (Section 2).

9.9.1.2 Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

The FACT-Lym is a validated cancer-specific QoL measure in people with lymphoma. The FACT-Lym combines a generic core consisting of the FACT-General which constitutes the core of all subscales, and can be used with patients of any tumor type, with 15 additional lymphoma-targeted items that cover symptoms cHL patients may experience (eg, swelling, night sweats). Core items are classified as: physical well-being, social/family well-being, emotional well-being, and functional well-being.

The FACT instruments use a 5-point intensity type of rating scale (from 'not at all' to 'very much'). Respondents are instructed to answer questions with respect to their experiences and functioning over the previous 7 days.

The FACT-Lym will be administered to all treated participants that are of the age 12 or older at the time of first treatment (C1D1). Assessments will be collected on-treatment during the induction and intensification phase as outlined in Study Assessments (Section 2).

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Due to high initial cure rates for pediatric Hodgkin lymphoma, a randomized trial in the retrieval setting was deemed not feasible due to low patient numbers, even with the combined COG and European networks. This single-arm study was initially targeting to treat approximately 40 participants in each risk cohort. Participants who are not response-evaluable in the R2 (SR) group will be replaced. See Section 10.2 for the definition of "response-evaluable."

Actual number of treated participants was 28 in R1 and 44 in R2.

10.2 Populations for Analyses

Population	Description
Enrolled Participants	All participants who signed informed consent.
Treated Participants	All participants who received at least 1 dose of study treatment.
Response-evaluable Participants	All treated participants who reach one of the following endpoints: PMR at any time, CMR at any time, or completion of six cycles of therapy (N+Bv x 4 plus Bv+B x ≥ 2). Participants who come off early for toxicity without a CMR or PMR are evaluable.
Responders	Participants who achieved CMR or PMR

Unless otherwise noted, the following specifies the populations for primary analyses. The primary analysis of EFS, PFS, and OS will be performed on the Treated Participants. The primary analysis of the CMR rate and ORR will be performed on the Response-evaluable Participants. The primary analysis of DOR will be performed on the Responders.

10.3 Statistical Analyses

Below is a summary of planned statistical analyses.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
R1 cohort: CMR rate prior to RT and EFS at 3 years. R2 cohort: CMR rate prior to HDCT/ASCT.	**R1 Cohort:** The estimated CMR rate and exact 2-sided 90% CI will be provided. See examples in Table 10.3.1-1). In addition to the Response-Evaluable Participants, the analysis of CMR rate will be carried out for All Treated Participants as well. The EFS function and the 3-year EFS rate will be estimated using the Kaplan-Meier product-limit method. Its corresponding 90% CI will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function s(t) -.

Endpoint	Statistical Analysis Methods
	In addition to the All Treated Participants, the EFS analysis will also be carried out for the following subgroup: - Participants who achieved CMR, went into RT, and did not receive HDCT/ASCT. **R2 Cohort:** The estimated CMR rate and exact 2-sided 90% CI will be provided. See examples in Table 10.3.1-1). In addition to the Response-Evaluable Participants, the analysis of CMR rate will be carried out for All Treated Participants as well. **The statistical analyses described above will apply to both the BICR assessments and the investigator assessments, respectively.**
R1 and R2 Cohorts: ORR following 4 cycles of N+Bv, PFS at 3 years, DOR	**ORR:** The estimated ORR rate and an exact 2-sided 90% CI will be provided. In addition to the Response-evaluable Participants **as of the start of 5th cycle**, the ORR analysis will also be carried out for All Treated Participants. **PFS:** The PFS function and the 3-year PFS rate will be estimated using the Kaplan-Meier product-limit method. In addition to All Treated Participants, the PFS analysis will also be performed for those who achieved CMR. **DOR:** The DOR will be estimated using the Kaplan-Meier product-limit method. In addition to the Responders (CMR or PMR), the DOR analysis will also be performed for the subgroup of those participants who achieved CMR. **The statistical analyses described above will apply to both the BICR assessments and the investigator assessments, respectively.**
OS	The OS will be estimated using the Kaplan-Meier product-limit method for the LR and SR cohorts, respectively.

Table 10.3.1-1: Examples of 90% CIs for the Response Rate (ORR Rate or CMR Rate)

Number of Response-evaluable Participants	Number of Responders	Observed Response Rate (%)	Exact 2-sided 90% CI	
			Lower Limit (%)	Upper Limit (%)
40	5	12.50	5.06	24.50
40	10	25.00	14.24	38.71
40	15	37.50	24.73	51.72
40	20	50.00	36.11	63.89
40	25	62.50	48.28	75.27
40	30	75.00	61.29	85.76
40	35	87.50	75.50	94.94
40	40	100.00	92.78	100.00

10.3.2 Safety Analyses

Safety analyses will be performed in all treated participants per cohort as well for LR/SR cohorts combined. Descriptive statistics of safety will be presented using NCI CTCAE version 4. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE 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 CTCAE criteria.

10.3.3 Other Analyses

10.3.3.1 Pharmacokinetic Analyses

Serum samples will be collected to characterize the PK of nivolumab and brentuximab. The PK data from this trial may be pooled with other trials to develop a population PK model. Model-determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The modeling results will be reported separately.

10.3.3.2 Immunogenicity Analyses

A listing will be provided of all available immunogenicity data. The frequency of participants with at least 1 positive anti-drug antibody (ADA) assessment, and the frequency of participants who develop ADA after a negative baseline assessment, will be provided. Detailed methodology for exploratory analyses including biomarkers and immunogenicity will be described in the statistical analysis plan.

10.3.3.3 Biomarker Analyses

Summary statistics for tumor and peripheral blood biomarkers such as, but not limited to, PD-L1, soluble factors, immune cells, and vaccinated antibody concentrations and their corresponding changes (or percent changes) from baseline will be tabulated by planned study visit to assess

pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically; if there is indication of meaningful pattern across time, further analysis may be performed to characterize the relationship. Results from tumor and peripheral blood biomarkers will be tabulated and associations between biomarkers and efficacy or safety measures will be assessed. Methods such as, but not limited to, logistic regression will be used to explore possible associations between measures of peripheral blood, tumor biopsies and clinical outcome. More details of biomarker analyses will be described in the statistical analysis plan.

10.3.3.4 EQ-5D-3L

All participants who have an assessment at baseline and at least 1 subsequent assessment while on treatment will be analyzed. Questionnaire completion rates at each assessment at each timepoint will be estimated for the EQ-5D questionnaire as a whole. Scores and post-baseline changes in scores for the EQ-5D-3L VAS and EQ-5D-3L utility index will be summarized at each assessment timepoint using appropriate descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum). Proportions of participants reporting no, moderate, or severe problems in each dimension will be reported. UK preference-weighting algorithm will be used to derive EQ-5D-3L VAS and EQ-5D-3L utility index in base case.

10.3.3.5 FACT-Lym

All participants who have an assessment at baseline and at least 1 subsequent assessment while on treatment will be analyzed. Questionnaire completion rates at each assessment at each timepoint will be estimated for the FACT-Lym. Scores and post-baseline changes in the core subscales of the FACT-Lym and the individual lymphoma-specific items will be summarized at each assessment timepoint using appropriate descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum). The Trial Outcome Index (TOI), which is summary index of the physical well-being, functional well-being and additional concerns scales will be calculated. Time to meaningful worsening in scale scores will be derived (for the lymphoma concerns scale, TOI and total score), if feasible.

10.3.3.6 Medical Resource Utilization

Medical resource utilization data will be analyzed separately.

10.3.4 Interim Analyses

Not applicable.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BP	blood pressure
BSA	body surface area
Bv+B	brentuximab vedotin plus bendamustine
cHL	classical Hodgkin's lymphoma
CMR	complete metabolic response
CMV	cytomegalovirus
COG	Children's Oncology Group
COV-19	Coronavirus Disease 2019
CRF	Case Report Form, paper or electronic
CT	computed tomography
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
EFS	event-free survival
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FI	functional imaging

Term	Definition
G-CSF	granulocyte colony stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HDCT/ASCT	high-dose chemotherapy followed by autologous stem cell transplant
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HR	heart rate
IB	Investigator Brochure
ICE	ifosfamide, carboplatin, etoposide
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFRT	involved field radiation therapy
IHC	immunohistochemistry
IMP	investigational medicinal products
IP	investigational product
IRB	institutional Review Board
IRT	Interactive response technology
ISRT	involved site radiation therapy
IV	ifosfamide with vinorelbine
IV	Intravenous
IVRS	interactive voice response system
LDi	longest diameter
LR	low risk
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
N+Bv	nivolumab plus brentuximab vedotin
NCI	National Cancer Institute
NMR	no metabolic response
ORR	overall response rate
OS	overall survival

Term	Definition
PBMC	peripheral blood mononuclear cells
PD	programmed death
PD	progressive disease
PF	physical examination
PFS	progression-free survival
PK	pharmacokinetics
PIL	Patient Information Leaflet
PMD	progressive metabolic diseases
PML	progressive multifocal leukoencephalopathy
PMR	partial metabolic response
PPK	population pharmacokinetics
PR	partial response
PS	performance status
R/R	relapsing/refractory
RR	respiration rate
RT	radiation therapy
SAE	serious adverse event
SARS-Cov-2	Severe acute respiratory syndrome coronavirus
SD	stable disease
SR	standard risk
SSC	Study Steering Committee
TA	tumor assessments
TBILI	total bilirubin
TBP	treatment beyond progression
TFT	thyroid function tests
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERANCE 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.

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 • 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

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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 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 must contact BMS prior to destroying any records associated with the study.

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

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, 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.

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

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.

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: o 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) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o 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 8.1.1 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

Note: the requirements for contraception are applicable to all participants treated with any of the IMPs administered in the study: nivolumab, brentuximab vedotin, and bendamustine.

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.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Two effective methods of contraception, with a minimum of one highly effective listed below, is required during study duration and until the end of relevant systemic exposure, defined as approximately 6 months after the end of study treatment with investigational drugs (IMPs).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 and bendamustine 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] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[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

Unacceptable Methods of Contraception
• 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 • 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 treatment with investigational drugs (IMPs).
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment with investigational drugs (IMPs).
- 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 treatment with investigational drugs (IMPs).
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of treatment with investigational drugs (IMPs).

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

APPENDIX 5 KARNOFSKY AND LANSKY CRITERIA

STATUS		STATUS
KARNOFSKY	**LANSKY**	**KARNOFSKY or LANSKY**
Normal, no complaints	Fully active, normal	100
Able to carry on normal activities; minor signs or symptoms of disease	Minor restrictions in physically strenuous activity	90
Normal activity with effort; some signs or symptoms of disease	Active, but tires more quickly	80
Cares for self. Unable to carry on normal activity or to do active work	Substantial restriction of, and less time spent, in play activity	70
Requires occasional assistance, but able to care for most of his needs	Out of bed, but minimal active play; keeps busy with quiet activities	60
Requires considerable assistance and frequent medical care	Gets dressed, but inactive much of day; no active play, able to participate in quiet play	50
Disabled. Requires special care and assistance	Mostly in bed; participates in some quiet activities	40
Severely disabled. Hospitalization indicated though death non imminent	In bed; needs assistance even for quiet play	30
Very sick. Hospitalization necessary. Active supportive treatment necessary	Often sleeping; play limited to passive activities	20
Moribund	No play; does not get out of bed	10

APPENDIX 6 IMAGING LESION EVALUATION CRITERIA

For PET-based assessments, a clinical response of progressive metabolic disease (PMD), no metabolic response (NMR), partial metabolic response (PMR), or complete metabolic response (CMR) will be determined. PMD/PD includes radiological evidence of progression per Lugano Classification Revised Staging System for malignant lymphoma. The PET scan metabolic uptake will be graded using the Deauville 5-point scale, with a score of ≤ 3 considered to represent a CMR.

Deauville 5-point scale: 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.

Table 1: CMR / CR

Response/Site	FDG PET-CT-Based (Complete Metabolic Response)	CT-Based (CR)[a] All of the following:
Lymph nodes and extralymphatic sites	Score 1, 2 or 3 with or without a residual mass on 5-Point-Scale 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.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured 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

[a] CT-Based could also apply to MRI-Based

Note: 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;32:3059-68.

Table 2: PMR / PR

Response/Site	FDG PET-CT-Based (Partial Metabolic Response)	CT-Based (PR)[a] 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 At interim, these findings suggest responding disease At end of treatment, these findings suggest residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value; when no longer visible, 0 X 0 mm; for a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	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

[a] CT-Based could also apply to MRI-Based

Note: 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;32:3059-68.

Table 3: NMR / SD

Response/Site	FDG PET-CT-Based (NMR)	CT-Based[a] (SD)
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 in SPD of up to 6 target measurable nodes and extranodal sites; no criteria for Progressive Disease met
Non-measured lesion	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

[a] CT-Based could also apply to MRI-Based

Note: 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;32:3059-68.

Table 4: PMD / PD

Response/Site	FDG PET-CT-Based (PMD)	CT-Based (PD)[a] At least one of the following:
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or 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 & Increase by ≥ 50% from PPD nadir & 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
Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., 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

[a] CT-Based could also apply to MRI-Based

Note: 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;32:3059-68.

APPENDIX 7 MANAGEMENT ALGORITHIMS FOR IMMUNO-ONCOLOGY AGENTS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

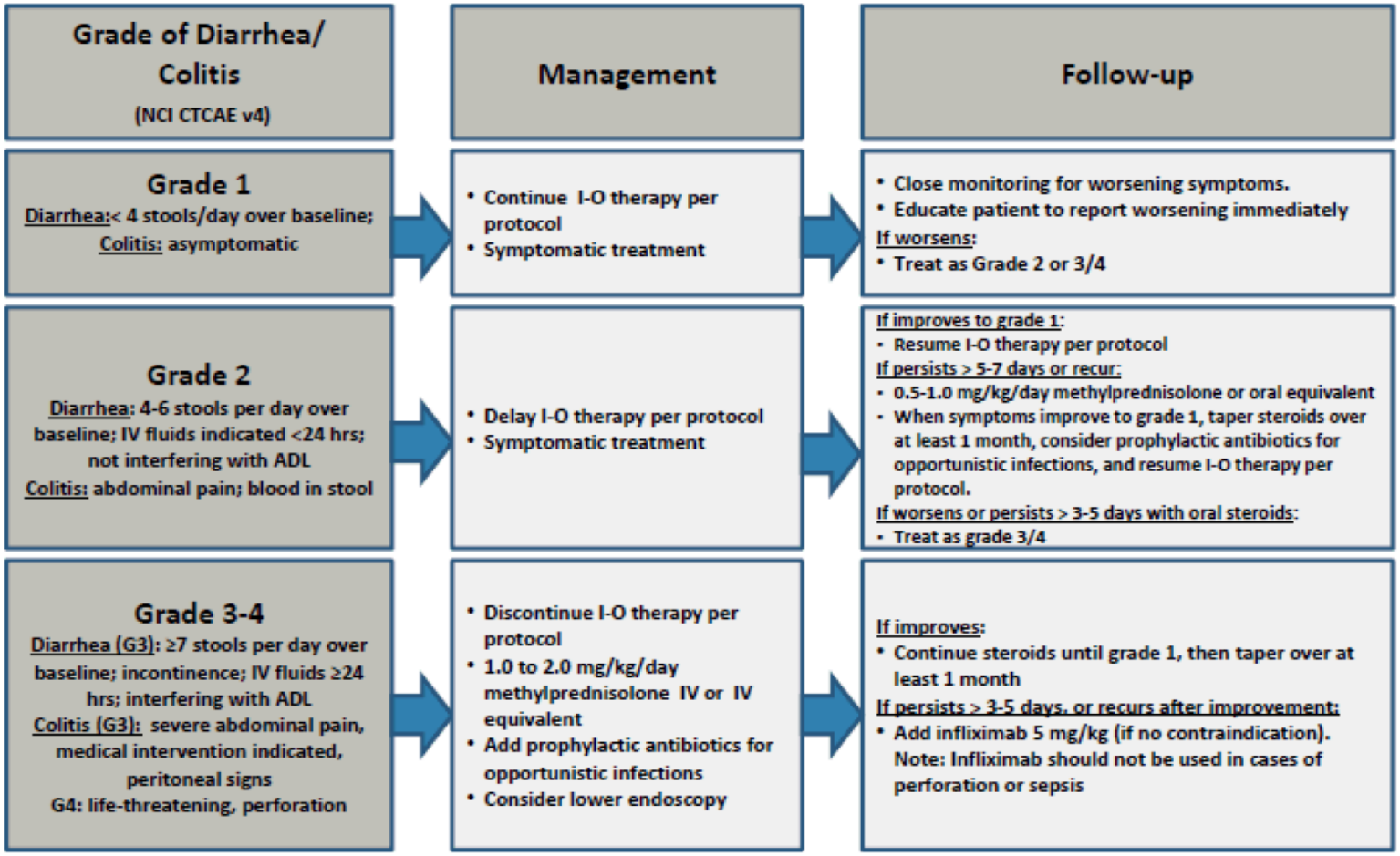
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

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

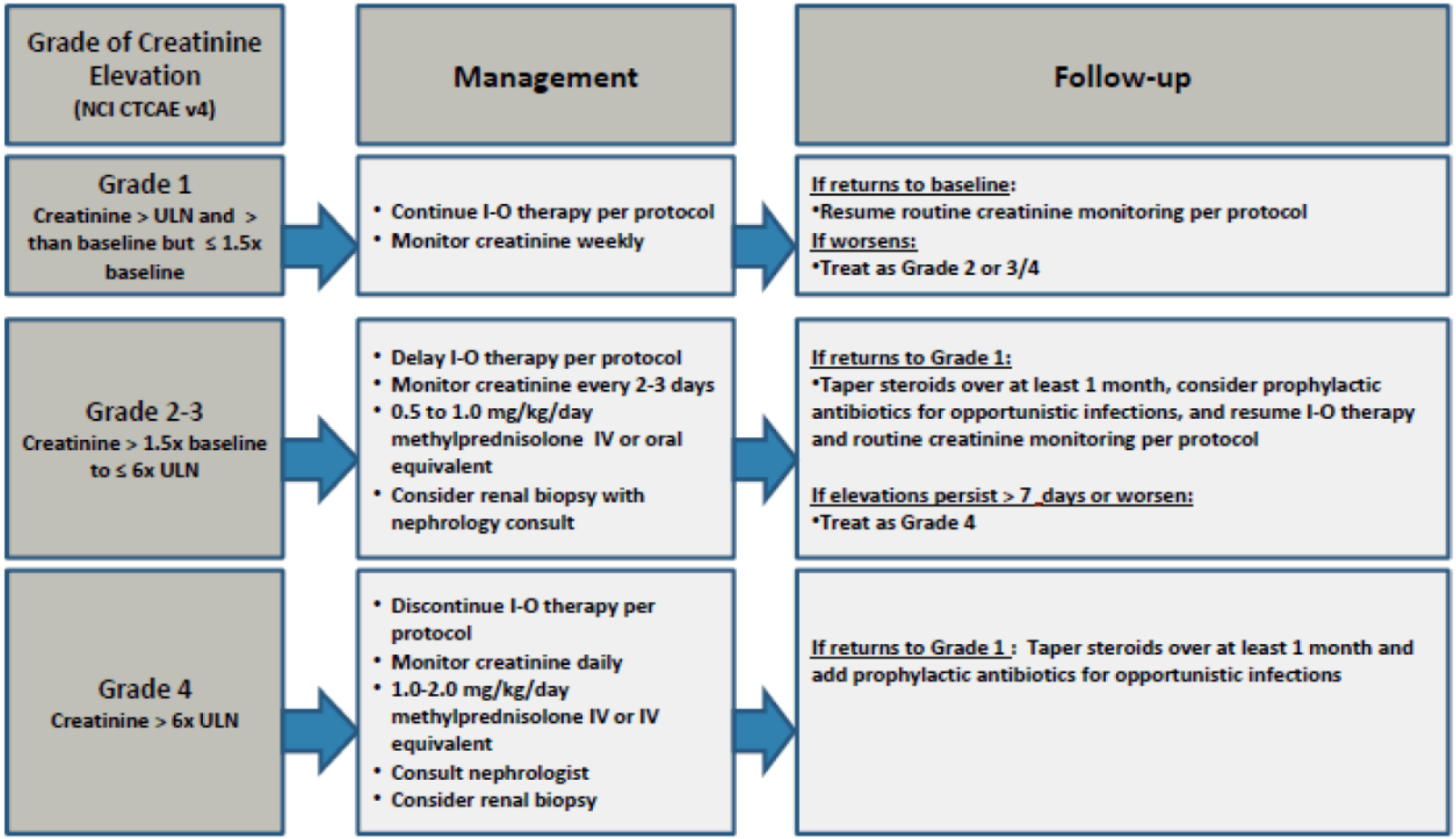


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

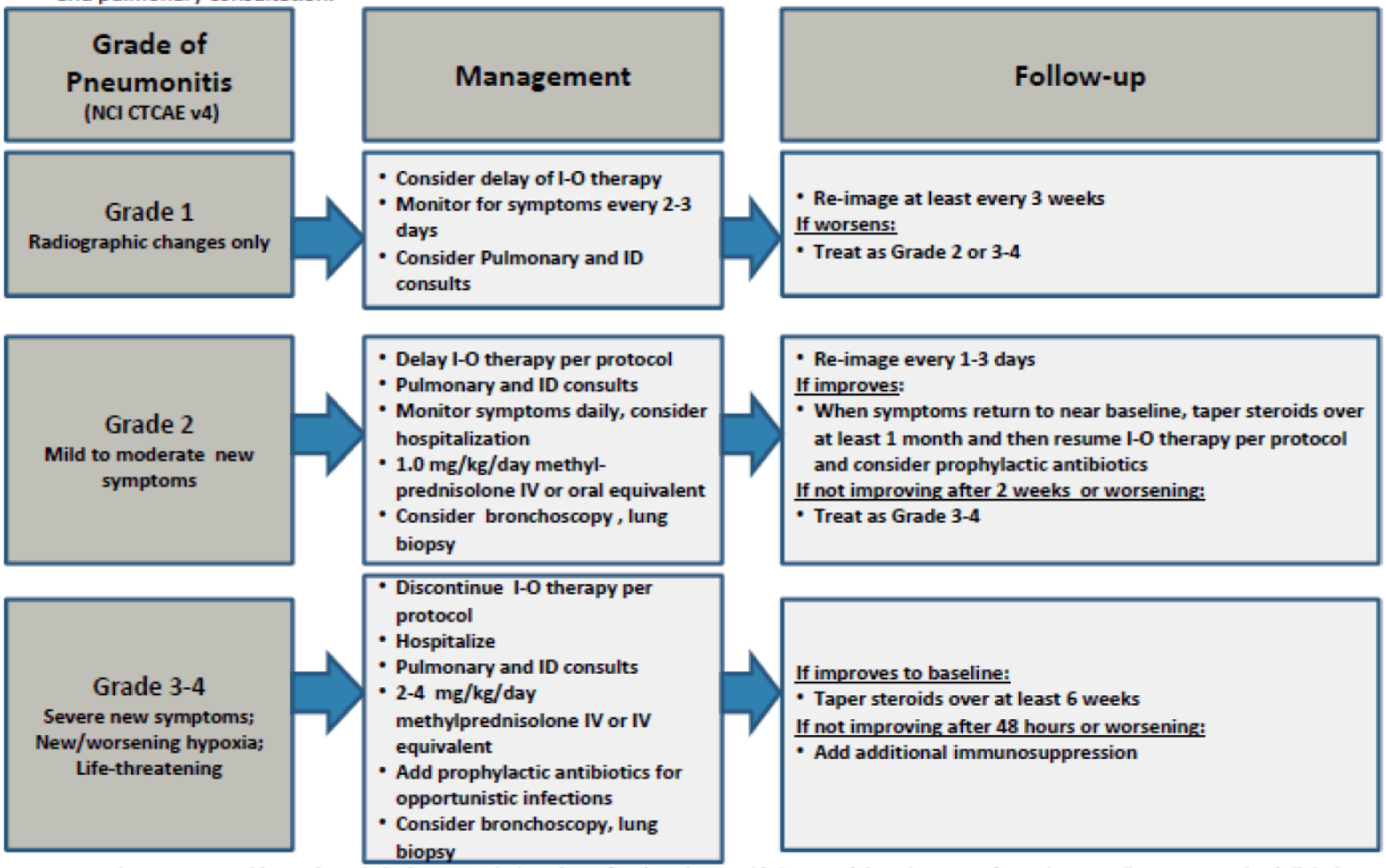


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

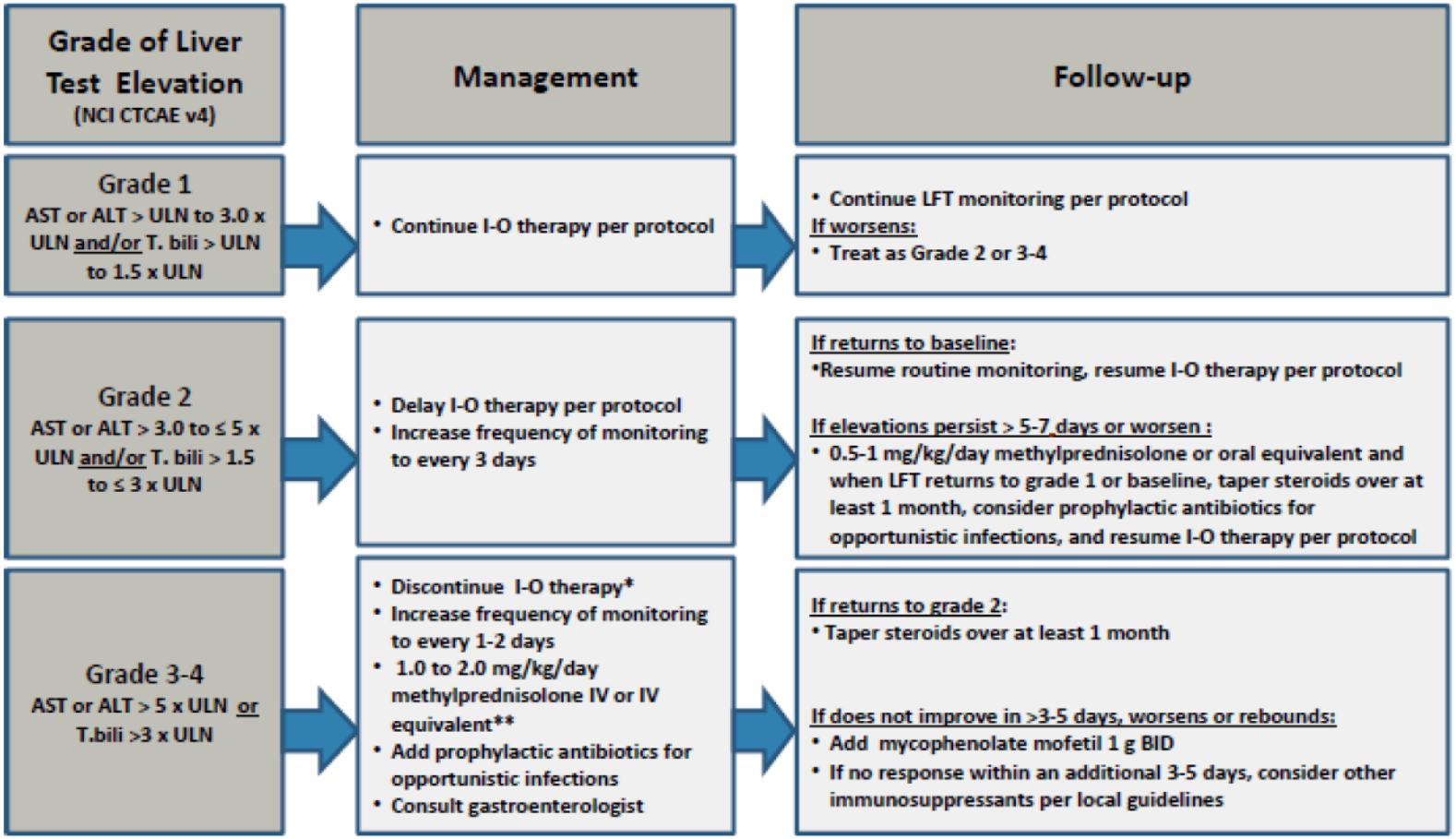


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

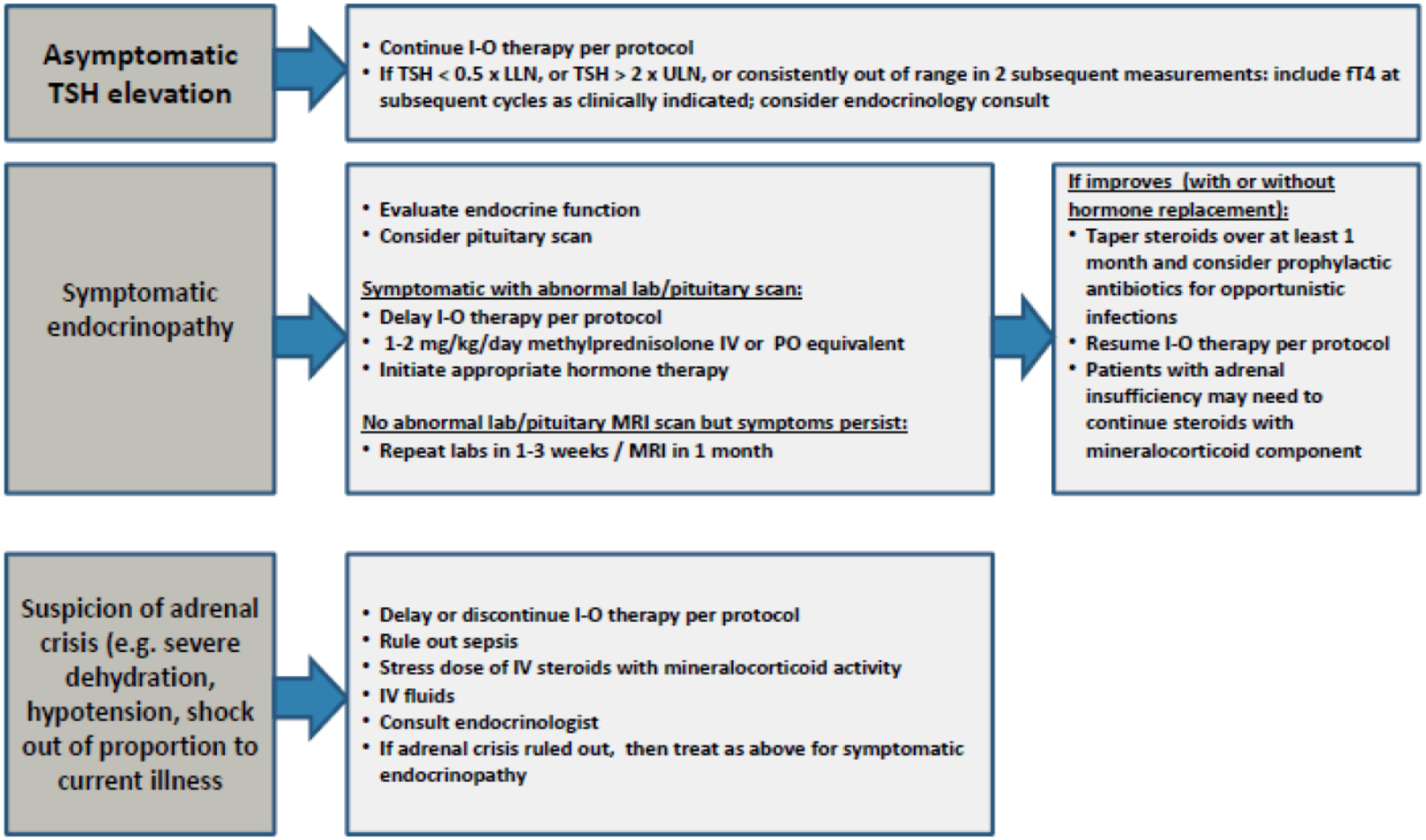
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

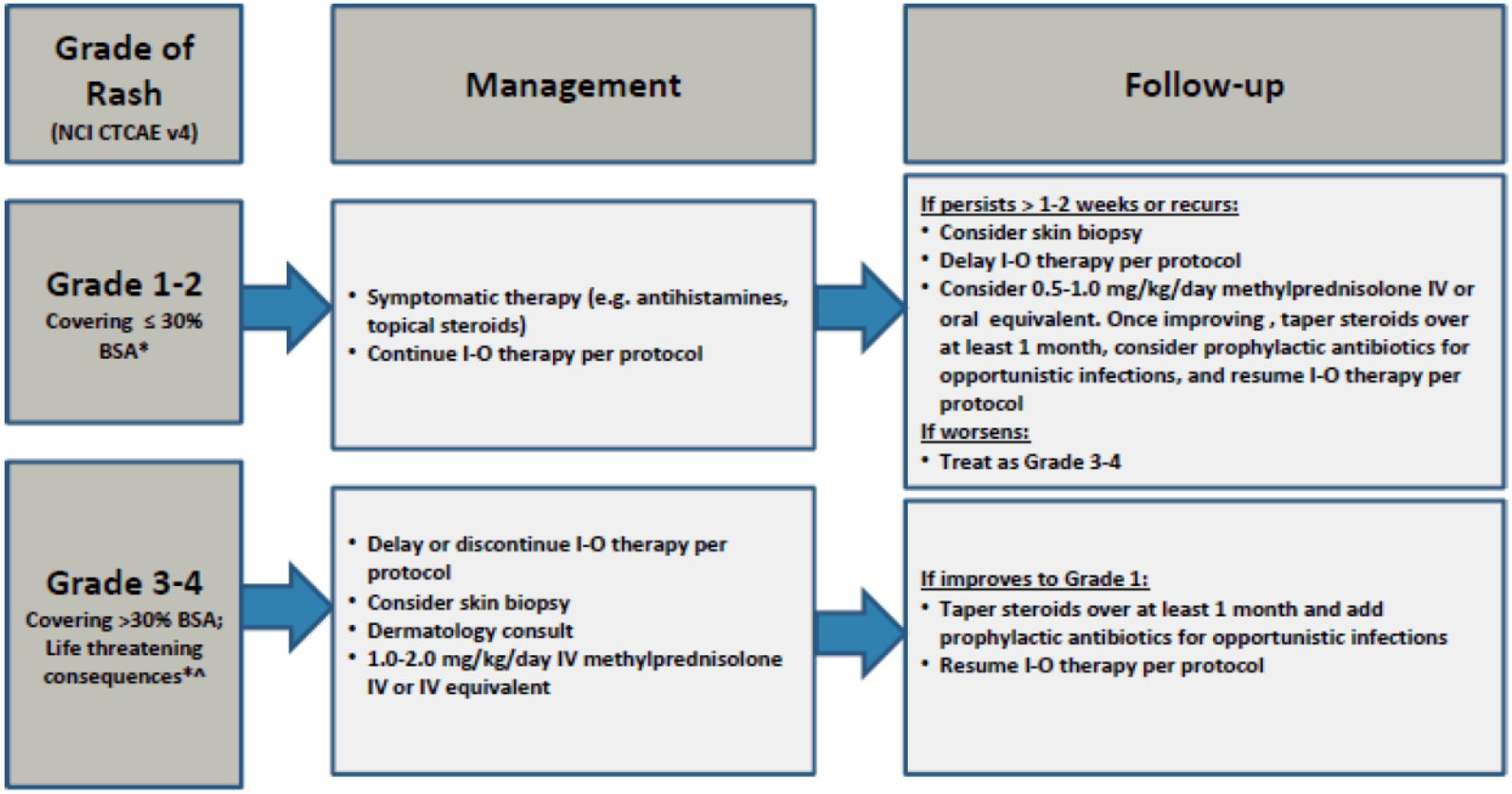


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

Updated 05-Jul-2016

APPENDIX 8 RADIOTHERAPY GUIDELINES FOR THE R1 COHORT

Radiotherapy is effective for selected patients with Hodgkin lymphoma and should be considered for incorporation into salvage programs. The purpose of this document is to provide radiation guidelines for patients in the R1 cohort. Relapse and refractory Hodgkin lymphoma is more aggressive than de novo disease, consequently radiotherapy recommendations are different than those found in the upfront COG and Euronet HL studies, including slightly higher radiation dose to 30-30.6 Gy. Radiotherapy volumes for the R1 cohort are expected to be of modest size, utilizing advanced radiation concept including modern field design based on PET and CT imaging and modern radiation techniques including breath-hold techniques, IMRT, VMAT, and/or proton therapy when available. Patients requiring excessively large radiation fields should be treated on the R2 cohort and receive high dose chemotherapy and autologous stem cell transplant instead of large field radiation. In instances where patients enrolled and treated on the R1 cohort are found to have large RT volumes or higher radiation doses to critical organs than the investigator or protocol allows, a discussion with the steering committee is recommended as the best course of action for the individual patient.

General Principles—Involved Site Radiation Therapy (ISRT)

The International Lymphoma Radiation Oncology Group (ILROG) recommended guidelines for consolidative radiotherapy is to use Involved Site Radiotherapy (ISRT)[1] [2]. ISRT targets the pre-treatment sites of involvement with margin based on the fusion of the CT simulation with the pre-treatment PET/CT scan, with larger margins utilized when there is less certainty between the fusion of the scans. For the purposes of this retrieval study, the pre-treatment scan will be the PET/CT scan obtained prior to starting Nivolumab + brentuximab vedotin. In the special instance**, where the patient relapsed quickly after initial chemotherapy and is enrolled in R1, the sum of all PET/CT scans within the prior 12 months should be used to develop the ISRT field.

Indications for Radiotherapy

Patients in the R1 cohort, who have:

1) CMR after 4 cycles of N+BV, will have 2 additional cycles of N+BV and then will receive ISRT.
2) Stable or partial response to the first 4 cycles of N + BV, who then achieve a CMR following 2 additional cycles of BV + B, will also receive ISRT.

[1] Hodgson DC, Diedkmann K, Terezakis S, Constine L. Implementation of contempoarary radiation therapy planning concepts for pediatric Hodgkin lymphoma: Guidelines from the International Lymphoma Radiation oncology Group. *Pract Radiat Oncol*. 2015 Mar-Apr;5(2):85-92.

[2] Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, Girinsky T, Hoppe RT, Mauch P, Mikhaeel NG, Ng A; ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group. *Int J Radiat Oncol Biol Phys*. 2014 Jul 15;89(4):854-62

Radiotherapy Dose and Schedule

The ISRT dose is 3000 cGy (150 cGy per day) or 3060 cGy (180 cGy per day) to the ISRT volume. Fractionation schedule among these two options is at physician's discretion.

The treatment will be given 5 days per week. The total elapsed treatment time will be approximately 3.5-4 weeks (17-20 sessions).

Timing of Radiotherapy and Starting Criteria

Treatment should begin no later than 6 weeks from the start of the last cycle of chemotherapy or when blood counts have recovered.

Modality

Photons with a nominal energy of ≥ 4 MV and ≤ 18 MV are preferred. In the unusual circumstance of an isolated superficial lesion, electron fields may be used. Conventional, conformal, and IMRT techniques are allowed in this study. Patients receiving IMRT should have this delivered with 6-10 MV photon beams, and 18 MV photon beams should not be used to deliver IMRT. Proton therapy is allowed.

Treatment Position

The patient should always be treated in the supine position. Some institutions may incline female patients to reduce breast dose, and this is acceptable. The use of a breast board to reduce breast dose in female patients is acceptable. Reproducible setups are critical, and appropriate immobilization devices should be used to ensure reproducible set up. Moderate deep inspiratory breath hold technique, respiratory gating or tracking techniques are recommended and should be considered and evaluated for patients with mediastinal involvement at institutions with experience and the technology to utilize this technique.

Treatment Planning

CT (volumetric) based planning is required to optimize dose to the target volume while reducing dose to normal tissues. Slices ≤ 5 mm thick should be taken throughout the extent of the irradiated volume., Where fields include the mediastinum or pulmonary hila the entire lung volume should be scanned to enable accurate estimates of whole lung dose. A Dose Volume Histogram (DVH) is necessary to determine target coverage and evaluate dose to normal tissues.

In-Room Verification of Spatial Positioning

Image guidance to verify patient position is an important standard feature of contemporary RT delivery. Institutional protocols should be in place common to verify patient position.

Target Volumes (see figure 1 below)

Recommendations of The International Commission on Radiation Units and Measurements (ICRU) for prescription methods and nomenclature will be utilized for this study.

ISRT volumes should be used for 3000 cGy (150 cGy/fraction) or 3060 cGy (180cGy/fraction)

ISRT should be limited to 4 or fewer sites (per German Hodgkin Study Group definition) if involvement is just above the diaphragm or 3 or fewer sites if involvement is above and below the diaphragm.

Post-Chemotherapy Clinical Target Volume (CTV)

For ISRT: The CTV should follow the ISRT volumes and include all the involved lymph nodes and lymphatic tissue at relapse just prior to initiating N+BV, but must take into account the reduction in axial diameter that has occurred with chemotherapy. Typically lymph nodes will be considered involved if they are PET-avid, but lymphadenopathy that is >2.5cm that appears to be pathological even if it is not PET avid (for example necrotic nodes) should be included. The concept is that all areas of lymphoma infiltration needs to be targeted, however following a good response to chemotherapy, previously displaced normal tissue should not be irradiated eg lung displaced by mediastinal lymph nodes, or bowel displaced by para-aortic nodes. Anterior mediastinal disease will shrink in axial diameter away from the lung with chemotherapy, and the width of the CTV should reflect this change. The superior and inferior volume of the ISRT CTV should correspond to the initial sites of involvement. When contouring the CTV volume, one should consider inaccuracies in matching patient positioning and the variable internal anatomy shifts that change with disease volume and patient position between diagnostic and treatment positions even with the best image fusion software. As a guideline, a margin of 1.5 cm above and below the involved lymph nodes is recommended. In the neck, on a given axial cut, the whole nodal fossa/level that contained the initially abnormal node(s) should be contoured as the CTV.

Internal Target Volume (ITV)

The ITV encompasses the CTV with an added margin to account for variation in shape and motion within the patient. Respiratory motion, for example, will produce movement of the mediastinal structures and spleen, and an additional margin around the CTV is required to account for this and should be based on institutional guidelines.

Planning Target Volume (PTV)

The PTV should encompass the CTV and ITV, and accounts for geometric variation in daily setup. It should take into account the reproducibility of the immobilization, and the accuracy of the daily setup imaging and should be based on institutional guidelines. The PTV margin may range from 3-5 mm on the CTV in the neck to 5-10mm on the ITV in the mediastinum and abdomen.

Targets at non-contiguous sites need to be separately identified. Generally, in cases for which two PTV targets are >3 cm apart, these should be treated separately unless there is a compelling reason to treat uninvolved tissue in between.

Figure 1

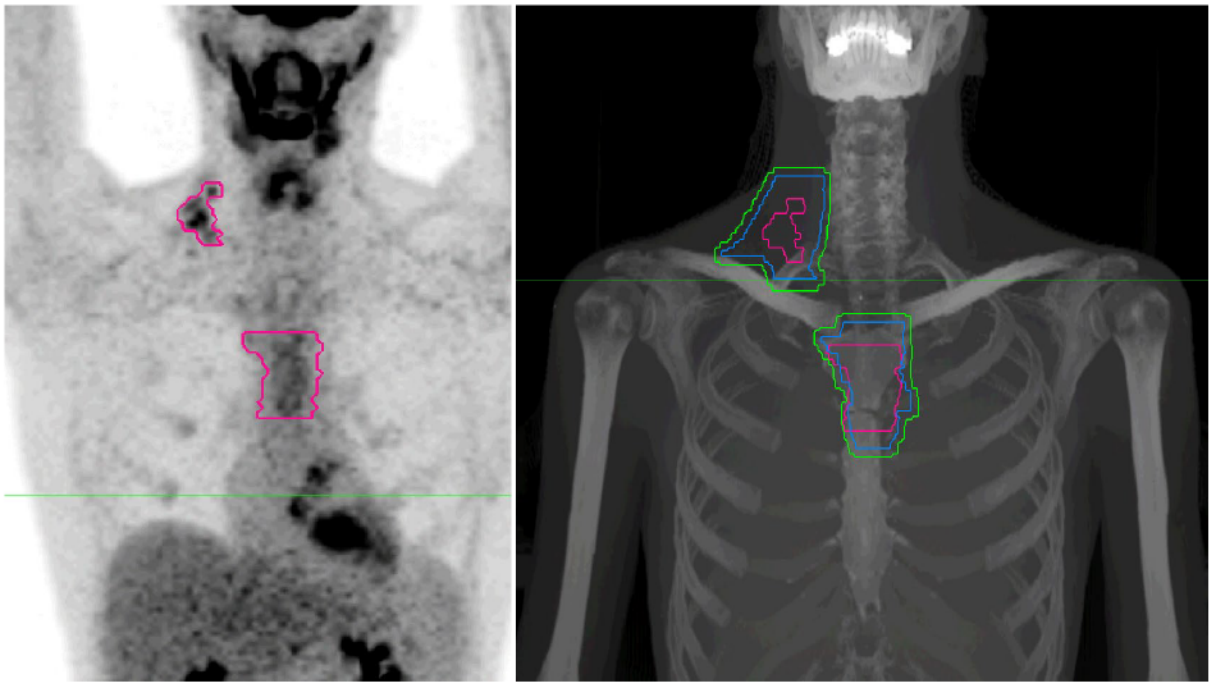


Figure 1: Depicts a patient who relapses 3 years following chemotherapy and is enrolled in R1. On the left is a PET image demonstrating the two sites of relapse in the right supraclavicular fossa and mediastinum drawn in pink. On the right is the ISRT target volumes being treated to 3000 cGy. This includes pink (prechemotherapy sites of relapse), blue (ITV), and green (PTV).

Target Dose

The total dose will be 3000-3060 cGy

In the special circumstance**, where patient recurs within 12 months of initial chemotherapy, the ISRT field that contains all PET avid disease since the original diagnosis will be included in the ITV (figure 2), with a volume reduction after 2100 cGy (150 cGy/fraction) or 1980 cGy (180

cGy/fraction) (Phase 1), to just the ISRT field based on involved sites at relapse for the remaining 900cGy (150cGy/fraction) or 1020 cGy (180 cGy/fraction) (Phase 2).

Figure 2:

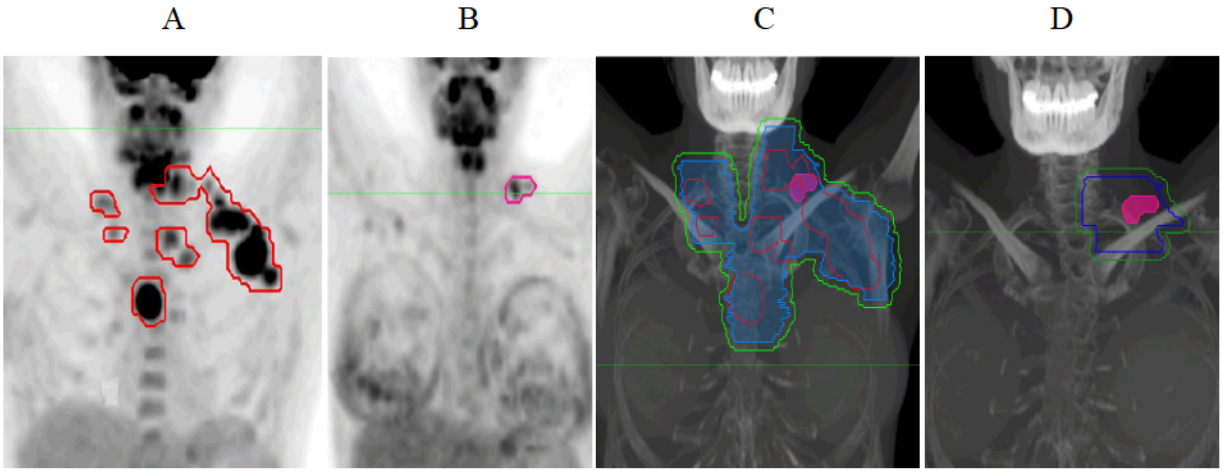


Figure 2: 23yo presents with Stage IIA HL treated with ABVD x 3 with initial PET/CT (A). Relapses 6 months later with PET/CT (B). RT for patient enrolled in R1 study includes site of recurrence (pink) and sites involved within the prior 12 months (red) in the ISRT field with ITV (blue) and PTV (green) (C) being treated to 21 Gy. Reduced volume to just the site of recurrence to an additional dose of 9 Gy for a total dose of 30 Gy (D).

Organs at Risk and Target coverage Goals

The following dose constraints should be considered for the protocol:

	preferred	unacceptable
CTV/ITV D99%	≥ 95%	<95%
PTV D10%	≤ 110%	>110%
PTV D95%	≥ 95%	<92%
PTV D0.03 cc	≥ 75%	<75%
Lungs (mean)	≤ 14 Gy	>14 Gy
Lungs V20	≤ 25%	>30%
Spinal cord max dose	≤35 Gy	>35 Gy
Spinal cord max dose, prior RT	Combined <44 Gy	Combined >50* Gy
Heart (mean)	≤15 Gy	>18.5 Gy
Heart (mean), prior RT	Combined <20 Gy	Combined > 20Gy
Breast (mean)	≤ 4 Gy	None
Parotids (mean)	≤ 15 Gy**	> 24 Gy

*50Gy (cumulative total dose to the spine) is associate with a risk of 0,2% myelopathy

** In nodal sites located close to parotid glands, at least one parotid gland is spared to a mean dose of less than 20 G

APPENDIX 9 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 03: 26-Mar-2018

The response assessment by investigators using Lugano 2014 response criteria was added as a secondary endpoint to allow for a comprehensive interpretation of the study data. For this response-adapted trial, BICR assessment is utilized for tumor assessments (TA) at study treatment-related decision time-points to determine further treatment. If the TA by investigator is CMR but BICR assessment differs and study treatment discontinued, collection of tumor assessments until investigator assessed radiographic progression, per Lugano 2014 will allow for the interpretation of these cases. Guidance for collection and submission of tumor assessments was added to support the evaluation of this new secondary endpoint.

Contraception requirements for female participants of child bearing potential were modified to properly align with Nivolumab clinical research standard guidelines (one highly effective method) and brentuximab label (two effective methods). Therefore the protocol was amended to require two effective methods, with one highly effective, to improve contraception options and flexibility for participants, while maintaining the requirements for all 3 IMPs.

Other minor edits were made, as described in the Summary of Key Changes.

This is applicable for all study participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section # 1: Synopsis and Section 4: Objectives and Endpoints	Addition of secondary endpoint	To additionally evaluate efficacy endpoints, per investigator assessments, using Lugano 2014 response criteria.
Section # 1: Synopsis and Section 5: Study Design	Deletion of examples for Radiation Therapy and addition of reference to RT Guidelines Appendix 8 Additional guidance for tumor assessments when investigator assessment is CMR, but BICR differs.	To reference RT guidelines, created by COG and Euronet, for R1 Cohort Consolidation Therapy. To support new secondary endpoint to evaluate efficacy endpoints, per investigator assessments, using Lugano 2014 response criteria.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section #.2: Table 2.-2	Amend Cycle 5 and 6, Day 1 and Day 15 Induction to both reference footnote c. Update Footnote c to reflect potential application for R2 cohort, if additional cycles are approved for consolidation therapy delay Amend footnote e to footnote d, in Consolidation Phase Column.	Administrative clarifications, for consistency with existing protocol language in the table footnotes and section 5.1.
Section #.2: Table 2.-4, and Section 9.1: Efficacy Assessment	Add reference to section 5.1, for cases where investigator assessments differ from BICR, at a real-time read.	To support new secondary endpoint to evaluate efficacy endpoints, per investigator assessments, using Lugano 2014 response criteria.
Section #.2: Table 2.-5, and Section 6.1: Inclusion Criteria 2c	The minimum number of slides (20) was removed for inclusion criteria 2c and added to Table 2.-5	In rare cases, <20 slides may still meet minimum eligibility requirements, therefore this language was relocated.
Section 7.1.1: Treatment for Infusion Reactions	Add reference to appendix 7	To reference additional treatment guidance immune mediated adverse events.
Section 10.3.1	Addition of Statistical Analysis Method for a new secondary endpoint.	To additionally evaluate efficacy endpoints, per investigator assessments, using Lugano 2014 response criteria.
Appendix 4: Contraception Guidance for Female Participants of Child Bearing Potential	Modification of contraception guidance to require 2 effective methods, with a minimum of one highly effective.	To increase flexibility of contraception options, while maintaining alignment with PI/SMPC requirements for all IMPs

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 8: Radiotherapy Guidelines for the R1 Cohort	Addition of appendix for RT Guidelines	Created by COG and Euronet, to provide further guidance for R1 Cohort Consolidation Therapy.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Overall Rationale for Revised Protocol 02: 01-Jun-2017

[redacted]

Clarification about contraception guidelines was needed in order to avoid confusion and to harmonize differences between the protocol and global product labels (Brentuximab and Bendamustine). A common approach for all IMPs requires 6 months of contraception after last IMP dose for WOCBP and 7 months for males with partners of WOCBP. Additionally, clarification was provided about the requirement for 2 contraception methods or complete abstinence.

Other minor edits were made, as described in the Summary of Key Changes.

This is applicable to all study patients.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section #2: Tables 2.-1 to 2.-4	Added reference to section 9.1-Efficacy Assessment.	Minor update, to cross-reference information in Section 9.1
Section #2: Table 2.-5, footnote b	Move footnote b to Cycle 3 Day 1 Soluble, Biomarker Sample	Minor correction, due to inconsistency with footnote language.
Section #1: Synopsis; Section #4	Added co-primary endpoint of CMR rate for R1 Cohort.	This co-primary endpoint was added [redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Objectives and Endpoints		
Section #5.1.1 Data Monitoring Committee and Other External Committees	Updated DMC language to better distinguish the 3 overarching categories (rash ≥ 3, pulmonary toxicity, and peripheral neuropathy) from subcategories and correcting inconsistency with number of observations and % required for events where N=40	Minor corrections, due to inconsistencies with other language within this section.
Section #6.1: Inclusion Criteria	Inclusion criteria 3d was modified to reflect 2 methods of contraception or complete abstinence (from Appendix 4) are required during study treatment until 6 months from last dose of all IMPs for WOCBP.	Corrected due to inconsistency with Section 7 reference to follow SMPC/PI for Bv and bendamustine administration guidelines.
Section #6.1: Inclusion Criteria	Inclusion criteria 3e was modified to reflect 2 methods of contraception or complete abstinence (from Appendix 4) are required during study treatment until 7 months from last dose of all IMPs for males with partners of WOCBP. Additionally, to refrain from sperm donation during this time.	Corrected due to inconsistency with Section 7 reference to follow SMPC/PI for Bv and bendamustine administration guidelines
Section #6.1: Inclusion Criteria	Inclusion criteria 5e was modified to require 3 half-life wash-out for biologics.	Minor correction, due to inconsistency with inclusion criteria 5 f for monoclonal antibodies.
Section #7.1:	Specify a minimum of 30 minutes is required between end of Bv infusion and bendamustine.	Minor clarification, for consistency with guidance provided for combination therapies in this trial.
Section #7.6.1	Deleted "See section 7.6.2.1 regarding stem cell collection (eg: Neulasta)"	Minor clarification, as this is not applicable nor further described in section 7.6.2.1.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section #9.1.1	Clarified imaging modality is per Standard of Care in follow-up for patients with PMR/NMR.	Minor clarification of language in this section.
Section # 10.3.1: Efficacy Analysis	Updated statistical analysis method for CMR rate.	Updated due to the addition of co-primary endpoint (CMR rate) for R1 cohort.
Appendix 4: WOCBP Definition and Methods of Contraception	Updated language regarding contraception requirements for all IMPs: 2 methods, 6 months after last dose of all IMPs for WOCBP, and 7 months after last dose of all IMPs for males with partners of WOCBP.	Corrected due to inconsistency with Section 7 reference to follow SMPC/PI for Bv and bendamustine administration guidelines.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized