CITY OF HOPE MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A phase II trial of response-adapted second-line therapy for Hodgkin lymphoma using anti-PD-1 antibody nivolumab ± ICE chemotherapy as a bridge to autologous hematopoietic cell transplant (NICE Trial)

CITY OF HOPE PROTOCOL NUMBER: IRB # 16403 Protocol Date 4/27/21

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DISEASE SITE: Hodgkin Lymphoma
STAGE: Relapsed/Refractory
MODALITY(IES): chemotherapy/monoclonal antibody
TYPE: Phase II

PRINCIPAL INVESTIGATOR: Alex Herrera, MD

PARTICIPATING CLINICIANS: Leslie Popplewell, MD, Tanya Siddiqi, MD, Jasmine Zain, MD, Elizabeth Budde, MD, Matthew Mei, MD, Ibrahim Aldoss, MD, Michael Rosenzweig, MD, Samer Khaled, MD, Eileen Smith, MD, Stephen Forman, MD, Steven Rosen, MD, Larry Kwak, MD, Saro Armenian, MD, Joseph Rosenthal, MD, Joo Song, MD, Liana Nikolaenko, MD, Amandeep Salhotra, MD, Geoffrey Shouse, M.D. Ammar Chaudhry, MD, Swetha Kambhampati, M.D., John Baird, M.D., Alexey Danilov, M.D., Ph.D., James Godfrey, M.D.

NURSE PRACTITIONER:	Yi-Ping Wen, NP (M.S.)
BIOSTATISTICIAN:	Joycelynne M. Palmer, PhD

City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Clinical Trial Protocol

A phase II trial of response-adapted second-line therapy for Hodgkin lymphoma using anti-PD-1 antibody nivolumab ± ICE chemotherapy as a bridge to autologous hematopoietic cell transplant (NICE Trial)

Protocol Version Date:	04/27/2021
Protocol Version No.:	14
COH Protocol No.:	16403
Agent:	Nivolumab, Ifosfamide, Carboplatin, Etoposide
Sponsor/IND#:	City of Hope/133829
NCT number	NCT03016871
Participating Sites	City of Hope, MD Anderson Cancer Center, Yale Cancer Center, Dana-Farber Cancer Institute

Principal Investigator
Alex Herrera, MD
City of Hope National Medical Center
Hematologic Malignancies and Stem Cell Transplantation Institute
1500 E. Duarte Road
Duarte, CA 91010
O: 626-256-4673 ext.82405
Email: aherrera@coh.org

Data Coordinating Center
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
Email: DCC@coh.org

Protocol Team

Biostatistician/Co-Investigator
Joycelynne M. Palmer, PhD
Department of Quantiative and Computational Medicine
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
O: 626-218-5266
Email: jmpalmer@coh.org

Co-Investigator
Ammar Chaudhry, MD
Department of Diagnostic Radiology
City of Hope National Medical Center
1500 E Duarte Road
Duarte, CA 91010
O : 626-218-6442
Email : achaudhry@coh.org

Participating Non-COH Sites

Co-Investigator
Hun Ju Lee, MD
MD Anderson Cancer Center
Department of Lymphoma/Myeloma
1515 Holcombe Boulevard Unit 429
Houston, Texas 77030-4009
O: 713-794-1829
F: 713-794-5656
Email: hunlee@mdanderson.org

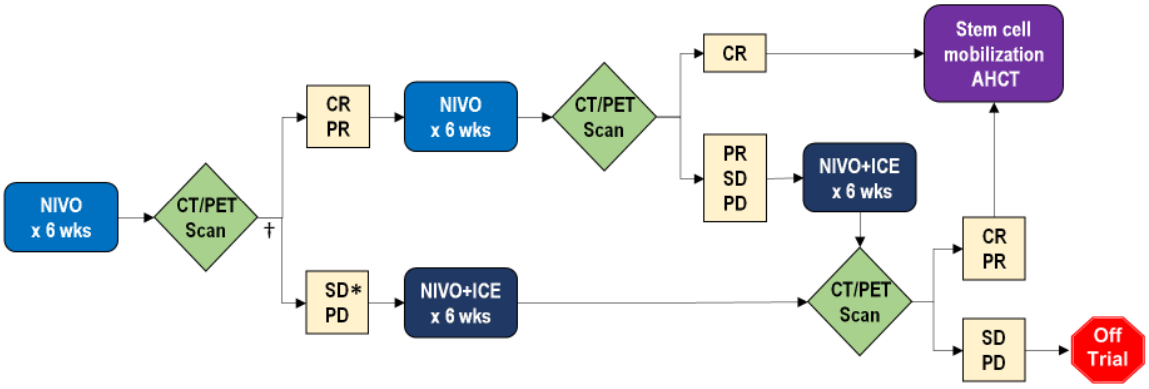
Co-Investigator
Iris Isufi, MD
Yale Cancer Center
333 Cedar Street
New Haven, Connecticut 06510
O: 203-737-5751
Email: iris.isufi@yale.edu

Translational Investigator
Margaret A. Shipp, MD
Dana-Farber Cancer Institute
Division of Hematologic Neoplasia
450 Brookline Avenue
Boston, MA 02215
O: 617-632-3874
F: 617-632-4734
Email: margaret_shipp@dfci.harvard.edu

Translational Investigator
Scott J. Rodig, MD, PhD
Dana-Farber Cancer Institute
Department of Pathology
450 Brookline Avenue
Boston, MA 02215
O: 617-732-7510
Email: srodig@partners.org

Experimental Design Schema

Original Design Schema (Cohort A)



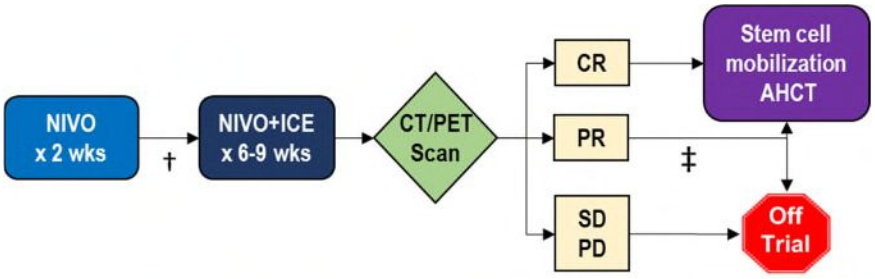
Note: Nivolumab dosing is 240 mg IV every 2 weeks for the first 12 weeks or 6 cycles.
When in combination with ICE, the dosing is 240 mg IV every 3 weeks for 6 weeks or 2 cycles.

ICE:Ifosfamide: 5000 mg/m^2 continuously on D2, IV
Carboplatin: AUC 5 on D2, IV
Etoposide: 100 mg/m^2 D1-3, IV
Mesna: 5000 mg/m^2 continously on D2, IV

†Tumor biopsy (if safe and accessible) must be performed after the first CT/PET response assessment (and only in patients who did not reach CR). For patients (with PR) who are going to a second 6-week treatment with single-agent NIVO, biopsy may be performed at any time after the first CT/PET scan (but before any NIVO+ICE treatment). For patients (with SD or PD at first CT/PET) who are instead going to a 6-week treatment with NIVO+ICE, biopsy must be performed before starting NIVO+ICE.

*Patients who only achieve SD after 6 weeks of single agent nivolumab can either receive an additional 6 weeks of single agent nivolumab, or receive a combination of nivolumab plus ICE for 6 weeks. The decision to go either way will be at the physician/investigator's discretion on a case-by-case basis.

New Cohort Design Schema (Cohort B)



To enroll after completion of Cohort A.

Note: Nivolumab dosing is 240 mg IV on the first week of the initial 14 day cycle. In combination with ICE, nivolumab dosing is 240 mg IV every 3 weeks for 2-3 cycles. ICE is as indicated in Section 5.1.2.

†Tumor biopsy (if safe and accessible) must be performed before starting NIVO+ICE.

‡ Patients achieving PR may proceed to AHCT at the at the physician/investigator's discretion on a case-by-case basis

Protocol Synopsis

Protocol Title:	
A phase II trial of response-adapted second-line therapy for Hodgkin lymphoma using anti-PD-1 antibody nivolumab ± ICE chemotherapy as a bridge to autologous hematopoietic cell transplant (NICE Trial)	
Brief Protocol Title (Lay Public):	
A phase II study of nivolumab with or without ICE for high-risk Hodgkin lymphoma	
Study Detail	
Indication(s):	Hodgkin lymphoma
Phase:	II / Single Arm
Number of Participants:	Original Cohort (A): 43; New Cohort (B): 35
Expected Accrual Duration:	24 months (1-2 subjects/month): New Cohort (B) 24 months
Estimated Study Duration:	72 months
Anticipated Participant Duration:	24 months:
Participating Sites:	• City of Hope; Duarte, CA • MD Anderson Cancer Center; Houston, TX • Yale Cancer Center, New Haven, CT • Dana Farber Cancer Institute, Boston, MA
Study Agents:	• Nivolumab (anti-PD-1 monoclonal antibody) • Ifosfamide • Carboplatin • Etoposide
Sponsor:	City of Hope National Medical Center
Industry Partner:	Bristol-Myers Squibb (BMS)
Study Rationale:	

Hodgkin lymphoma is a neoplasm of lymphoid tissue that is histopathologically defined by the presence of malignant Hodgkin-Reed-Sternberg (HRS) cells in a background of inflammatory cells. The characteristic surface antigen expressed on HRS cells is CD30. In 2016, it is estimated there will be approximately 8,500 new cases of HL diagnosed in the United States, and 1,120 patients will die of their disease.[1] Approximately 30-40% of patients presenting with HL will become refractory to initial therapy or will relapse; for these patients, the only potentially curative therapy is salvage combination chemotherapy followed by autologous hematopoietic cell transplantation (AHCT).[2] Typically, the response rate to regimens such as ICE/DHAP/GDP ranges between 60-80%, with a complete response (CR) of 9-21% in the pre-PET era.[3-5] In the post PET era, the CR of salvage therapy such as augmented ICE or IGEV is 54%-60% according to small studies. It is well known that patients who are PET negative at the time of AHCT will have improved progression-free survival (PFS) post AHCT.[6]

Nivolumab is a humanized monoclonal antibody designed to block the interaction between PD-1 and PD-L1. PD1 expression downregulates T cell response and allows tumors to suppress immune control of the host. Nivolumab has been shown to be active in Hodgkin lymphoma.[7] OPDIVO (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014) in a variety of solid tumors. Based on its high response rate of 66% in patients who progressed after AHCT and brentuximab vedotin(BV), nivolumab was granted accelerated FDA approval for relapsed/refractory HL after failure of AHCT and BV in 2016.[8]

Nivolumab is minimally myelosuppressive and should be easily combined with ICE salvage chemotherapy. Since nivolumab is an immunotherapy that may provide a stronger response in patients who are immunocompetent, we would like to examine its efficacy in the pre-AHCT population. We propose a sequential study of using nivolumab as 1st salvage therapy post induction failure. For patients who achieve CR, they can go directly to AHCT. For patients not in CR after 12 weeks of nivolumab or who have not achieved at least a PR after 6 weeks of nivolumab, we will combine nivolumab plus ICE for 2 cycles. Patients achieving a SD at the end of the first 6 weeks of single agent nivolumab can be allowed to continue with nivolumab alone at the physician/investigator's discretion on a case-by-case basis. This approach is meant to increase the proportion of patients who are in CR at the time of AHCT.

During the progress of Cohort B, prior to the formal assessment of safety, we have observed promising efficacy in this group of high-risk patients with primary refractory or early relapsed HL treated thus far (CR in all, n = 13). In this group salvage regimens are often associated with lower CR rates in patients with primary refractory cHL compared to relapsed cHL [9,10]. Therefore, with poorer outcomes after both conventional and even more novel immunotherapy-containing regimens, improving the efficacy of salvage therapy remains critical in patients with high-risk cHL. Given the exceptionally high CR rate observed thus far and without any signals of excess toxicity to date, we will expand Cohort B to a full Phase 2 efficacy cohort to assess whether the CR rate after 3-4 cycles of therapy (Nivolumab x 1, Nivolumab+ICE x 2-3) in high-risk patients is promising compared to historical data.

Objectives:

In Hodgkin lymphoma patients with relapsed or primary refractory disease post induction chemotherapy:

Primary:

Evaluate the anti-tumor activity of nivolumab as single agent and in combination with ICE chemotherapy (NICE) as assessed by complete response (CR) rate prior to autologous hematopoietic cell transplantation.

Secondary:

1) Assess the safety and tolerability of nivolumab ± ICE chemotherapy through evaluation of toxicities, including type, frequency, severity, attribution, time course and duration.
2) Obtain estimates of overall response rate (ORR), response duration and survival (overall and event-free).
3) Summarize stem cell mobilization outcomes (e.g., total CD34+ cell yield, number of apheresis days, proportion of patients who achieve ≥2 $x10^6$ CD34+ cells/kg).
4) Evaluate Hodgkin lymphoma biological markers in subjects treated with nivolumab.
5) Among subjects who undergo autologous hematopoietic cell transplantation (AHCT):
    1. Estimate the post-AHCT overall/PFS probability and cumulative incidence of relapse/progression, non-relapse mortality (NRM) at 100-days, 1-year and 2-years
    2. Characterize post-AHCT toxicities during the first 30- and 100- days post stem cell infusion by type, frequency, severity, attribution, time course and duration.
    3. Evaluate short and long-term post-AHCT complications, including: delayed engraftment (neutrophil and platelet) and infection, and sinusoidal obstruction syndrome.

New Cohort (B):

Primary Objectives

- To estimate the proportion of patients experiencing unacceptable adverse events.
- To determine the anti-lymphoma activity of nivolumab+ICE as first salvage therapy in high-risk relapsed/refractory HL, as defined by complete response (CR) rate at the end of salvage therapy.

Secondary Objectives

- To assess the safety and tolerability of nivolumab+ICE chemotherapy through evaluation of toxicities, including type, frequency, severity, attribution, time course and duration.
- To obtain estimates of overall response rate (ORR), response duration and survival (overall and event-free).
- Summarize stem cell mobilization outcomes (e.g., total CD34+ cell yield, number of apheresis days, proportion of patients who achieve $\geq 2 \times 10^6$ CD34+ cells/kg).
- Evaluate Hodgkin lymphoma biological markers in subjects treated with nivolumab (see correlative studies).

Exploratory:

1) Evaluate biomarkers predictive of response to nivolumab/ICE in Hodgkin lymphoma
2) Evaluate biomarkers predictive of PFS post nivolumab/ICE in Hodgkin lymphoma
3) To assess the association between baseline total metabolic tumor volume and complete response and PFS after PET-adapted nivolumab +/- ICE in all treated patients
4) To assess the association between change in total metabolic tumor volume between baseline, 6 weeks, and 12 weeks with complete response to and PFS after PET-adapted nivolumab +/- ICE in all treated patients
5) To assess the association between outcomes (complete response, PFS) and other baseline quantitative PET (qPET) parameters including total lesion glycolysis and SUVmax in all treated patients.

Study Design:

Study Design Rationale: This multicenter, single-arm, phase II trial is designed to evaluate the anti-lymphoma activity of the NICE 2nd-line regimen, in patients with relapsed or primary refractory HL post induction therapy. Activity will be assessed by CR rate prior to AHCT. Recent studies evaluating NIVO, an anti-PD-1 monoclonal antibody show efficacy in relapsed/refractory HL. In a phase I trial, NIVO was shown to have an ORR of 87% with a CR rate of 17%[7]. This response rate was recently confirmed in a phase II trial[11], and the drug received accelerated FDA approval for HL after failure of AHCT and BV treatment. In the Moskowitz study of PET imaging normalization prior to AHCT, 60% of patients who received 2nd-line ICE or augmented ICE achieved CR prior to AHCT[12]. The MSKCC trial, which used augmented ICE, accrued 46 patients in 2 years, of whom 44 proceeded to AHCT, with 34 in CR (74%)[13]. In our study of PET-adapted BV ± chemotherapy prior to AHCT, 65% of enrolled/treated patients attained a CR pre-transplant[14]. Based on these data, a CR rate of 70% prior to AHCT will be considered promising, qualifying the regimen worthy of further investigation.

Study Design Characteristics: This phase II trial will implement a Simon Two-Stage Optimal Design[15] to evaluate the anti-lymphoma activity of NIVO± ICE chemotherapy. The trial is expected to enroll a minimum of 15 and a maximum of 43 subjects. The sample size is based on the desire to discriminate a promising CR rate of 70% from a disappointing CR rate of 50% (a rate below what can be achieved with ICE/augmented ICE) using a type I error rate of 0.05 and power of 80%. At stage 1, 15 subjects will be entered on the study. If ≤ 8 complete responses are seen, the study will be terminated. If at least 9 subjects achieve a CR, the trial will continue to the second stage. At stage 2, 28 additional subjects will be entered. At the end of stage 2, if 27 or more subjects experience a complete response, the combination will be considered worthy of further study. If ≤ 26 subjects experience a complete response then no further investigation of the regimen is warranted.

Safety Monitoring Segment: NIVO is already FDA approved for treatment of HL and thus does not require special safety monitoring. Since the combination of nivolumab and ICE has not been tested before, the trial will include a 6-patient safety monitoring cohort for patients treated with nivolumab plus ICE

(cycle 1). If ≤ 1/6 patients experience unacceptable toxicity, then the study will continue. If 2 or more patients experience unacceptable toxicity, we will stagger the dose of nivolumab and ICE by 1 week so that nivolumab will start on day 1 and ICE will start on day 8 of a 21 day cycle. There will then be another 6 patient cohort added to the monitoring. If ≤ 1/6 patients experience unacceptable toxicity in the staggered cohort, then the study will continue. If, however, 2 or more patients experience unacceptable toxicity in the staggered cohort, then nivolumab will not be given in combination with ICE.

New Cohort (B): Due to the high CR rate with nivolumab alone, only a small number of patients have been treated with NIVO + ICE thus far. Based on the small number of patients treated with NIVO + ICE, it is not possible to adequately characterize the full spectrum of toxicities with NIVO + ICE, nor is it possible to obtain an adequate preliminary estimate of the anti-tumor efficacy. Therefore, a separate cohort has been added to the study, which will be enrolled after the completion of the original PET-adapted cohort. In this new cohort, all patients will receive a cycle of nivolumab and then NIVO + ICE x 2-3 cycles. **Updated April 27, 2021:** Given the exceptionally high CR rate observed thus far and without any signals of excess toxicity to date, we will expand Cohort B to a full Phase 2 efficacy cohort to assess whether the CR rate after 3-4 cycles of therapy (Nivolumab x 1, Nivolumab+ICE x 2-3) in high-risk patients is promising compared to historical data. Implementing a Simon two-stage minimax design, we plan to enroll and treat a minimum of 19 and a maximum of 35 patients at the Cohort B schedule in order to discriminate a promising CR rate of 74% from a disappointing response rate of 50% using a type I error rate of 0.05 and power of 90%. At stage 1, 19 patients will be entered on the study (which includes the n=13 patients treated thus far in Cohort B), therefore we expect to enroll only 22 new patients on the Cohort B phase 2 trial portion of the study to count toward the 35 patients required. If ≤ 9 complete responses are seen, the study will be terminated. If at least 10 patients achieve CR, the trial will continue to the second stage. At stage 2, 16 additional patients will be entered. At the end of stage 2, if 23 or more patients experience complete response, the combination will be considered worthy of further study. If ≤22 patients achieve a complete response then no further investigation of the combination is warranted.

Endpoints:

Original Cohort: The *primary study endpoint* is complete response (CR) rate at the time of AHCT and is based on the Lugano Criteria.[16] The primary endpoint for the patient *safety monitoring* segment of the study is toxicity. Toxicity will be scored using the NCI CTCAE v4.03 Scale. Unacceptable toxicity in a given patient is defined as any non-hematologic or hematological grade 3/4 toxicity that does not resolve to a grade 1/2 within 14 days per NCI CTCAE v4.03 toxicity criteria and is considered at least possibly related to nivolumab and/or ICE, or any other regimen-related cause of death.

New Cohort (B): The first primary endpoint is unacceptable toxicity. Toxicity will be scored using the NCI CTCAE v4.03 Scale. Unacceptable toxicity in a given patient is defined as any non-hematologic or hematological grade 3/4 toxicity that does not resolve to a grade 1/2 within 14 days per NCI CTCAE v4.03 toxicity criteria and is considered at least possibly related to nivolumab and/or ICE, or any other regimen-related cause of death. **Updated Apr 27, 2021:** The phase 2 portion will evaluate the anti-lymphoma activity of the two-agent combination as assessed by CR rate using Lugano criteria, in patients with high-risk HL as the second primary endpoint.

Sample Size:

Original Cohort (A): Assuming 1) the nivolumab 240 mg flat dose and ICE doses are well tolerated and 2) the study does not close for futility, 43 evaluable (received at least one cycle of treatment) patients will be enrolled on the phase II portion of the study. Expected accrual for safety monitoring segment: n=6.

New Cohort (B): We plan to enroll and treat 18 eligible patients. With 18 patients, we can estimate the proportion of patients experiencing unacceptable adverse events with sufficient precision (standard error ≤ 0.12, half width ≤ 0.23).). Expanded Sample Size (Anti-Lymphoma Activity): The Cohort B phase 2

portion is expected to enroll and treat a minimum of 19 and a maximum of 35 patients at the Cohort B schedule.

Estimated Duration of the Study

In the event that the study does not close for futility, accrual is expected to be completed in 56 months, with ~1-2 patients enrolled each month. In the nivolumab only stage, patients will be treated every 2 weeks for 12 weeks. For patients in the NIVO + ICE stage, patients will be treated every 3 weeks for 6 weeks. Patients will be followed to collect further anticancer treatment (including AHCT) and survival information until death, loss to follow-up, withdrawal of consent, and study termination, or up to 24 months post completion/ discontinuation of treatment.

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

- Relapsed/refractory biopsy-proven CD30+ Hodgkin lymphoma
- Age $\geq$ 18 years old and > 40kg
- Can only have received induction chemotherapy. However, mixed induction chemotherapy is allowed (ABVD/BEACOPP hybrid). Pediatric induction therapy also allowed.
- Prior consolidative radiation therapy is allowed.
- Patients may be on steroids before initiation of treatment, provided that use is tapered down to ≤10 mg prednisone or equivalent by cycle 1 day 1.

New Cohort (B) Inclusion Criteria

In addition to the inclusion/exclusion criteria as outlined above, to be eligible for treatment in the new cohort, patients must have high-risk disease, defined as having any one of the following:

- B symptoms at relapse
- Extranodal disease at relapse
- Primary refractory disease
- Relapsed < 1 year after completion of frontline therapy
- Have received brentuximab vedotin as initial therapy

Exclusion Criteria:

- Patients cannot have received any salvage chemotherapy for HL.
- Prior exposure to PD-1 or PD-L1 inhibitors is not allowed.
- Platelet count <75,000, ANC < 1,500, hemoglobin < 8.5. (Growth factor support or transfusions to achieve targets are allowed provided that patients have not received growth factor support for at least 14 days prior to entering trial)
- Patients should not have any uncontrolled illness or active infection.
- Patients must not be vaccinated with live, attenuated vaccines within 4 weeks of the first dose of the study drugs.
- Patients with active CNS disease or history of brain metastases are ineligible.
- Patients with active autoimmune disease requiring systemic treatments are not allowed. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger

Investigational Product Dosage and Administration:
Nivolumab only stage: nivolumab 240 mg IV flat dose every 2 weeks x 6 doses. NIVO + ICE: nivolumab 240 mg IV every 3 weeks x 2 doses. ICE per standard dosing.
Clinical Observations and Tests to be Performed:
Physical exams, tumor measurements by radiographic imaging, biopsy of lymphoma, blood tests, and analysis on lymphoma and peripheral blood specimens. See section 10.0 for details.
Statistical Considerations:
Response rates will be calculated as the percent of evaluable patients that have confirmed CR by radiographic response including CT and/or PET scans; 95% Clopper Pearson confidence limits will be calculated for this estimate. Time to response and survival will be estimated using the product-limit method of Kaplan and Meier. Cumulative incidence of relapse/progression will be calculated taking into account incidence of NRM as a competing risk[17]. Toxicity recording will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity. Baseline information (e.g., the extent of prior therapy) and demographic information will be presented as well, to describe the patients treated in this study. In addition to response assessment, using the Lugano criteria,[16] survival, toxicity information, and lymphoma specimens/plasma samples will be collected for exploratory biomarker evaluation.
Sponsor/Licensee:
This is a COH investigator-initiated trial with COH holding the IND and BMS providing funding support and drug supply.
Case Report Forms
Medidata Rave EDC®

Table of Contents

Abbreviations

Abbreviation	Meaning
AE	Adverse Event
AHCT	Autologous Hematopoietic Cell Transplantation
BV	Brentuximab Vedotin
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
HL	Hodgkin Lymphoma
IB	Investigator Brochure
ICE	Ifosfamide, Carboplatin, Etoposide
ICF	Informed Consent Form
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NICE	Nivolumab, Ifosfamide, Carboplatin, Etoposide
NIVO	Nivolumab
NCI	National Cancer Institute
NRM	Non-Relapse Mortality
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PI	Principal Investigator
PMT	Protocol Monitoring Team
PPK	Population Pharmacokinetics
PR	Partial Response
RCC	Renal Cell Carcinoma
SAE	Serious Adverse Event
SD	Stable Disease
ULN	Upper Limit of Normal

1 Goals and Objectives

This is an open label, multi-center phase II study of nivolumab as single agent and in combination with ICE chemotherapy in patients with relapsed/refractory Hodgkin lymphoma. Patients will receive single agent nivolumab for 6 weeks. For patients who achieved CR/PR, they will receive an additional 6 more weeks of nivolumab. Among those patients, those who are in CR after the additional 6 weeks will go directly to AHCT; those not in CR after the 12 weeks of nivolumab will receive a combination of nivolumab plus ICE, for 6 weeks. Patients who only achieve SD after 6 weeks of single agent nivolumab can either receive an additional 6 weeks of single agent nivolumab, or receive a combination of nivolumab plus ICE for 6 weeks. The decision to go either way will be at the physician/investigator's discretion on a case-by-case basis. The rationale is that in patients with a radiographic response of SD who are clinically doing well, an immune response or tumor flares could be masking an actual PR or CR. For patients who only achieve PD after 6 weeks of single agent nivolumab, they will directly move onto NIVO + ICE.

1.1 Primary Objective:

- Evaluate the anti-tumor activity of nivolumab as single agent and in combination with ICE chemotherapy (NICE) as assessed by complete response (CR) rate prior to autologous hematopoietic cell transplantation.

1.2 Secondary Objectives:

- Assess the safety and tolerability of nivolumab ± ICE chemotherapy through evaluation of toxicities, including type, frequency, severity, attribution, time course and duration.
- Obtain estimates of overall response rate (ORR), response duration and survival (overall and event-free).
- Summarize stem cell mobilization outcomes (e.g., total CD34+ cell yield, number of apheresis days, proportion of patients who achieve $\geq 2 \times 10^6$ CD34+ cells/kg).
- Evaluate Hodgkin lymphoma biological markers in subjects treated with nivolumab (see correlative studies).
- Among subjects who undergo autologous hematopoietic cell transplantation (AHCT):
    - Estimate the post-AHCT overall/PFS probability and cumulative incidence of relapse/progression, non-relapse mortality (NRM) at 100-days, 1-year and 2-years
    - Characterize post-AHCT toxicities during the first 30- and 100- days post stem cell infusion by type, frequency, severity, attribution, time course and duration.
    - Evaluate short and long-term post-AHCT complications, including: delayed engraftment (neutrophil and platelet) and infection, and sinusoidal obstruction syndrome.

1.3 Exploratory Objectives:

- Collect DNA/RNA from lymphoma specimens and serial plasma samples for future biomarker evaluation. Evaluate potential changes in Hodgkin lymphoma biological markers of patients treated with nivolumab. See Section 9.0 (Correlative/Special Studies) for details.
- To assess the association between baseline total metabolic tumor volume and complete response and PFS after PET-adapted nivolumab +/- ICE in all treated patients
- To assess the association between change in total metabolic tumor volume between baseline, 6 weeks, and 12 weeks with complete response to and PFS after PET-adapted nivolumab +/- ICE in all treated patients
- To assess the association between outcomes (complete response, PFS) and other baseline quantitative PET (qPET) parameters including total lesion glycolysis and SUVmax in all treated patients.

1.4 Objectives for New Cohort (Cohort B):

1.4.1 Primary Objectives

- To estimate the proportion of patients experiencing unacceptable adverse events.
- To determine the anti-lymphoma activity of nivolumab+ICE as first salvage therapy in high-risk relapsed/refractory HL, as defined by complete response (CR) rate at the end of salvage therapy.

1.4.2 Secondary Objectives

- To assess the safety and tolerability of nivolumab+ICE chemotherapy through evaluation of toxicities, including type, frequency, severity, attribution, time course and duration.
- To obtain estimates of overall response rate (ORR), response duration and survival (overall and event-free).
- Summarize stem cell mobilization outcomes (e.g., total CD34+ cell yield, number of apheresis days, proportion of patients who achieve $\geq 2 \times 10^6$ CD34+ cells/kg).
- Evaluate Hodgkin lymphoma biological markers in subjects treated with nivolumab (see correlative studies).

2 Background

2.1 Introduction/Rationale for Development

Hodgkin lymphoma:

Hodgkin lymphoma (HL) is a neoplasm of lymphoid tissue that is histopathologically defined by the presence of malignant Hodgkin-Reed-Sternberg (HRS) cells in a background of inflammatory cells.[18] The characteristic surface antigen expressed on HRS cells is CD30. In 2008, it was estimated that approximately 9,110 new cases of HL would be diagnosed in the United States and 1,180 patients would die of their disease.[19,20] It was also estimated that approximately 7,882 new cases of HL would be diagnosed in 2008 in 5 major EU countries (UK, France, Germany, Italy, and Spain; Mattson Jack's Cancer Impact Epidemiology Database).[21] Similarly, it was estimated that approximately 890 new cases of HL would be diagnosed in 2008 in Canada and 110 would die of their disease.[22]

Advances in the use of combined chemotherapy and radiotherapy in HL over the past half-century have resulted in a durable remission rate of approximately 70%.[18] However, these multi-agent regimens are associated with significant morbidity, including secondary malignancies, cardiac disease, pulmonary disease, and infertility.[23-25] Furthermore, approximately 30-40% of patients presenting with HL will become refractory to initial therapy or will relapse. For patients with relapsed or refractory disease, the only potentially curative therapy is salvage combination chemotherapy followed by autologous hematopoietic cell transplantation (AHCT).[2] The therapeutic options for patients with refractory or relapsed disease have historically been very limited and carry a high morbidity rate.[26]

In the last several years, however, new agents are changing the landscape of therapy for both upfront and relapsed HL. Brentuximab vedotin (BV), a CD30-targeted antibody-drug conjugate was initially approved for HL patients who had relapsed following AHCT,[27] but has since been used as a bridge to transplant,[13,14] as post-AHCT consolidation,[28] and is currently being tested in the upfront setting in conjunction with combination chemotherapy . The recent randomized phase III AETHERA trial[28] showed that in high-risk patients with HL, the use of BV as consolidation therapy post-AHCT increased the 2-year PFS from 51% in the placebo arm to 63% in the BV arm. The randomized phase III ECHELON-1 trial comparing ABVD vs. AVD + BV has finished accrual and may change the standard of care induction regimen for all advanced stage patients with HL.

BV targets CD30-expressing HRS cells; however, the majority of the HL tumor mass is made up of

inflammatory and infiltrating T cells and macrophages. Multiple publications have implicated the tumor microenvironment in the pathogenesis of HL. Steidl et al. showed that CD 68 staining macrophages in the tumor microenvironment are associated with poor outcome to induction.[29] This, coupled with the possible future movement of BV to first-line treatment, makes the exploration of new immunotherapy agents in the first salvage setting a necessity. Immune checkpoint inhibitor therapies utilize monoclonal antibodies against CTLA4, PD-L1, and PD-1 to target tumor-induced immunosuppression. For Hodgkin lymphoma this strategy is particularly relevant since the majority of the tumor mass is immune cells.

We have shown in a prior study that sequential therapy with BV followed by ICE can lead to high rates of CR at the time of AHCT. However, we expect that when final results of the ECHELON-I study are released, BV may become part of standard induction therapy, necessitating development of new salvage regimens that utilize other novel agents.

2.2 Nivolumab

It is also well known that the Reed–Sternberg cells exploit the programmed death 1 (PD-1) pathway to evade immune detection. In classic Hodgkin lymphoma, alterations in chromosome 9p24.1 increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, and promote their induction through Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling.[30,31] Thus, it is reasonable to target the PD-1 and PDL1/L2 pathway to treat Hodgkin lymphoma.

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[32] Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014) in a variety of solid tumors. In a phase I trial, it was shown to have an ORR of 87% with a CR of 17%.[7]This response rate was recently confirmed in a phase II trial,[33] and the drug received accelerated FDA approval for Hodgkin lymphoma after failure of AHCT and brentuximab vedotin treatment.[8]

2.2.1 Preclinical studies

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family.[34] Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro.[35,36] Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release.[31] In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. Although nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.[31]

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg (area under the concentration-

time curve [AUC] from time zero to 168 hours [AUC (0-168 h)] 117,000 µg•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.[37]

2.2.2 Human studies

The pharmacokinetics, clinical activity, and safety of nivolumab have been assessed in subjects not only with Hodgkin lymphoma but with non-small cell lung cancer (NSCLC), melanoma, and clear-cell renal cell carcinoma (RCC). Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

Nivolumab is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma and previously treated, metastatic squamous NSCLC; the EU for treatment of previously treated, unresectable or metastatic melanoma; and Japan for treatment of unresectable melanoma. In the nivolumab Investigational Brochure, see Appendix 1 for US Prescribing Information (USPI) and Appendix 2for the EU Summary of Product Characteristics (SmPC).

2.2.3 Clinical efficacy

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, and some lymphomas.[38-43] In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC[44] and in subjects with unresectable or metastatic melanoma. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.[45] Given the extensive but ineffective infiltrate of immune cells in classic Hodgkin lymphomas, it was hypothesized that nivolumab would reverse immune evasion in patients with relapsed/refractory HL. A phase I trial with 23 heavily pretreated patients with HL (78% of whom relapsed after receipt of brentuximab vedotin) was performed and revealed an ORR of 87% and PFS rate of 86% at 24 weeks.[7] An extended analysis with a median of 20 months revealed durable responses, as 35% of responders (7 out of 20) maintained a response for over 1.5 years.[46] A phase II trial was conducted in patients who relapsed post AHCT and brentuximab vedotin, reporting an ORR of 66% after a median follow up of 8.9 months.[8] On the basis of these data, nivolumab was granted accelerated FDA approval for patients who progressed after AHCT and brentuximab vedotin.

2.2.4 Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase III controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and using timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab in subjects with unresectable or metastatic melanoma. Results to date suggest that the safety profile of nivolumab + ipilimumab

combination therapy is consistent with the mechanisms of action of the two drugs. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

Phase I and phase II studies in HL have both been published, showing that nivolumab is well tolerated with a response rate of 73% in patients with HL who progressed after AHCT and brentuximab vedotin. The dose studied in the phase II trial was 3 mg/kg IV every 2 weeks.

The phase I and II studies of nivolumab for patients with HL have indicated a favorable safety profile.[7,33] In the phase I trial, drug-related adverse events were reported in 78% of patients, most commonly rash (22%) and decreased platelet count (17%). Drug related grade 3 events occurred in 22% patients and included myelodysplastic syndrome, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, increased lipase level, decreased lymphocyte level, and leukopenia. No grade 4 or 5 adverse events were observed.

In the phase II trial, 89% of patients experienced drug-related adverse events, the most common being fatigue, infusion-related reaction, rash, arthralgia, pyrexia, nausea, diarrhea, and pruritus. Grade 3 events included rash, dyspnea, abdominal pain, increased lipase, neutropenia, increased amylase, increased AST or ALT, pneumonia, maculo-papular rash, decrease neutrophil count, arthritis, and syncope. Two patients had grade 4 increased lipase, and one had decreased neutrophil count. There were no grade 5 drug-related adverse events.

2.2.5 Rationale for flat dosing

Nivolumab monotherapy has been extensively studied in a number of tumor types including NSCLC, melanoma, RCC, and colorectal cancer with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected these studies, together with PK data from several phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Population PK (PPK) analyses have shown that the PK of nivolumab are linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg, and are similar across tumor types. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients.

Using the PPK model, nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) were predicted for a flat nivolumab dose of 240 mg Q2W and compared to those following administration of 3 mg/kg Q2W in NSCLC subjects. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 Phase 2 and 3 BMS clinical studies of nivolumab monotherapy. The geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Across the various tumor types in the BMS clinical program, nivolumab has been shown to be be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

Thus a flat dose of 240 mg every 2 weeks is recommended for investigation in this study.

2.2.6 Shorter Infusion Duration

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration, wherein nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical programs. In CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 240 mg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Overall, a change in safety profile is not anticipated with a 30 minute infusion of nivolumab.

2.3 ICE Salvage Chemotherapy

Disease control with salvage chemotherapy is a central goal in the treatment of relapsed/refractory Hodgkin lymphoma. Multiple studies have shown that the extent of response to salvage chemotherapy is a chief determinant of outcome post-ASCT.[47-49] In one study, patients with a CR before transplant had a 5-year PFS rate of 79%, compared with 59% for those with a PR, and only 17% among patients with resistant disease.[50] Similarly, Gopal et al. reported a 17% PFS rate for patients undergoing ASCT with chemoresistant disease.[51] We therefore plan salvage chemotherapy for patients who do not attain CR with nivolumab alone.

Many salvage regimens are available for the medical health practitioner to choose from.[3,4,52,53] These regimens include those that are based on platinum, such as ASHAP (doxorubicin, solumedrol, cytarabine, cisplatin), DHAP (cisplatin, cytarabine, dexamethasone), and ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin). Regimens may also be gemcitabine-based and include GDP (gemcitabine, dexamethasone, cisplatin) and GVD (gemcitabine, vinorelbine, pegylated liposomal doxorubicin). Salvage regimens may also contain ifosfamide, as in IGEV (ifosfamide, gemcitabine, and vinorelbine). The ICE regimen (ifosfamide, carboplatin, and etoposide) contains both ifosfamide and a platinum-based agent. Rarely, salvage radiation therapy may be used, but this approach is generally limited to selected patients with localized disease.[54] The frequently used salvage regimens yield overall response rates of 60-80% for relapsed/refractory Hodgkin lymphoma (ASHAP: 70%,[55] DHAP: 89%,[56] ESHAP: 73%,[57]GDP: 62%, ICE: 88%,[3] IGEV: 81%[58]), with myelosuppression commonly noted as a main toxicity.[59] CR rates were ~9-21%. The selection of salvage regimen is based on the preference and experience of the investigator and the institution. Because ICE is among the most well studied and administered regimen, it is our choice for this trial.

A combined analysis of patients from 1994 through 2003 revealed that functional imaging pre-HDT/AHCT was the strongest predictor of outcome: The 5-year event free survival was 75% for patients with negative functional imaging, versus 31% among those with persistent abnormalities as detected by imaging. This report combined with further studies was impetus for a clinical trial using both pre-salvage chemotherapy prognostic factors and post-salvage therapy FDG-PET response to improve PFS after HDT/AHCT. Patients who were PET-negative after 2 cycles of ICE proceeded to transplant, whereas those who were PET-positive received 4 doses of the non-cross-resistant therapy GVD. 17 of the 33 patients who received GVD went on to transplant and had similar favorable outcomes to those achieving PET-negative status from ICE alone. Now, in the post PET era, the CR of salvage therapy such as aug ICE or IGEV is 54%-60% according to small studies.

2.4 Overview of Proposed Study

This is an open label, multi-center phase II study of nivolumab as single agent and in combination with ICE chemotherapy in patients with relapsed/refractory Hodgkin lymphoma to induction chemotherapy. Nivolumab will be given 240 mg IV every 2 weeks in the nivolumab only stage for 12 weeks or 6 cycles.

Patients who only achieve stable disease after 6 weeks of single agent nivolumab can either receive an additional 6 weeks of single agent nivolumab, or receive a combination of nivolumab plus ICE for 6 weeks. The decision to go either way will be at the physician/investigator's discretion on a case-by-case basis. The rationale is that in patients with a radiographic response of SD who are clinically doing well, an immune response or tumor flares could be masking an actual PR or CR.

For those with progressive disease after 6 weeks/3 cycles, or those not in CR after 12 weeks/6 cycles, they will be given 240 mg IV every 3 weeks for 6 weeks or 2 cycles in the combination study with ICE. ICE will be given as per standard use. The primary efficacy endpoint of this study is complete response rate. Response will be assessed according to modified criteria for malignant lymphoma, based on Lugano criteria.[16] Response assessment will be performed after 6 weeks of nivolumab alone, then after 12 weeks of nivolumab alone. In the NIVO + ICE stage, response assessment will be performed after 6 weeks. Patients who achieve a complete response (CR) after 12 weeks can go directly to AHCT. Patients who achieve a CR or PR to NIVO + ICE will go to AHCT.

We had performed a similar study using brentuximab vedotin (BV), an antibody drug conjugate against CD30, in patients with relapsed/refractory Hodgkin lymphoma, as a bridge to AHCT. That study was also a multicenter phase II trial, with patients receiving BV as 1st line salvage therapy post induction failure, and if they did not achieve a CR or very good PR, they would then receive ICE chemotherapy. Our results show that 65% of patients were in CR at the time of AHCT,[14] and that the 2 year PFS post AHCT was71%, which is superior to historical control.[60] These findings indicate that our approach was effective in increasing the CR rate at the time of AHCT and improving outcome post AHCT. Dr. Alison Moskowitz published a similar study showing that BV can be given as first salvage therapy as a bridge to AHCT[13] using a response-adapted strategy with BV ± augmented ICE. 75% of patients were in CR pre-AHCT and post AHCT PFS was 80% at 2 years. However, as BV is being incorporated into front line therapy with AVD as in the ECHELON-1 trial, the use of single agent BV as 1st line salvage therapy may become less relevant. Therefore, novel methods are needed to treat HL patients who are relapsed/refractory to induction therapy.

Although there is insufficient evidence to suggest a benefit in continuing to treat patients in PR with the goal of attaining CR before ASCT, the first PET/CT scan in this study occurs at the relatively early time point of 6 weeks; by contrast, the first PET/CT scan in the initial phase II trial of nivolumab for HL was performed after 12 weeks.[8] We therefore anticipate that, in the context of nivolumab, the 6 week response determination would not indicate futility in reaching CR for those who are in PR. Conversely, because of the inadequate data at the 6 week mark, we postulate that 6 weeks of nivolumab may be insufficient to yield a molecular response in the event of a CR declaration. These factors motivated our decision to treat responding patients with nivolumab for at least 12 weeks.

Because a number of patients are expected to be given ICE salvage therapy in combination with nivolumab, it will not be possible in these patients to isolate the treatment effect of nivolumab. Our clinical endpoint, however, is complete response rate at the time of transplantation. Our design is to assess 1) the toxicity of nivolumab + ICE chemotherapy and 2) the sequential approach of nivolumab alone, potentially followed by nivolumab + ICE, and the effect of this strategy on the CR rate at the time of transplant.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

2.5 Rationale for New Cohort (Cohort B).

With enrollment on the original design almost completed (Cohort A), we have found that 22 out of 28 patients responded to NIVO and have proceeded to AHCT without receiving the combination of NIVO+ICE. Thus we have not completely assessed the safety of NIVO+ICE, nor have we obtained a preliminary estimate of the anti-lymphoma activity of the combination, which was the primary objective for Cohort A. We therefore are unable to fully characterize the NIVO+ICE combination using the original trial design. An additional consequence of a large majority of patients achieving a complete response with

nivolumab alone and proceeding directly from NIVO to AHCT is that very few on-treatment biopsies have been obtained for the correlative studies that were designed to address the exploratory objectives. We propose to include a cohort of high-risk patients with relapsed or refractory HL after frontline therapy to receive a single dose of NIVO prior to NIVO+ICE combination. We have restricted this cohort to only include high-risk patients (e.g. primary refractory HL, extranodal disease at relapse) since these patients have the highest risk of treatment failure using salvage therapy and autologous stem cell transplantation and thus justify the use of combination therapy rather than a PET-adapted approach. In addition, patients who have received brentuximab vedotin as part of frontline therapy will be eligible since identification of a novel salvage regimen that does not contain brentuximab vedotin is an important unmet need in this population. On treatment biopsies will be obtained on all these patients after the single dose NIVO and prior to the first dose of NIVO+ICE.

Updated Apr 27, 2021

During the progress of Cohort B, prior to the formal assessment of safety, we have observed promising efficacy in the patients treated thus far (CR in all, n = 13). This is outstanding efficacy in a particularly high-risk group of patients with primary refractory or early relapsed HL. To provide context for these results, the efficacy of conventional platinum- or gemcitabine-based chemotherapy regimens is similar, with ORR and CR rates by PET ranging between 70- 89% and 54-73%, respectively [3,9,58,61-63]. Achievement of a complete metabolic response (CMR) prior to transplant is a critical prognostic factor for auto-HCT outcome [64-67]. Several studies incorporating BV and/or PD-1 blockade into initial salvage therapy have aimed to improve the CMR rate prior to auto-HCT. Sequential and combination BV-based salvage regimens have been studied [10,14,68-74]. Although a minority of patients will have a CR with BV alone as initial salvage therapy (27-43%) [68,69], the CMR rates after sequential BV-chemotherapy or combined BV/chemotherapy range from 68-76%. BV (1.8 mg/kg) and nivolumab (3 mg/kg) combined as initial salvage therapy q3 weeks for 4 cycles (n=91) yielded an ORR of 85% and CR rate of 67% [75] with excellent durability of responses (3-year PFS of 77% in all patients). However, among high-risk patients who had primary refractory HL after frontline therapy, salvage regimens are often associated with lower CR rates in patients with primary refractory cHL compared to relapsed cHL, including some chemotherapy regimens (BeGeV: 59% refractory vs 84% relapsed) [9], BV+chemo regimens (BV+bendamustine: 64% refractory vs 84% relapsed) [10], and BV+Nivo (48% refractory vs 71% relapsed). Notably, the 3-year PFS in patients with primary refractory cHL versus relapsed cHL after BV+nivolumab as first salvage therapy was 61% in primary refractory cHL versus 90% in patients with relapsed cHL.

Therefore, with poorer outcomes after both conventional and even more novel immunotherapy-containing regimens, improving the efficacy of salvage therapy remains critical in patients with high-risk cHL. Given the exceptionally high CR rate observed thus far and without any signals of excess toxicity to date, we will expand Cohort B to a full Phase 2 efficacy cohort to assess whether the CR rate after 3-4 cycles of therapy (Nivolumab x 1, Nivolumab+ICE x 2-3) in high-risk patients is promising compared to historical data.

3 Patient Eligibility

The eligibility criteria listed below are interpreted literally and cannot be waived. An abnormal test (such as a WBC) may be repeated, or a low hemoglobin or platelet count may be corrected with transfusion to make the patient eligible for study. Blood tests and ECG should be performed within 10 days of treatment initiation. (For patients who re-enter the study after receiving autologous or allogeneic transplantation, they will be re-screened for eligibility per the inclusion and exclusion criteria).

3.1 Inclusion Criteria

- Patients must have histologically documented or cytologically confirmed Hodgkin lymphoma; confirmation must include CD30 expression.

- Patients must be either refractory to or relapsed after only induction therapy. Patients who do not achieve CR after induction therapy are considered primary refractory and are allowed to enter study.
- Age ≥ 18 years old and > 40 kg
- Patients must have ANC ≥1500/μL, Plt ≥ 75,000/μL, and hemoglobin ≥ 8.5 g/dl. Filgrastim can be given before and during treatment to achieve target ANC≥1500 μL. Platelet transfusion and packed red blood cell transfusion can also be given prior to the start of treatment and during treatment to achieve a target plt ≥ 75,000/ μL and hemoglobin of ≥ 8.5 g/dl, provided that patients have not received growth factors for at least 14 days prior to entering trial.
- Patients must have measurable disease > 1.5 cm evidenced by CT scan of the neck/chest/abdomen/pelvis or CT/PET scans.
- Life expectancy of greater than 3 months.
- ECOG of 0-2.
- Documented informed consent of the participant or legally responsible guardian.

Patients must have normal organ and marrow function as defined below:

- DLCO ≥ 60%
- Total bilirubin within 1.5x the upper limit of normal (ULN) institutional limits. Patients with elevation of unconjugated bilirubin alone, as in Gilbert's disease, are eligible.
- AST/ALT ≤3.0x the institutional upper limit of normal (unless demonstrated Hodgkin lymphoma involvement of the liver). Estimated creatinine clearance ≥ 30 ml/min (Cockcroft-Gault) and/or 24 urine analysis as needed
- For patients with HL involvement of the liver, AST/ALT ≤5.0 x institutional ULN. Total bilirubin within 3.0 x institutional ULN. (Although patients with HL involvement of the liver are frequently excluded from trials, their liver function tests often improve after treatment. The studies that led to nivolumab approval did not reveal any increased signals of liver toxicities attributed to nivolumab.)
- PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN.

3.1.1 Child Bearing Potential

- Female subject is either post-menopausal, surgically sterilized, or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study. 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 nivolumab.
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.

3.1.2 Informed Consent

All participants will undergo standard written informed consent procedures as dictated by the City of Hope Human Research Protections Office prior to performing any screening procedures that are not part of standard-of-care. Informed consent will be obtained by the principal investigator, collaborating investigators, or other IRB designated personnel who will meet the training requirements established by the IRB. With the support of research personnel, he/she will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective research participants will be informed that they may withdraw from the study at any time and for any reason without prejudice. Prospective research participants will be afforded sufficient time to consider whether or not to participate in the research.

3.1.3 Prior Therapy

Patient must be either refractory to or relapsed after 1 line of therapy.

Prior radiation therapy is allowed.

3.2 Exclusion Criteria

- Prior exposure to PD-1 or PD-L1 inhibitors is not allowed
- Must not have had second line chemotherapy for Hodgkin lymphoma.
- Active autoimmune diseases requiring systemic treatments.
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
- Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
- Unwilling or unable to participate in all required study evaluations and procedures.
- Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
- Patients should not have any uncontrolled illness including ongoing or active infection.
- Patients may not be receiving any other investigational agents, or concurrent biological therapy, chemotherapy, or radiation therapy.
- Patients must not have received prior chemotherapy or radiation for $\leq$ 3 weeks before study enrollment, or those who have not recovered from the adverse events due to agents administered more than 3 weeks earlier are excluded.
- Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the Investigator as not medically relevant.
- Significant screening electrocardiogram (ECG) abnormalities including, but not limited to, left bundle branch block, 2nd degree atrioventricular (AV) block type II, 3rd degree block, or corrected QT interval (QTc) $\geq$470 msec. Subjects with a cardiac pacemaker who have a QTc interval of $\geq$470

msec may be eligible if these findings are considered not clinically significant as documented via a cardiology evaluation.

- DLCO <60%. The clinical studies in support of accelerated approval for nivolumab in cHL after failure of ASCT required DLCO > 60%. Certain HL induction regimens have the potential for pulmonary toxicity, and nivolumab carries the potential of pneumonitis or other pulmonary toxicities.
- Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
- Patients with active CNS disease or history of brain metastases are excluded from study.
- Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued.
- Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
- Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Patients with past HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) are eligible if HBV DNA is undetectable. Patients who are positive for HCV antibody are eligible if PCR is negative for HCV RNA. Testing to be done only in patients suspected of having infections or exposures.
- Known active human immunodeficiency virus (HIV) infection. Subjects who have an undetectable or unquantifiable HIV viral load with CD4 > 300 and are on HAART medication are allowed. Testing to be done only in patients suspected of having infections or exposures.
- History of allergy or adverse drug reaction to study components.

3.3 Inclusion Criteria for Cohort B

In addition to the inclusion/exclusion criteria as outlined above, to be eligible for treatment in the new cohort patients must have high-risk disease, defined as having any one of the following:

- B symptoms at relapse
- Extranodal disease at relapse
- Primary refractory disease
- Relapsed < 1 year after completion of frontline therapy
- have received brentuximab vedotin as initial therapy

3.4 Inclusion of Women and Minorities

The study is open to anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are

noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4 Participant Enrollment

4.1 Pre-Enrollment Informed Consent and Screening Procedures

The investigational nature and objectives of the trial, the procedures and treatments involved, their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject, and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that were performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained. Screening procedures are listed in **Section 9.0 Study Activity Calendar**.

4.2 Participant registration

4.2.1 COH DCC Availability and Contact Information

Eligible subjects will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope. DCC staff is available between the hours of 8:00 a.m. and 5:00p.m. PST, Monday through Friday (except holidays). DCC contact information is as follows:

phone: (626) 218-7904

e-mail: DCC@coh.org

4.2.2 Slot verification and reservation

As the study accrues, study team personnel (including physicians, protocol nurses and/or CRCs) may wish to contact the DCC to verify slot availability and to reserve an open slot or be placed in queue for slot opening. Slots may only be held for a limited time, which will be determined by the Protocol Monitoring Team. The Data Coordinating Center should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3 Registration procedure

To register a participant, the subsequent procedure is to be followed:

The participating site's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate the desired timeline of the registration, especially if it must be completed promptly to meet the registration window.

The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:

- Registration Cover Sheet (non-COH sites only) (see Appendix A)
- Completed Eligibility Criteria List (printed from Section 3.0 of the protocol)
- Source documentation to support eligibility criteria*
- Signed informed consent document
- Signed HIPAA authorization form (if separate from the informed consent document)
- Signed subject's Bill of Rights (COH only)

*For COH participants, provide copies of source documentation only if not readily available as a finalized record in the COH EMR.

After having received all documentation, the DCC will complete the review of the documents to verify eligibility, working with COH staff or the participating site staff as needed to resolve any missing required source elements. A subject failing to meet all protocol eligibility requirements will not be registered.

Once eligibility has been confirmed, the DCC staff will register the participant by assigning a subject accession number, register the subject on study centrally into MIDAS for outside institutions (the COH CRC will directly access into MIDAS), and enter the subject into the eCRF system, Medidata RAVE.

Once registration has been completed, DCC staff will send a Confirmation of Registration Form, including the participant study number and dose level assigned, to the following:

- the site study team: site PI, treating physician, protocol nurse, and CRC
- the COH Protocol Monitoring Team: Dr. Herrera, Dr. Palmer and the COH CRN and CRC.

4.3 Dose Level Assignment

The Data Coordinating Center will be responsible for centrally registering all subjects for this trial and therefore will provide the participating sites the specific information pertaining to the dose level for each patient.

5 Treatment Program

5.1 Treatment Overview

Treatment will be given on an outpatient basis unless patients are already hospitalized for symptoms of Hodgkin lymphoma.

5.1.1 Nivolumab Dose and Administration

Nivolumab will be given at 240 mg IV over approximately 30 minutes (see Section 5.6.1 for allowable infusion interruptions), every 2 weeks in the nivolumab only stage. In the NIVO + ICE stage, nivolumab will be given at 240 mg IV every 3 weeks in combination with ICE.

Subjects may be dosed no fewer than 12 days from the previous dose of drug. There are no premedications recommended for nivolumab on the first cycle.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 5.1.3.

Doses of nivolumab may be interrupted, delayed, or discontinued on the basis of subject tolerance to treatment.

5.1.2 ICE Dose and Administration

The ICE components may be administered as per institutional standard of care. Inpatient or outpatient administration is allowed. Dosing should be based on the patient's baseline (predose, Cycle 1 Day 1) height and weight or per institutional standards at the site. Doses will be adjusted for patients who experience a ≥10% change in weight during the study. Rounding is permissible according to institutional standards.

	Agent	Dose	Route	Schedule (Days within each 21-day cycle)
ICE (Inpatient Schedule)**	Etoposide	100 mg/m^2	IV	Days 1-3
	Carboplatin	AUC 5 (750 mg max)	IV	Day 2
	Ifosfamide *	5000 mg/m^2	IV	Day 2

* ***Outpatient treatment is allowed*** and schedule is similar to Inpatient schedule, except for ifosfamide which will be given at a dose of 1670 mg/m^2 on Days 1-3 (instead of 5000 mg/m^2 on Day 2). Ifosfamide is always given with Mesna, according to institutional standards.

5.1.3 Nivolumab Required Premedication and Postmedication

Routine premedication should not be administered prior to the first dose of nivolumab. However, patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent nivolumab infusions with premedication as described in Section 5.6.1 below. Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with nivolumab at the discretion of the Investigator.

5.1.4 ICE Prophylaxis Regimen

Routine anti-emetic prophylaxis regimen should be administered with each cycle of ICE per institutional standard and should include oral or IV dexamethasone at a dose of at least 12 mg on Day 1 and 8 mg on Days 2 and 3. Omission or discontinuation of steroid antiemetic treatment may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to dexamethasone) upon discussion with the medical monitor.

Patients should receive prophylactic growth factor support (e.g. filgrastim [Neupogen®], a recombinant form of G-CSF, or polyethylene glycol [PEG]-filgrastim, per institutional standard) following each cycle of chemotherapy to shorten the duration of neutropenia. As per National Comprehensive Cancer Network (NCCN) guidelines, it is recommended that:

- PEG-filgrastim be given as 1 dose of 6 mg subcutaneously (s.c.) per cycle, administered the day after completion of chemotherapy
- Filgrastim be given as a daily dose of 5 mcg/kg (total dose rounded to the nearest vial size per institutional-defined weight limits) initiated the next day or up to 3-4 days after completion of chemotherapy until post-nadir ANC recovery to normal or near normal levels by laboratory standards. The preferred route of administration is s.c., but may also be given IV.

Refer to the United States Prescribing Information (USPI) for the applicable growth factor support in order to determine the appropriate administration window for use with cytotoxic chemotherapy.

Patients should also receive levofloxacin, acyclovir, and fluconazole for 10 days, or per institution guidelines.

There are no protocol-required pre- or postmedications for etoposide, ifosfamide, or carboplatin, other than those mentioned above.

5.1.5 Treatment Schedule

For a tabular view of the treatment, monitoring, and follow-up schedule, see study calendar in Section 10. Cycle length is 21 days for NIVO + ICE and 14 days for Nivolumab only.

	Nivolumab	ICE

Nivolumab only	240 mg IV every 2 weeks for 6 or 12 weeks.	N/A
NIVO + ICE stage, Dose Level 1	240 mg IV every 3 weeks (to synchronize with the ICE schedule) for 6 weeks on D1	Ifosfamide 5000 mg/m^2 IV on Day 2 Carboplatin AUC 5 IV on Day 2 Etoposide 100 mg/m^2 IV on Days 1-3
NIVO + ICE stage DoseLevel -1 (De-escalation)	240 mg IV at 3 weeks and 6 weeks on Day 1	ICE to begin on Day 8 instead of Day 1
Cohort B – 1 dose Nivolumab, then NIVO + ICE	240 mg IV at week 1, then week 3 (Cycle 2), week 6 (Cycle 3), optional week 9 (Cycle 4)	ICE to begin at week 3/Cycle 2

Nivolumab only and NIVO + ICE dosing can be given during a window of ±3 day due to scheduling issues.

*Criteria for dose de-escalation in the 6-patient safety monitoring cohort for patients treated with nivolumab plus ICE (cycle 1):*If ≤ 1/6 patients experience unacceptable toxicity, then the study will continue. If 2 or more patients experience unacceptable toxicity, we will stagger the dose of nivolumab and ICE by 1 week so that nivolumab will start on day 1 and ICE will start on day 8 of a 21 day cycle. There will then be another 6 patient cohort added to the monitoring. If ≤ 1/6 patients experience unacceptable toxicity in the staggered cohort, then the study will continue. If, however, 2 or more patients experience unacceptable toxicity in the staggered cohort, then nivolumab will not be given in combination with ICE.

5.2 Definition of Unacceptable Toxicity

Unacceptable toxicity in a given patient is defined as any hematologic or non-hematologic grade 3/4 toxicity that does not resolve to a grade 1/2 within 14 days per NCI CTCAE v4.03 toxicity criteria and is considered at least possibly related to nivolumab and/or NIVO + ICE, or any other regimen-related cause of death.

5.3 Criteria for Discontinuation of Therapy

Disease progression, intolerable AEs, non-compliance, or patient withdraws consent.

5.4 Planned Duration of Therapy

5.4.1 Original trial design (Cohort A)

Nivolumab will begin as single agent for 6-12 weeks, depending on interim response rate. The nivolumab and ICE combination arm will be given for 6 weeks (max 2 cycles only).

5.4.2 Cohort B

To be enrolled only after Cohort A is completed. Nivolumab will be given as single agent for 2 weeks. The nivolumab and ICE combination arm will be given for 6-9 weeks (max 3 cycles, i.e. 9 weeks).

5.5 Subject Follow-Up

Patients will be followed for the duration of active treatment per treatment visit. After end of treatment, patient will be followed every 6 months (+/- 2 months) for survival until withdrawal of consent, death, or

study closure. Patients that discontinue study treatment due to disease progression or toxicity, or experience disease progression after the completion of treatment will remain on study for survival follow up. Patients enrolled to cohort A and B prior to Amendment 14 will remain in survival follow-up until 2 years after the last enrolled patient has completed treatment or autologous HCT. Survival follow up data will be collected by electronic medical records (EMR), telephone, email or public records. Evidence of clinical progression mentioned by patient/family member or documented in EMR need to be to be reviewed and collected at each timepoint if patient has yet to progress after ending treatment.

5.6 Supportive Care, Other Concomitant Therapy, Prohibited Medications

Use of neutrophil growth factors or biosimilars is mandatory when ICE is given per institutional policy and the American Society of Clinical Oncology (ASCO) guidelines. Transfusions may be given in accordance with institutional policy.

5.6.1 Management of Nivolumab Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE 4.03 guidelines.

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

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated): Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial

improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

6 Anticipated Adverse Event List

6.1 Nivolumab

Per the IB (version 19, June 2020) the expected toxicities for nivolumab are as follows:

System Organ Class	Adverse Reactions
Cardiac disorders	
Rare	Atrial fibrillation, pericardial effusion, pericarditis, myocarditis, arrhythmia,
Very rare	ventricular arrhythmia
Endocrine disorders	
Uncommon	Adrenal insufficiency, hyperglycemia, hypophysitis, hypothyroidism
Rare	Hyperthyroidism, hypopituitarism, diabetes mellitus, diabetic ketoacidosis, Type 1 diabetes mellitus, fulminant type 1 diabetes Mellitus, autoimmune thyroiditis
Very rare	Autoimmune hypothyroidism, thyroiditis
Eye disorders	
Rare	Iridocyclitis, uveitis
Gastro-intestinal disorders	
Uncommon	Diarrhea, colitis, nausea, vomiting, pancreatitis
Rare	Autoimmune colitis abdominal pain, gastritis, stomatitis, enteritis, enterocolitis, autoimmune pancreatitis, pancreatitis acute
Very rare	Constipation
General disorders and administration site conditions	
Uncommon	Pyrexia, fatigue
Rare	Asthenia, chills, mucosal inflammation, peripheral edema
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis, hepatitis
Rare	Immune-mediated hepatitis, drug-induced liver injury, hepatitis acute, hyperbilirubinemia
Very rare	Hypertransaminasemia

System Organ Class	Adverse Reactions
Immune system disorders	
Uncommon	Infusion-related reaction,
Rare	Hypersensitivity, anaphylactic reaction, sarcoidosis
Infections and infestations	
Rare	Bronchitis, upper respiratory tract infection
Investigations	
Uncommon	Increased ALT, increased AST
Rare	Increased lipase, increased transaminases, increased liver function test, increased amylase, increased blood bilirubin, increased blood creatinine, increased blood alkaline phosphatase
Very rare	Increased blood glucose
Metabolism and nutrition disorders	
Uncommon	Hyponatremia
Rare	Dehydration, decreased appetite
Musculoskeletal and connective tissue disorders	
Rare	Myositis, arthritis, polyarthritis, myalgia, arthralgia, back pain, polymyalgia rheumatica, polymyositis, rhabdomyolysis
Nervous system disorders	
Rare	Headache, myasthenia gravis, dizziness, encephalitis, Guillain-Barre syndrome, peripheral motor neuropathy , demyelination, peripheral neuropathy, peripheral sensory neuropathy, myasthenic syndrome
Very rare	Polyneuropathy
Renal and urinary disorders	
Uncommon	Acute kidney injury
Rare	Tubulointerstitial nephritis, renal failure, autoimmune nephritis, immune-mediated nephritis
Very Rare	Nephritis
Respiratory, thoracic and mediastinal disorders	
Common	Pneumonitis
Uncommon	Interstitial lung disease, dyspnea
Rare	Respiratory failure, organising pneumonia, cough, immune-mediated pneumonitis
Skin and subcutaneous tissue disorders	
Rare	Rash, rash maculo-papular, pemphigoid, Stevens-Johnson syndrome, erythema multiforme, psoriasis, dermatitis, drug eruption, pruritus, rash generalized, rash papular, rash pustular
Very rare	Rash macular, rash pruritic, Toxic epidermal necrolysis
Vascular disorders	
Rare	Hypotension

Adverse reactions reported for patients treated with nivolumab monotherapy (N = 14,192).
Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

6.2 Ifosfamide

In clinical trials of ifosfamide monotherapy, the most common (≥10%) adverse reactions were alopecia, nausea/vomiting, leukopenia, anemia, CNS toxicity, hematuria, and infection.

According to the package insert for ifosfamide, ifosfamide can cause:

- *Myelosuppression:* Can be severe and lead to fatal infections.
- *Neurotoxicity:* Severe and fatal neurotoxicity can occur. Carefully monitor the patient for CNS toxicity and other neurotoxic effects.
- *Urotoxicity:* Severe nephrotoxicity with renal failure and death can occur. Monitor for nephrotoxicity with serum and urine chemistries. Mesna should be used to reduce hemorrhagic cystitis.
- *Cardiotoxicity:* Arrhythmias, other ECG changes, and cardiomyopathy can occur and result in death. Use with caution in patients with cardiac risk factors and in patients with preexisting cardiac disease. The risk of cardiotoxicity is dose dependent.
- *Pulmonary toxicity:* Interstitial pneumonitis, pulmonary fibrosis, and other forms of pulmonary toxicity with fatal outcomes can occur. Monitor for signs and symptoms of pulmonary toxicity and treat as clinically indicated.
- *Secondary malignancies* as late sequelae have occurred.
- *Veno-occlusive Liver Disease.*
- *Pregnancy:* Can cause fetal harm. Women should not become pregnant and men should not father a child during therapy.
- *Effects on Fertility.* Sterility may be irreversible in some patients.
- *Anaphylactic/anaphylactoid reactions* have been reported.
- *Impairment of wound healing.*
- *Nursing:* Ifosfamide is excreted in breast milk.

6.3 Carboplatin

According to the package insert for carboplatin, carboplatin can cause:

- *Hematologic Toxicity:* Bone marrow suppression is the dose-limiting toxicity of carboplatin. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of the patients; neutropenia with granulocyte counts below 1000/mm^3 occurs in 16% of the patients; leukopenia with WBC counts below 2000/mm^3 occurs in 15% of the patients. The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm^3; 74% have neutrophil counts above 2000/mm^3; 67% have leukocyte counts above 4000/mm^3.

  Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin.

  Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.
- *Gastrointestinal Toxicity:* Vomiting occurs in 65% of the patients and in about one-third of these patients it is severe. Nausea alone occurs in an additional 10 to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures.

Emesis was increased when carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6%; and constipation, also in 6%.

- *Neurologic Toxicity:* Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin with mild paresthesias occurring most frequently.

  Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.

- *Nephrotoxicity:* Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them were reversible.

- *Hepatic Toxicity:* The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients.

- *Electrolyte Changes:* The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%.

- *Allergic Reactions:* Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

- *Injection Site Reactions:* Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.

- *Other Events:* Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely.

  Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

- *Pregnancy:* Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women.

6.4 Etoposide

The most common adverse reaction is neutropenia.

According to the package insert for etoposide, etoposide can cause:

- *Myelosuppression:* Etoposide causes myelosuppression that results in thrombocytopenia and neutropenia. Fatal infections and bleeding have occurred.
- *Secondary Leukemias:* Secondary leukemias have occurred with long term use of etoposide.
- *Hypersensitivity Reactions:* Etoposide can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis.
- *Embryo-Fetal Toxicity:* Based on animal studies and its mechanism of action, etoposide can cause fetal harm when administered to a pregnant woman.
- *Lactation:* There is no information regarding the presence of etoposide in human milk or its effects on breastfed infant milk production. There is a potential for serious adverse reactions in nursing infants from etoposide.
- *Infertility:* Etoposide may result in permanent loss of fertility.
- *Gastrointestinal Toxicity:* Nausea and vomiting are the major gastrointestinal toxicities. The severity of nausea and vomiting is generally mild to moderate, with treatment discontinuation required in 1% of patients.

Other clinically important adverse reactions in clinical trials were:

- *Gastrointestinal:* abdominal pain, constipation, dysphagia.
- *General:* fever.
- *Ocular:* transient cortical blindness, optic neuritis.
- *Respiratory:* interstitial pneumonitis/pulmonary fibrosis.
- *Skin:* pigmentation, radiation recall dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
- *Neurologic:* seizure, aftertaste.

Hepatobiliary disorder: hepatotoxicity.

7 Dose Modification for Adverse Events

7.1 Dose Delay Criteria for nivolumab alone

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories.

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab). All study drugs must be delayed until treatment can resume.

Nivolumab administration should be delayed for the following:

Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 drug-related skin AE

Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:

- Grade 3 lymphopenia or leukopenia does not require dose delay.

- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects 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.

7.2 Dose Delay Criteria for NIVO + ICE

Dose delays for NIVO + ICE are allowed under the following criteria:

- Hematological toxicity: Platelets ≤ 75,000, Hemoglobin ≤ 8.5, ANC ≤ 1,500
- Non-hematological toxicity: All drug-related grade 3/4 AEs. These AEs need to resolve to grade 2 or lower before NIVO + ICE is given.

A delay of up to 14 days is allowed. After 14 days of delay, patients must be taken off the trial.

Filgrastim/packed red blood cells/platelet transfusions are allowed during this period, even during DLT assessment, as ICE therapy itself is supported by these transfusions.

7.3 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if Investigator allows.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment if Investigator allows.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in the discontinuation criteria below.

7.4 Management Algorithms for Immune-related Events

Guidelines for the management of immune-related events can be found in the current Investigator Brochure AND in the approved USPI. Investigators should decide the appropriate source of AE management for each protocol.

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

Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological, and Myocarditis.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in the Nivolumab IB. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

7.5 Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related adverse reactions: 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 those noted below
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - For patients <u>without</u> liver involvement and without higher AST or ALT levels at baseline, any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
        - AST or ALT > 5 x ULN
        - Total bilirubin > 3 x ULN

- For patients with liver involvement (and higher AST or ALT levels at baseline), or those who otherwise have higher AST/ALT levels as allowed in the inclusion criteria, any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - 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 lymphopenia or leucopenia.
- Grade 4 hypophysitis, Grade 3 or 4 adrenal insufficiency, or Grade 4 hyperglycemia. Other Grade 4 drug-related endocrinopathy adverse events, such as ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance other than Grade 4 hyperglycemia, which resolve within 14 days 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 Investigator (as allowed by protocol).
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed.
  - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

8 Agent Information and Risks

8.1 Nivolumab

Nivolumab was selected for dosage form development and is also referred to as BMS-936558-01or BMS-936558. Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The product description and physical and chemical properties of nivolumab are provided in Tables 7.1-1 and 7.1-2, respectively

Table 7.1-1**Product Description**:(Other names = MDX-1106, ONO-4538, anti-PD-1)					
Dosage Form	Potency	Primary Packaging	Secondary Packaging	Appearance	Storage Conditions (per label)

		(Volume)/ Label Type	(Qty) /Label Type		
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL).	Carton of 5 or 10 vials	10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.	Clear to opalescent, colorless to pale yellow liquid. May contain particles	**BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

Table 7.1-2:	**Physical and Chemical Properties**
BMS Number	**BMS-936558-01**
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
pH	5.5 to 6.5

8.2 Pharmaceutical Properties and Formulation

8.2.1 Description of the Dosage Form

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug products is the vial fill volume.

8.2.2 Drug Product Preparation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL): Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC) and non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components

or glass bottles have been observed. The placebo for nivolumab injection is administered in a similar manner as described above for the active drug product.

8.2.3 Recommended Storage and Use Conditions

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL): Vials of nivolumab injection must be stored at 2° to 8°C (36° to 46°F) and protected from light and freezing. Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container: The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2° to 8°C, 36° to 46°F) for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20° to 25°C, 68° to 77°F) and room light conditions. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

8.2.4 Clinical Pharmacokinetics

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% coefficient of variation) clearance (CL) was 9.5 mL/h (49.7%), the geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and the geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The population pharmacokinetic (PPK) analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at a 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials.

9 Correlative/Special Studies

9.1 Lymphoma specimen studies

9.1.1 Tissue collection timepoints

Each subject will have either a fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or will have available archival tissue from a biopsy that was performed after induction therapy.

Patients who are not in CR by CT/PET scan at 6 weeks will undergo biopsy of lymphoma samples (if tumor is accessible, and the procedure is medically safe) to assess for biomarkers for lack of CR. Tumor biopsy (if safe and accessible) must be performed after the first CT/PET response assessment. For patients (with PR) who are going to a second 6-week treatment with single-agent NIVO, biopsy may be performed at any time after the first CT/PET scan (but before any NIVO+ICE treatment). For patients (with SD or PD at first CT/PET) who are instead going to a 6-week treatment with NIVO+ICE, biopsy must be performed before starting NIVO+ICE (**except** for patients on Cohort B, enrolled after approval of Version 14.0). If feasible, all subjects will also undergo biopsy of tumor lesion at the time of disease progression or relapse.

9.1.2 Tissue processing guidelines

Guidelines for tumor sampling are as follows:

9.1.2.1 Non-COH sites

Three core biopsies will be obtained and embedded in paraffin as per standard institutional procedure and 3 similar additional cores (or fewer if it is not feasible to take 3 biopsies for research purposes) or 3 portions (1cm x 1cm) of excisional biopsy tumor specimens should be flash frozen and kept at -80°C until batch shipment.

9.1.2.2 COH only

Three core biopsies will be obtained for diagnostic purposes and 3 similar additional cores will be obtained for research. If fewer than 3 core biopsies for research are available because of safety, then 1 or 2 cores may be submitted.

Core biopsies:

- In pathology, one core biopsy will be snap frozen in OCT fixative, and an additional half of a core will be snap frozen without OCT fixative.
- Fresh tissue from 2 needle cores will be minced into smaller fragments. Using a lysis buffer, the nuclei will be released and isolated using a gradient solution. The pelleted nuclei will then be stained with DAPI and sorted by flow cytometry by DNA content/ploidy at the City of Hope Cytometry Core. The supernatant from the gradient, which contains the cytoplasmic contents of the Hodgkin cells and inflammatory background cells, will be saved for RNA extraction. DNA will be extracted from the Hodgkin nuclei as well as normal/diploid cells.

For excisional biopsies:

- An approximately 1cm x 1cm tumor sample will be divided into 5 equal portions and processed as described for core biopsies.

The diagnostic portion of the specimen:

- Process in a routine fashion by hematopathology. Using the formalin-fixed paraffin embedded (FFPE) tissue block, 15 x 5 micron unstained slides will be obtained

For archival specimens:

Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:

- 10 x 5 micron paraffin slices
- 10 x 5 micron unstained slides

9.1.3 Labeling of samples

Samples will be labeled with the study number, institution (for non-COH sites), subject ID (issued by DCC), date, time point of collection (i.e. baseline or progression) and if applicable patient initials.

9.1.4 Sample shipment and receiving lab

Tissue specimens collected at the above indicated time points will either be taken to (COH only) or batch-shipped (non-COH sites) to COH Pathology Core. For all sites, please include the Correlative Tissue form (Appendix C) with your shipment.

Please note that samples should only be **batch shipped from non-COH sites on Monday-Wednesday** in time for receipt Tuesday-Friday. **Refer to Section 9.1.5 for tissue shipping details.**

9.1.5 Tissue shipping guidelines to City of Hope Pathology Core

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to the applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with City of Hope Pathology Core DL-PATHCORE-BiospecimenSupport@COH.org).
2. Notify City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org) of impending shipment. To request a FedEx shipping label, email DCC@coh.org and indicate the planned shipment date.
3. **Slides/ Blocks:** Batch ship at room temperature via FedEx. During extreme heat, include refrigerated (not frozen) gel packs or gel insulators.

   It is recommended to ship samples via FedEx overnight (for a delivery by 3 pm or earlier the next day) or FedEx 2-day (with a morning delivery). During extreme heat, ship via FedEx overnight (for a delivery ideally by 10.30 am, or 3 pm the next day).

4. **Frozen samples** should be batch shipped on dry ice via FedEx overnight (for a delivery by 10.30 am the next day). The shipment should contain enough dry ice to last at least 72 hours.
5. On the day of shipment, email the sample shipment information to City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).
6. Ship samples with a **copy of the correlative tissue form (Appendix C)** and a **copy of the pathology report** to:

   Karen Miller
   COH Pathology Core
   City of Hope National Medical Center
   1500 E. Duarte Road
   Familian Science (Building 084), Room 1207
   Duarte, CA 91010
   T: 626-218-8408
   Email: DL-PATHCORE-BiospecimenSupport@COH.org

9.2 Peripheral blood specimens

Correlative studies will be performed with the goal of tracking the temporal dynamics of the host immune response and minimal residual disease after therapy. We will also bank samples for future research.

Samples will be stored for up to 10 years following the end of the study. Dr. Alex Herrera will be the administrator.

9.2.1 Overview and timepoints of collection

Blood samples will be collected from an indwelling venous catheter or by venipuncture.

Timepoint of collection	Total volume per timepoint	Tube Type	Processing/ Receiving Laboratory	Type of Laboratory Analysis
Timepoints for <u>all blood studies</u>: • Patients receiving **nivolumab only** treatment initially o baseline (C1D1, C2D1, C3D1)	~21 mL	Green-top (sodium or lithium heparin)	Analytical Pharmacology Core Facility (APCF) at COH	**Dr. Tim Synold (COH)** • PBMC isolation to assess immune reconstitution • Plasma for cytokine analysis
• Patients receiving **nivolumab with ICE** o C1D1, C2D1, and C2D21*. • Patients receiving **nivolumab x 1 followed by NIVO+ICE (Cohort B)** o C1D1, C2D1, C3D1†	~20 mL	**COH only**: Purple-top (K+EDTA)	APCF at COH	Minimal residual disease (MRD) assessment using next-generation sequencing (NGS)
	~20 mL	**Non-COH**: Cell-free BCT® DNA tubes Sites should request tubes from the COH DCC or designee		

* Can be C2D21 or any day post-C2D21, but must be prior to AHCT.
† Peripheral blood will be collected prior to study treatment/procedures at the indicated time points.

9.2.2 Site notification to COH APCF, Blood sample collection and Labeling

Notification to COH APCF of Pending Collection	Site	Tube Type	Labeling and Collection Details	Post-collection Instructions
• Notify **at least one** day in advance • **Send calendar invite via e-mail**: DL-APCF@coh.org	COH	• Green-top • Purple-top	1. Label tubes with COH protocol #, subject ID (issued by DCC), institution (for non-COH sites), date and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Timepoints of collection are stated in Section 8.2.1 3. Blood samples will be collected from an indwelling venous catheter or by venipuncture 4. Invert tubes eight times after collection. 5. **Immediately** place the tubes **on ice**.	**Promptly** deliver the blood samples on ice to the APCF, Shapiro room 1042 for processing **within 4 hours.**
	Non-COH	Green-top		• Peripheral blood samples will be **shipped overnight at ~+4ºC** to COH APCF laboratory (See Section 9.2.3 for shipment details). • **Include** with shipment: - Copy of the latest CBC results (with differential) and the date of the test
	Non-COH	Cell free DNA BCT® tubes	1. Label tubes with COH protocol #, subject ID (issued by DCC), institution, date and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Timepoints of collection are stated in Section 8.2.1. 3. If applicable, follow recommendations for order of draw outlined in Clinical and Laboratory Standards Institute (CLSI) H3-A6. a. BCT® tubes may not be drawn immediately following a heparin tube; if necessary collect a non-additive or EDTA tube as "waste tube" prior to collection in the BCT® tube. 4. Blood samples will be collected from an indwelling venous catheter or by venipuncture. 5. Below guidelines to **avoid possible backflow** from the tube should be followed since BCT® tubes contain a formaldehyde-free preservative: a. Keep patient's arm in the downward position during collection. b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection. c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of aapplication. 6. Completely fill the tube. 7. Remove tube from adapter and immediately invert the tubes 8 to 10 times. 8. **DO NOT FREEZE** samples. Store samples at **18-25 ºC** until shipment.	See Section 9.2.3 for shipment details to COH APCF.

9.2.3 Shipment details for non-COH sites

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.	
When to ship and temperature of shipment:	**BCT tubes:** As soon as possible, and within 5 days of collection*, via overnight courier at **ambient temperature**. **Green-tops:** On the day of collection, via overnight courier, at **around +4 ºC with a refrigerated cool pack** in an appropriate container. Cell-free BCT tubes may be shipped together with green-top tubes **as long as the BCT tubes are wrapped in a way that prevents them from coming in contact with the cold packs.** BCT tubes must be stored at room temperature while awaiting shipment as cold temperatures can affect future analyses.
Days to ship:	**Monday-Wednesday** for receipt Tuesday-Friday by the laboratory. If this is not feasible, advance arrangements should be made with the COH Analytical Pharmacology Core Facility (DL-APCF@coh.org).
Notification on the day of shipment	Email the FedEx shipment # to: • DL-APCF@coh.org, Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org)
*What to include **with** the shipment*	- Copy of the latest CBC results (with differential) and the date of the test - Blood collection form (Appendix D)
Shipment address	Dr. Tim Synold Analytical Pharmacology Core Facility Shapiro 1042 City of Hope National Medical Center 1500 E. Duarte Road Duarte, CA 91010

* Please make every effort to ship the blood on the same day, especially for blood collected on Wednesdays.

9.2.4 Sample Processing by COH APCF

COH samples only: Blood samples will be kept on a rocker set at low speed to mimic circulation and avoid clot formation until processing.

Tube Type and Volume	Processing Details		Downstream assay
Green-top (~21 mL)	Plasma	1. About 14 mL of whole blood will be used to process for plasma. 2. Centrifuge for 10 minutes at 1800 x g at 4 ºC. 3. The resulting upper plasma layer from each tube will be drawn up sequentially into a sterile 5 mL syringe and pushed through a sterile 0.2/0.8 micron disposable filter.	Cytokine analysis

Tube Type and Volume	Processing Details		Downstream assay
		a. **Save** the plasma-depleted portion **for isolation of PBMC**. 4. The filtered plasma will then be transferred in 500 µL aliquots into multiple appropriately-labeled Starstedt microfuge tubes. 5. To **one aliquot**, add 0.5 mL glycerol/0.02% sodium azide solution to dilute the plasma 50/50 v/v. Keep the diluted plasma sample at -20˚C and do not freeze. 6. All the remaining plasma aliquots will be stored frozen at -80˚C until use.	
	Peripheral blood mononuclear cells (PBMC)	7. Any blood remaining following processing of ~14 mL whole blood used to prepare plasma above will be diluted 1:1 with Hank's Balanced Salt Solution and combined with the ~ 7 mL whole blood in a sterile 50 ml conical centrifuge tube. 8. PBMC will then be isolated from the combined whole blood sample by Ficoll-gradient per COH APCF procedures. 9. Isolated PBMC will be stored in liquid nitrogen until use.	FACS
Purple-top (~20 mL)	Plasma and Plasma depleted whole blood cells (PDWB)	1. Centrifuge for 10 minutes at 1800 x g at 4 ºC. 2. Remove the tubes from the centrifuge. Do not disturb the cellular layer. 3. Extract plasma carefully. a. **Do not disturb** the **buffy coat** while pipetting plasma; leave ~3-4mm of plasma behind to ensure the buffy coat is undisturbed. 4. Freeze plasma at -80°C in 1-2mL aliquots. Do not fill tubes beyond 70% capacity.	Sequencing-cell free circulating tumor DNA and germline DNA
		5. Mix the remaining PDWB. 6. Freeze at -80°C in 1-2mL aliquots.	
Cell free DNA BCT® (~20 mL)	Plasma and Plasma depleted whole blood cells (PDWB)	1. Centrifuge for 10 minutes at 1600 x g at **room temperature.** 2. Remove the upper plasma layer and transfer to a new conical tube. a. **Save** the PDWB portion (see below). 3. Centrifuge the plasma at 16000 x g for 10 minutes. 4. Collect the plasma. 5. Freeze plasma at -80°C in 1-2mL aliquots. Do not fill tubes beyond 70% capacity.	Sequencing-cell free circulating tumor DNA and germline DNA
		6. Mix the remaining PDWB. 7. Freeze at -80°C in 1-2mL aliquots.	

9.3 Biomarkers to be analyzed:

The below description is an anticipated rather than an exact list of studies that will be performed, as the investigators reserve the right to adjust the studies to be performed as techniques evolve and new data may become available that is relevant to the study agent and/or study population.

We will perform correlative studies on peripheral blood and tumor tissue with the intention of exploring biomarkers of outcome after study therapy, improved understanding of the biology of HL, and the impact of study therapy on immune reconstitution. Using these pre-treatment and post-treatment samples, we will aim to assess whether tumor-specific, immune effector cell-associated, or microenvironmental characteristics correlate with clinical response to combined nivolumab/NIVO + ICE therapy. Correlative analyses in Dr. Chan's lab will assess the relationship between response to study treatment and gene expression profiles (GEP) performed using RNA-seq as well as genetic mutations determined by WES in pre-study treatment and on treatment tumor samples with the goal of identifying biomarkers associated with response to nivolumab/NIVO + ICE therapy.

Correlative analyses performed in Dr. Lee's laboratory will also explore the biology of combined therapy in the study population, with the goal of understanding the impact on both tumor cells and effector immune cells. To identify biomarkers associated with response to combined nivolumab/ICE, we propose the following correlative studies to analyze tumor cells, immune effector cells, and cells in the stromal/microenvironment, as well as immune cells in peripheral blood, before and after therapy.

The list of planned correlatives includes the following:

a) Immunohistochemistry (Dr. Joo Song) for expression of CD25, CD68, HLA class I and II molecules, PD-1, PD-L1, and PD-L2 in tumor samples (LN, BM). Expression of other receptors/checkpoint molecules may also be assessed. IHC for these markers will be performed on pre- and post-treatment biopsies and expression will be scored in deciles by a hematopathologist blinded to the clinical results. We will compare baseline to on-treatment expression levels.

b) FISH of the 9p24.1 region will be performed as previously described[76] in the City of Hope Cytogenetics Core Laboratory on pre-treatment HL tumor samples and results will be defined as previously - disomy, polysomy, copy gain, amplification. The association between 9p24.1 alteration type and response to nivolumab/NIVO + ICE therapy will be evaluated.

c) RNA sequencing of whole tumor samples (to include Hodgkin cells and immune/stromal cells in the tumor microenvironment) of pre-study treatment tumor samples to assess the potential relationship between genetic alterations of the tumor or tumor microenvironment and response. We will also evaluate GEP by RNA sequencing in on-treatment biopsies. With sophisticated de-convolution algorithms, we will identify and quantitate all the major immune cell populations based on the GEP data.

d) Perform quantitative spatial image analysis (Dr. Peter Lee) of immune and tumor cells in pre-study treatment, on-treatment, and post-progression tumor samples via 8-color histology using the Vectra system to assess the presence of and spatial relationships between tumor infiltrating lymphocytes/immune cell populations (e.g., CD8+ and regulatory T cells) and immune checkpoint ligand/receptors (i.e., PD-1 and PD-L1).

e) Perform peripheral blood flow cytometry of immune cell subsets (including PD-L1 and PD-L2 bearing lymphocytes) (CISCL) at various time points of blood collection to determine the impact of study therapy on immune cell subsets during study therapy and immune reconstitution after AHCT. We will also perform T-cell receptor (TCR) repertoire analysis to assess the TCR repertoire diversity after study therapy.

f) TCR repertoire analysis on the tumor sample will be performed via NGS to assess the TCR repertoire and diversity of tumor infiltrating lymphocytes.

9.4 Circulating DNA Assessment

Despite the relative paucity of RS cells in the tumor, the detection of cell free circulating tumor DNA (ctDNA) is feasible in cHL. A number of next generation sequencing (NGS)-based ctDNA detection methodologies have been studied in cHL. NGS-based ctDNA detection performed by NGS of the immunoglobulin (Ig) genes can identify ctDNA in the peripheral blood mononuclear cells (PBMC) and plasma (cell-free ctDNA) at diagnosis in 73% of patients with cHL. Using a separate NGS method, Vandenberghe and colleagues identified cHL-specific genomic imbalances in ctDNA at diagnosis that became undetectable after treatment. In another study using digital droplet PCR, XPO1 mutations were detected at diagnosis in cHL patients and the persistence of this mutation in patients with a negative PET scan at the end of treatment showed a possible association with relapse. Most recently, using a panel-directed NGS-based approach, noninvasive genotyping of cHL was validated in cHL (feasible in 87.5% of patients evaluated) and enabled monitoring of clonal evolution in patients with patients with treatment failure. Most notably, the presence and rate of ctDNA decline with standard treatment as well as with nivolumab treatment was found to be highly associated with the presence of active lymphoma and with PFS. This latter, panel-directed NGS method has the greatest potential for being the most sensitive and specific tool for ctDNA detection in cHL. The validation of ctDNA in cHL, as a sensitive and specific marker of the eradication of the malignant clone, has the potential to supplant PET-CT scans as a dynamic disease assessment tool. Dynamic response to therapy and the detection of residual cHL are suboptimal with PET scans, which are the current gold standard. There remain a high number of disease progression events in patients who have negative interim and end of treatment PET scans. Furthermore, interpreting PET scans remains particularly challenging in the setting of PD-1 inhibition, even requiring a modification to the standard lymphoma response assessment criteria (i.e. LYRIC criteria). We propose to evaluate the ability of ctDNA assessment to detect 9p24.1 molecular abnormalities, a known prognostic/predictive marker that would be advantageous to detect using a non-invasive method due to the labor intensive methods required for FISH. In addition, in order to determine the most sensitive and specific measure of cHL eradication, we will compare detection of ctDNA at interim and end of treatment time points to PET-CT results to reliably identify disease progression events. This analysis will be carried out in collaboration with Margaret Shipp, MD at the Dana Farber Cancer Institute.

9.5 Quantitative PET Assessment in Hodgkin Lymphoma

For better characterization of therapeutic response and prediction of outcome in patients with lymphoma, significant progress has been made in standardizing qualitative methods and integration of FDG PET in the international working group criteria (IWG) for lymphoma assessment [16]. However, there is a growing need for the development of quantitative imaging metrics as operator-independent surrogate measures to predict treatment response and survival. In this regard, standardized uptake values (SUV) have been the most widely used quantitative measure for assessing tumor metabolic activity and treatment response. In Hodgkin lymphoma (HL), SUVmax cut-off was investigated as a predictor of progression after two cycles of chemotherapy[77], however, without validation studies to define a widely accepted cut off value, these criteria have not yet been adopted for HL.

The PET-derived whole body metabolic metrics, metabolically active tumor volume (MTV*) and total lesion glycolysis (TLG**) measure metabolic activity in an entire tumor mass to reflect tumor biology. With the recent development of software based automated assessments, volume-based metabolic parameters have become increasingly available quantitative PET (qPET) indices. Although, these metrics have the potential to become a useful index for assessing treatment response and survival they are yet to be standardized and validated to translate to a clinical practice platform. Recent studies have reported that a high total MTV predicted a lower survival in various retrospective studies in HL showing variation in the strength of outcome prediction but promising data in early stage HL[78-82]. Based on these encouraging

results, there is interest in utilizing qPET parameters, including MTV, to tailor treatment in HL, but these metrics require validated in larger, prospective studies. In addition, there is controversy with respect to the methodologies used among various investigators[78,79,83], though studies that have evaluated different methodologies have shown similar utility to the various methods[84]. Preliminary results suggest that qPET metrics may not be applicable across treatment regimens. As part of the HD18 trial by the German Hodgkin Lymphoma Study Group Mettler et al found that baseline MTV was a predictive factor for early response to BEACOPP after two cycles. However, no prognostic value for end of treatment response and ultimate outcome was observed with an interim PET-adapted treatment strategy[83]. However, in the LYSA AHL2011 trial, which utilized a similar PET-adapted BEACOPP-based approach in advanced stage HL, MTV was prognostic for PFS. When combined with interim PET status, MTV and interim PET results together identified a subset of patients at high risk for treatment failure[85].

In patients with relapsed or refractory HL treated with sequential BV followed by ICE chemotherapy (in patients not in complete response after BV), baseline MTV and TLG were found to be strong prognostic factors for outcome. In multivariate analyses, baseline MTV remained the main independently prognostic factor associated with treatment outcome along with end of treatment PET status, and baseline MTV enhanced the prognostic value of end of treatment PET status for outcome[86]. Thus, there are data to support the use of qPET parameters as a prognostic factor in HL, both alone and in combination with the dynamic response data gained with interim or end of treatment PET.

The intention of this work is to validate the prognostic value of qPET metrics, in particular MTV, in a prospective trial incorporating novel immunotherapy into the treatment of relapsed/refractory HL.

*MTV measure the total volume, hence measured in cm^3 or ml, of the metabolically active tumor volume encompassed by a VOI, both for a single lesion and for multiple lesions.

**TLG is the product of SUVmean in the defined VOI and the MTV; the rationale is to combine tumor burden and its metabolic activity, having an index that is correlated to the volume and the uptake of the volume.

9.5.1 Methods of qPET parameters:

PET/CT scans were performed after 6–8 hours of fasting and after the intravenous administration of ~10–15 mCi (370–555 Mbq) of 18F-FDG. After 50–70 minutes of radiotracer uptake, PET images were acquired on a non-contrast 16-slice PET/CT system (GE Medical Systems). Three-dimensional (3D) iterative reconstruction using a 168 × 168 matrix with a zoom of 1.0, FWHM filter of either 5.0 or 6.0 mm, and 2 iterations with 8 subsets was used generate PET images. The non-contrast whole body CT data was utilized for lesion anatomic localization and attenuation correction. 18F-FDG PET/CT images region-of-interest (ROI) will be performed using the commercially available, FDA-approved "Mirada Medical PET/CT XD Oncology Review" software (Mirada Medical) and SECTRATM. The ROI measurement - Standard uptake value (SUV; g/mL) – attempts to measure the normalized amount of radioactive concentration found on qualitative (visual) PET inspection in selected part of the body at a certain time. Some variation of the normalization factor for the SUV exist, including: body weight (SUVbw), lean body weight (SUVlbw), and body surface area (SUVbsa). Calculations reported in this study will rely on the general standard of care: SUVbw and it is calculated using the formula recommended by the QIBA SUV Subcommittee:

SUVbw(pixel) in g/mL= activity (pixel) in (Bql/ml)/injected dose in Bql/patient weight in grams).

Image DICOM tags are used to perform the calculation, including: patient's weight, acquisition date time, radionuclide half-life and radiopharmaceutical start date/time.

The background red marrow of each patient was defined by using a 1 cm3 diameter region of interest in the most inferior vertebral body which did not demonstrate focally increased FDG uptake or vertebroplasty material. Focal lesions for each patient were defined as focal areas, measuring at least 1 cm in diameter, not otherwise demonstrated to be artifacts by comparison with coregistered CT, recognizable as discrete foci

of increased 18F-FDG uptake on maximum intensity projection images (MIP), and exhibiting a max SUV (SUVmax) greater than the SUVmax for the patient's background red marrow.

The volume of each lesion and its 3D margins were determined by incorporating all contiguous pixels with activity greater than 0.1 g/mL above that of the background marrow. Because of the considerable statistical variability inherent in the acquisition, reconstruction, and display of accumulations of radiopharmaceuticals in the clinical imaging setting, SUVs obtained from larger regions of interest (ROI) are more reproducible than single pixel determinations such as SUVmax. For this reason, we have chosen to quantify activity by calculating the SUVmax defined as the average SUVs, corrected for lean body mass, of the pixels in a sphere 1.2 cm in diameter (1 cc) centered to include the most intense pixel.

The total MTV for disease in each patient was defined as the sum of MTVs of all the individual focal lesions identified in the analysis. The TLG of each focal lesion was calculated by multiplying the MTV of that lesion with its corresponding mean SUV (TLG = SUVmean × MTV). The global TLG of each patient was defined as the sum of the TLGs for all the focal lesions in the analysis.

Lesions will be identified by the software based on the thresholds set in the workflow that works on adaptive thresholding. MTV will be obtained by summing the metabolic volumes of all nodal and extranodal lesions (TMTV = ΣMTVL). All volumes of interest that are drawn by the automated computer system will be evaluated by the reader to delete those regions that are not deemed to be associated with tumor. The review computer system will automatically calculate all quantitative assessments (SUVmax, MTV, TLG) for each lesions at baseline, mid therapy (when available) and end of therapy (EOT). In addition, at EOT, we will calculate the percentage of change from baseline for each qPET parameter.

10 Study Calendar

10.1 Calendar of Events: Original Study Design (Cohort A)

Study Parameters and Calendar	Within 28[a] days of D1	Nivolumab only, 1st 6 weeks (Wks)			Nivolumab only, 2nd 6 weeks (not all pts)			NIVO + ICE[b] 6 weeks (not all pts)		End of Treatment [l]	Post AHCT f/u
		Wk1 D1 (± 3 day)	Wk3 D1 (± 3 day)	Wk5 D1 (± 3 day)	Wk1 D1 (± 3 day)	Wk3 D1 (± 3 day)	Wk5 D1 (± 3 day)	Wk1 D1 (± 3 day)	Wk4 D1 (± 3 day)		
Nivolumab		X	X	X	X	X	X	X	X		
Ifosfamide[c]								X	X		
Carboplatin[d]								X	X		
Etoposide[e]								X	X		
Informed consent	X										
Demographics	X										
Medical history	X									X	
Concurrent meds	X	X	X	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	
Height	X							X			
Weight	X	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X	X	X	X	X	X	X	X	
CBC w/diff, plts†	X	X	X	X	X	X	X	X	X	X	
Serum chemistry* †	X	X	X	X	X	X	X	X	X	X	
PT/PTT/INR†	X	X	X	X	X	X	X	X	X	X	
TSH, T3, T4 †	X	X	X	X	X	X	X	X	X	X	
EKG (as indicated)†	X										
PFTs	X										
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X [m]
Tumor measurements	X[k]			X[k]			X[k]		X[k]		
Radiologic evaluation[f]	X[a]			X[f]			X[f]		X[f]		
Tumor Biopsy[g]	X			X[h]						X[i]	
B-HCG†	X	X**									
Research blood collection [j]		X[j]	X[j]	X[j]				X[j]	X[j]		
Survival											X [n]

[a] Except for screening PET/CT, which can occur within 35 days of D1.
[b] Filgrastim 5 mcg/kg given on days 5 to 12
[c] 5 g/m^2 with equivalent dose of Mesna given over 24 hours by continuous infusion on day 2
[d] area under the curve (AUC) of 5 with a maximum of 750 mg day 2
[e] 100 mg/m^2/day on days 1 to 3
[f] PET-CT scans will be performed at end of weeks 6, 12, and 18. Once PET-CT is negative, it does not need to be performed again. Instead, a diagnostic quality CT of the neck, chest, abdomen, and pelvis will be performed.
[g] Each subject will have either a fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or will have available archival tissue from a biopsy that was performed after induction therapy.
[h] Tumor biopsy (if safe and accessible) must be performed after the first CT/PET response assessment (and only in patients who did not reach CR). For patients (with PR) who are going to a second 6-week treatment with single-agent NIVO, biopsy may be performed at any time after the first CT/PET scan (but before any NIVO+ICE treatment). For patients (with SD or PD at first CT/PET) who are instead going to a 6-week treatment with NIVO+ICE, biopsy must be performed before starting NIVO+ICE.
[i] If feasible, all subjects will undergo biopsy of tumor lesion at the time of disease progression or relapse.
[j] On Day 1 of Wks 1, 3, 5 of nivolumab, on Day 1 of Wks 1 and 4 of NIVO + ICE, and on last day of Wk 6 (C2D21) of NIVO + ICE or any day post-C2D21, but must be prior to AHCT.
[k] Tumor measurements will be performed at the same time points indicated for PET-CT scans in footnote f.
[l] Includes all patients, regardless of reason for end of protocol therapy; refer to Section 5.5 for follow-up.
[m] For patients who receive AHCT
[n] Refer to Section 5.5 for post-AHCT survival assessments.
*Serum chemistry includes comprehensive metabolic profile: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, AST, ALT, Alkaline phosphate, total bilirubin, calcium, albumin, total protein, magnesium, phosphate
** Women of childbearing potential 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 nivolumab.
† Must be performed within 10 days of treatment initiation.

10.2 Calendar of Events: New Design (Cohort B)

Study Parameters and Calendar	Within 28[a] days of D1	Cycle 1 (14 days) D1 (± 3 day)	Cycle 2+ (21 days) C2, D1 (± 3 day)	C3, D1 (± 3 day)	C4, D1[m] (± 3 day)	End of Treatment [l]	Post AHCT f/u
Nivolumab		X	X	X	(X)		
Ifosfamide[c]			X	X	(X)		
Carboplatin[d]			X	X	(X)		
Etoposide[e]			X	X	(X)		
Informed consent	X						
Demographics	X						
Medical history	X					X	
Concurrent meds	X	X	X	X	(X)	X	
Physical exam	X	X	X	X	(X)	X	
Vital signs	X	X	X	X	(X)	X	
Height	X		X				
Weight	X	X	X	X	(X)	X	
Performance Status	X	X	X	X	(X)	X	
CBC w/diff, plts†	X	X	X	X	(X)	X	
Serum chemistry* †	X	X	X	X	(X)	X	
PT/PTT/INR†	X	X	X	X	(X)	X	
TSH, T3, T4 †	X	X	X	X	(X)	X	
EKG (as indicated)†	X						
PFTs	X						
Adverse event evaluation		X	X	X	(X)	X	X [n]
Tumor measurements	X[k]			X[k]			
Radiologic evaluation[f]	X[a]			X[f]	(X)		
Tumor Biopsy[g]	X					(X[i])	
B-HCG†	X	X**					
Research blood collection [j]		X[j]	X[j]	X[j]			
Survival							X [o]

[a] Except for screening PET/CT, which can occur within 35 days of D1.

[b] Filgrastim 5 mcg/kg given on days 5 to 12

[c] 5 g/m^2 with equivalent dose of Mesna given over 24 hours by continuous infusion on day 2 (inpatient schedule) or 1670 mg/m^2 with Mesna on Days 1-3 (outpatient schedule).

[d] area under the curve (AUC) of 5 with a maximum of 750 mg day 2

[e] 100 mg/m^2/day on days 1 to 3

[f] PET-CT scans will be performed at end of week 8. Once PET-CT is negative, it does not need to be performed again. Instead, a diagnostic quality CT of the neck, chest, abdomen, and pelvis will be performed.

[g] Each subject will have either a fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or will have available archival tissue from a biopsy that was performed after induction therapy.

[i] If feasible, all subjects will undergo biopsy of tumor lesion at the time of disease progression or relapse.

[j] On C1D1, C2D1, C3D1 or any day post-C3D21, but must be prior to AHCT.

[k] Tumor measurements will be performed at the same time points indicated for PET-CT scans in footnote f.

[l] Includes all patients, regardless of reason for end of protocol therapy; refer to Section 5.5 for follow-up.

[m] Optional cycle of NIVO +ICE at the investigator's discretion. PET/CT after Cycle 3, see footnote f.

[n] For patients who receive AHCT

[o] Refer to Section 5.5 for post-AHCT survival assessments.

*Serum chemistry includes comprehensive metabolic profile: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, AST, ALT, Alkaline phosphate, total bilirubin, calcium, albumin, total protein, magnesium, phosphate

** Women of childbearing potential 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 nivolumab.

† Must be performed within 10 days of treatment initiation

11 Endpoint Evaluation Criteria/Measurement of Effect

11.1 Definitions

Evaluable for toxicity: All participants will be evaluable for toxicity from the time of their first treatment with nivolumab.

Evaluable for objective response: Only those participants who have measurable disease present at baseline, have received at least 4 weeks of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR, per 2014 Lugano Criteria,[16] (whichever is first recorded) until the first date that relapsed or progressive disease is objectively documented.

Duration of overall CR: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, per 2014 Lugano Criteria,[16] taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Overall Survival (OS): OS is defined as the duration of time from start of treatment to time of death (due to any cause).

Progression-Free Survival (PFS): PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.2 Transplant Endpoint Definitions

Overall Survival (OS): OS is defined as the duration of time from start of AHCT treatment to time of death (due to any cause). Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

Progression-Free Survival (PFS): PFS is defined as the duration of time from start of HCT treatment to time of progression or death, whichever occurs first. Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

Relapse/Progression (CIR): The event is relapse/progression. The time to this event is measured from start of HCT treatment. Deaths without relapse/progression are considered a competing risk. Surviving patients with no history of relapse/progression are censored at time of last follow-up. Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

Non-relapse mortality (NRM): NRM is defined as death occurring in a patient from causes other than relapse or progression. NRM is measured from start of treatment until non-disease related death, or last follow-up, whichever comes first. Deaths from relapse/progression are considered a competing risk. Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

11.2.1 Toxicities and Adverse Events:

The worst grade of all toxicities will be collected from start of conditioning to day -1, and again from day 0 to 30 post-transplant. From day 31 to 100 post-transplant toxicities that are considered serious adverse events will be collected. Toxicity will be assessed and reported using the CTCAE v4.03 scale.

Stem cell mobilization: mobilization regimen used, median number of cells collected, median number of days to reach minimum collection.

Engraftment (Recovery of Granulopoiesis and Megakaryopoiesis): Engraftment will be assessed using two distinct milestones: 1) ANC (neutrophils) ≥0.5 $x10^3/\mu L$ achieved and sustained for 3 consecutive lab values on different days with no subsequent decline; and 2) Platelets (PLT) ≥20 $x10^3/\mu L$ independent of platelet transfusion support. For platelet recovery, date should reflect no transfusions in previous 3 days and the first of 3 consecutive lab values on different days.

11.3 Response Criteria and Methods for Evaluation of Measurable Disease

PET-CT scans will be performed after Week 6and Week 12of nivolumab single agent therapy, and also after C2 of NIVO + ICE therapy. Once the PET-CT result is negative, it does not need to be performed again. Instead, a diagnostic quality CT of the neck, chest, abdomen, and pelvis will be performed. The determination of anti-tumor efficacy will be based on objective response assessments made according to the Lugano Criteria[16] and treatment decisions by the investigator will be based on these assessments. Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or complete remission (CR) will be determined at each assessment. CR will be defined as a Deauville Score of 3. Selection of up to 6 of the largest dominant nodes or nodal masses to follow for response assessment must be PET FDG-avid at baseline. Investigator evaluation of baseline radiographic assessment will enable study enrollment per inclusion criteria based on the presence of measurable disease > 1.5 cm evidenced by CT scan of the neck/chest/abdomen/pelvis or CT/PET scans. In addition, per the Lugano Criteria, these nodes or masses should be selected according to all of the following: They should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

If the bone marrow was positive at baseline, a follow-up bone marrow aspirate and biopsy is required and must be negative for assessment of a CR. If the follow-up morphology is indeterminate, the biopsy tissue must be negative by immunohistochemistry or the patient will be assessed as a PR.

12 Statistical Considerations

12.1 Study Design

12.1.1 Phase II

This multi-institution, single-arm, phase 2 trial is designed to evaluate the anti-lymphoma activity of the nivolumab ± ICE chemotherapy salvage regimen, in patients with relapsed or primary refractory Hodgkin lymphoma (HL) post induction chemotherapy. Activity will be assessed by complete response (CR) rate prior to autologous hematopoietic cell transplantation.

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, and some lymphomas.[38-43] A phase I trial with 23 heavily pretreated patients with HL (78% of whom relapsed after receipt of brentuximab vedotin) was performed and revealed an ORR of 87% (17% CR, 70% PR) and PFS rate of 86% at 24 weeks.[7] An extended analysis with a median of 20 months revealed durable responses, as 35% of responders (7 out of 20) maintained a response for over 1.5 years.[46] A phase II trial was conducted in patients who relapsed post AHCT and brentuximab vedotin, reporting an ORR of 66% (IRRC assessed: 9% CR, 58% PR) after a median follow up of 8.9 months.[8] On the basis of these data, nivolumab was granted accelerated FDA approval for patients who progressed after AHCT and brentuximab vedotin. ICE salvage chemotherapy was shown to yield an ORR of 88% (26% CR, 58% PR, 3% minor response).[3] The only potentially curative therapy for relapsed/refractory HL is salvage combination chemotherapy followed by autologous hematopoietic cell transplantation (AHCT).[2] Because the overarching research goal of this trial is to increase the proportion of subjects in CR just prior to AHCT, we will target a CR rate of 60%.

Patients will receive nivolumab single agent for 6 weeks. (See **Section 5.1.5.** for treatment schedule.) For patients who achieved CR/PR, they will receive additional 6 more weeks of nivolumab. For patients who

are in CR at this time, they will go directly to AHCT. For patients not in CR after 12 weeks of nivolumab, they will receive NIVO + ICE (combination of nivolumab plus ICE) x 6 weeks. Patients who only achieve SD after 6 weeks of single agent nivolumab can either receive an additional 6 weeks of single agent nivolumab, or receive a combination of nivolumab plus ICE for 6 weeks. The decision to go either way will be at the physician/investigator's discretion on a case-by-case basis. The rationale is that in patients with a radiographic response of SD who are clinically doing well, an immune response or tumor flares could be masking an actual PR or CR. For patients who only achieve PD after 6 weeks of single agent nivolumab, they will directly move onto the NIVO + ICE portion.

Study Design Rationale: This multicenter, single-arm, phase II trial is designed to evaluate the anti-lymphoma activity of the NICE 2nd-line regimen, in patients with relapsed or primary refractory HL post induction therapy. Activity will be assessed by CR rate prior to AHCT. Recent studies evaluating NIVO, an anti-PD-1 monoclonal antibody show efficacy in relapsed/refractory HL. In a phase I trial, NIVO was shown to have an ORR of 87% with a CR rate of 17%[7]. This response rate was recently confirmed in a phase II trial[11], and the drug received accelerated FDA approval for HL after failure of AHCT and BV treatment. In the Moskowitz study of PET imaging normalization prior to AHCT, 60% of patients who received 2nd-line ICE or augmented ICE achieved CR prior to AHCT[12]. The MSKCC trial, which used augmented ICE, accrued 46 patients in 2 years, of whom 44 proceeded to AHCT, with 34 in CR (74%)[13]. In our study of PET-adapted BV ± chemotherapy prior to AHCT, 65% of enrolled/treated patients attained a CR pre-transplant[14]. Based on these data, a CR rate of 70% prior to AHCT will be considered promising, qualifying the regimen worthy of further investigation.

Study Design Characteristics: This phase II trial will implement a Simon Two-Stage Optimal Design[15] to evaluate the anti-lymphoma activity of NIVO± ICE chemotherapy. The trial is expected to enroll a minimum of 15 and a maximum of 43 subjects. The sample size is based on the desire to discriminate a promising CR rate of 70% from a disappointing CR rate of 50% (a rate below what can be achieved with ICE/augmented ICE) using a type I error rate of 0.05 and power of 80%. At stage 1, 15 subjects will be entered on the study. If ≤ 8 complete responses are seen, the study will be terminated. If at least 9 subjects achieve a CR, the trial will continue to the second stage. At stage 2, 28 additional subjects will be entered. At the end of stage 2, if 27 or more subjects experience a complete response, the combination will be considered worthy of further study. If ≤ 26 subjects experience a complete response then no further investigation of the regimen is warranted.

Safety Monitoring Segment: NIVO is already FDA approved for treatment of HL and thus does not require special safety monitoring. Since the combination of nivolumab and ICE has not been tested before, the trial will include a 6-patient safety monitoring cohort for patients treated with nivolumab plus ICE (cycle 1). If ≤ 1/6 patients experience unacceptable toxicity, then the study will continue. If 2 or more patients experience unacceptable toxicity, we will stagger the dose of nivolumab and ICE by 1 week so that nivolumab will start on day 1 and ICE will start on day 8 of a 21 day cycle. There will then be another 6 patient cohort added to the monitoring. If ≤ 1/6 patients experience unacceptable toxicity in the staggered cohort, then the study will continue. If, however, 2 or more patients experience unacceptable toxicity in the staggered cohort, then nivolumab will not be given in combination with ICE.

Cohort B: Due to the high CR rate with nivolumab alone, only a small number of patients have been treated with NIVO + ICE thus far. Based on the small number of patients treated with NIVO + ICE, it is not possible to adequately characterize the full spectrum of toxicities with NIVO + ICE, nor is it possible to obtain an adequate preliminary estimate of the anti-tumor efficacy. Therefore, a separate cohort has been added to the study, which will be enrolled after the completion of the original PET-adapted cohort. In this new cohort, all patients will receive a cycle of nivolumab and then NIVO + ICE x 2-3 cycles. We plan to enroll and treat 18 eligible patients in this new cohort. The sample size is based on assessing unacceptable toxicities with NIVO + ICE. With 18 patients, we can estimate the proportion of patients experiencing unacceptable adverse events with sufficient precision (standard error ≤ 0.12, half width ≤ 0.23).

Updated April 27, 2021:

Given the exceptionally high CR rate observed thus far and without any signals of excess toxicity to date, we will expand Cohort B to a full Phase 2 efficacy cohort to assess whether the CR rate after 3-4 cycles of therapy (Nivolumab x 1, Nivolumab+ICE x 2-3) in high-risk patients is promising compared to historical data. See full rationale provided in Section 2.5.

The phase 2 portion will implement a Simon two-stage minimax design[15,87] to evaluate the anti-lymphoma activity of the two-agent combination as assessed by CR rate, in patients with high-risk HL. The Cohort B phase 2 portion is expected to enroll and treat a minimum of 19 and a maximum of 35 patients at the Cohort B schedule. The sample size is based on the desire to discriminate a promising CR rate of 74% from a disappointing response rate of 50%[3] using a type I error rate of 0.05 and power of 90%. At stage 1, 19 patients will be entered on the study. Note: The n=13 patients treated thus far as part of the safety evaluation portion of the study will count toward the 35 patients required; given this, we expect to enroll only 22 new patients on the Cohort B phase 2 trial. If ≤ 9 complete responses are seen, the study will be terminated. If at least 10 patients achieve CR, the trial will continue to the second stage. At stage 2, 16 additional patients will be entered. At the end of stage 2, if 23 or more patients experience complete response, the combination will be considered worthy of further study. If ≤22 patients achieve a complete response then no further investigation of the combination is warranted.

12.2 Sample Size Accrual Rate

Assuming 1) nivolumab and NIVO + ICE are well tolerated and 2) the study does not close for futility, 43 evaluable patients will be enrolled on the phase II portion of the study. Study enrollment will be complete within 24 months from activation (accrual of 1-2 participants per month). Expected accrual for the safety monitoring segment: n=6.

Sample Size, Cohort B: We plan to enroll and treat 18 eligible patients. With 18 patients, we can estimate the proportion of patients experiencing unacceptable adverse events with sufficient precision (standard error ≤ 0.12, half width ≤ 0.23). Expanded Sample Size (Anti-Lymphoma Activity): The Cohort B phase 2 portion is expected to enroll and treat a minimum of 19 and a maximum of 35 patients at the Cohort B schedule.

12.3 Safety Analysis and Stopping Rules for Excessive Toxicity

Following the *patient safety monitoring segment*, the early stopping rule for safety/toxicity will continue to be assessed for each patient after cycle 1. The expected rate of unacceptable toxicity should not be ≥33%. See **Section 5.2** for unacceptable toxicity definition. This rule is in addition to the quarterly review of all toxicities submitted to the COH DSMC. Given the number of patients treated, if the unacceptable toxicity rate is ≥33%, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee (DSMC) will be mandated.

Cohort B: The early stopping rule for safety/toxicity will be assessed for each patient after C2, which is the first cycle of NIVO+ICE combination therapy.

12.4 Statistical Analysis Plan

In general, data will be summarized by using counts and percents for discrete parameters, and by descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) for continuous parameters. Response rates will be calculated as the percent of evaluable patients that have confirmed CR by radiographic response including CT and/or PET scans; 95% Clopper Pearson confidence limits will be calculated for this estimate. Toxicity information recorded will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity. Baseline information (e.g., the extent of prior therapy) and demographic information will be presented as well to describe the patients treated in this study. Time to response and survival endpoints will be estimated using the product-limit method of Kaplan and Meier. The

cumulative incidence of relapse/progression and non-relapse mortality will be calculated as competing risks using the method of Gooley et al[17].

12.5 Analysis of Correlative Endpoints

Because of the limited sample size inherent to phase II studies, the analysis of correlative endpoints is primarily exploratory. Standard descriptive methods will be used to summarize: 1) the role of PDL1/L2, CD68 on lymphoma specimens and 2) the role of T/B/NK cell subsets in the peripheral blood. If nivolumab or NIVO + ICE is not found to have sufficient activity, these patterns may help explain the lack of activity. If sufficient activity is found, then participants who experience an objective response will be compared to those who did not in terms of correlates. Estimates of variation will also prove useful for future clinical research on this regimen. Formal testing of these comparisons is not planned. All analysis will clearly document the exploratory nature of these studies, although no attempt will be made to adjust for multiple comparisons inherent in correlative studies.

13 Data Handling, Data Management, Record Keeping

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigators or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

12.2 Data Capture Methods and Management

Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system. Medidata RAVE is a web based, password protected system that is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF). A system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

The Data Coordinating Center will run monthly data expectation reports that will list any outstanding and overdue data. The Data Coordinating Center will send via email to the participating site a report monthly on any missing and/or overdue data forms. The participating site will be required to complete the missing and/or overdue data forms within 1 week of receipt of the report.

Query reports will be generated on a monthly basis by the Data Coordinating Center. The Data Coordinating Center will send via email to the participating site a report monthly on any outstanding queries.

The participating site staff (whether the Principal Investigator or the staff collecting data at site) are required to take an eLearning Module within Medidata RAVE in order to obtain full access. The participating site staff will receive training via teleconference by COH DCC staff to review eCRFs that are specific to this protocol. Continuous training will be offered to participating sites if any amendments affect changes to the eCRFs during the course of the trial. The eCRFs within Medidata RAVE for this trial will have detailed instructions in the form of Help Text that provide instructions for completing each required field on each form.

12.3 Case Report Forms/Data Submission Schedule

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be collected using the electronic data collection system described in **Section 12.2**, and will be submitted according to the timelines indicated in Table 12.3.1.

All data will be collected within 1-2 weeks using standard Medidata Electronic Data Capture (EDC) case report forms. Data will be collected and stored on secure computers as indicated in **Section 12.2**. After 2 years, we will access the COH CIBMTR data repository to retrieve data regarding post-HCT long-term outcomes through study termination.

Table 12.3.1 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 10 business days of registration
Baseline Assessment Forms	Within 10 business days of registration
Treatment Forms	Within 10 business days of treatment administration
Adverse Event Report Forms	Within 5 business days For transplant patients: within 10 business days of the end of evaluation period.
Response Assessment Forms	Within 10 business days of response assessment
Other assessment forms (e.g., concomitant meds, transplant data including mobilization, etc.)	Within 10 business days of the assessment
Transplant Core Intake Form	Within 10 business days of stem cell infusion
Post Transplant Disease Assessment Form	Within 14 days of the end of evaluation period
Off Treatment/Off Study Forms	Within 10 business days of completing treatment or being taken off study for any reason
Follow up/Survival Forms	Within 10 business days of the protocol defined follow up visit date or call

12.4 Regulatory Records

The Investigator will maintain records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations. Additional information regarding required documents is provided in the DCC Operations Manual, a supplement to this protocol.

14 Adverse Events and Unanticipated Problems

The research team is responsible for classifying AEs and UPs as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, assessing the severity (i.e. grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Adverse events will be characterized using the descriptions and grading scales found in the most recent version of CTCAE version 4.03. A copy of the scale can be found at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. The determination of severity for all other events not listed in the CTCAE version 4.03 should be made by the investigator based on medical judgment.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated -**The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant..
- **Unlikely** -The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible** -The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable** - The event is most likely related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug, and is unlikely related to the participant's clinical state, therapeutic interventions, or concomitant drugs.
- **Definite** - The event is clearly related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

14.2 Reporting of Adverse Events

14.2.1 Routine Recording of Non-Serious Adverse Events

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin once the patient is consented and will continue until 100 days after discontinuation of dosing. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported

through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

14.2.2 Expedited Reporting Requirements of SAEs and UPs to the COH Regulatory Committees

Adverse Events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Reporting of SAEs will begin after the patient signs the study consent, and must be followed until the event is resolved, stabilized, or determined to be irreversible by the participating investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event. For ongoing reportable adverse events that are unrelated to study agent, the follow-up period may end at the 30-days post study-drug assessment.

Non COH Sites:

Serious Adverse Events meeting the criteria specified in the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy will be reported to the Data Coordinating Center (DCC) and Study PI within **24 hours** of notification that the event occurred.

Procedure for reporting SAEs/UPs to the COH DCC

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the SAE/UP on each of the following:
    a. MedWatch 3500A: Downloadable form at http://www.fda.gov/medwatch/getforms.htm
    b. UP/SAE Coversheet (Appendix B): A modifiable Microsoft Word document is available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to aherrera@coh.org and DCC@coh.org with the subject title as "COH IRB 16403 SAE". If an email receipt from Coordinating Center personnel is not received within one working day, please email DCC@COH.org.

14.2.3 Adverse Events of Special Interest (AESI)

For this protocol only, specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to BMS per SAE reporting timelines.

14.2.3.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

**All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03.*

Events meeting the definition of major hemorrhage will be captured as an event of special interest.

14.2.4 Additional AE Reporting Requirements

14.2.4.1 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, the Study PI will submit annually within 60 days (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

14.2.4.2 Reporting to BMS

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study including periodic reconciliation.

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information (see Section 14.2.4.1 above). BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

14.2.4.3 Reporting to Participating Investigators

The Study PI (or designee) will report all reportable serious adverse events to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.

The Study PI will also forward to participating sites all IND safety reports received from BMS, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

15 Protocol Deviations and Single Subject Exceptions

Deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the Clinical Research Protocol Deviation policy.

Non-COH Sites:

Deviations meeting the criteria specified in the Clinical Research Protocol Deviation policy (Appendix X) will be reported to the Data Coordinating Center (DCC) and PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet to aherrera@coh.org and DCC@coh.org **within 24 hours** of notification of the deviation with the email subject title of "COH IRB # Deviation". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.
3. Sites are to report to their local IRB and DSMC per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB and/or DSMC submission and corresponding response(s).

16 Study Oversight, Quality Assurance, and Data & Safety Monitoring

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT) minimally consisting of the study principal investigator, collaborating investigators, site investigators, research nurse, clinical research associate/coordinator, and the study biostatistician is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study-related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

16.4 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials and Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

16.5 Risk Determination

This is a High Risk study as defined in the City of Hope Institutional DSMP. This determination was made because the study involves a COH IND.

16.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

17 Ethical and Regulatory Considerations

17.1 Ethical Standards

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for

the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocoland according to the following considerations:

US Code of Federal Regulations (CFR) governing clinical study conduct

Title 21 Part 11 – Electronic Records; Electronic Signatures

Title 21 Part 50 – Protection of Human Subjects

Title 21 Part 54 – Financial Disclosure by Clinical Investigators

Title 21 Part 56 – Institutional Review Boards

Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies

Title 21 Part 312 – Investigational New Drug Application

Title 45 Part 46 – Protection of Human Subjects

US Federal legislation, including but not limited to:

Health Insurance Portability and Accountability Act of 1996

Section 801 of the Food and Drug Administration Amendments Act

Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17.

Applicable institutional research policies and procedures.

17.3 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federalwide Assurance issued by and registered with the Office for Human Research Protections (OHRP). Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document will be in the possession of the Investigator, and, for sites external to COH, the possession of the coordinating center, before the study is initiated. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

The IRB will be informed of revisions to other documents originally submitted for review; serious unexpected or unanticipated adverse experiences occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol document and accompanying informed consent document/template, as developed and provided by the Study PI, will require review and approval by the IRB before the changes are implemented in the study. The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

17.4 Informed Consent

For a multi-site study, each participating institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the Data Coordinating Center.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patient or the patient's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Site Investigator and available for inspection sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Recruitment of Subjects

Patients of both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in **Section 3.0**. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to accrue a representative sample. If differences in outcome appear to be associated with gender or ethnic identity, then a follow-up study will be designed to investigate those differences more fully.

17.6 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line^{SM} website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

17.7 Study Location and Performance Sites

This study will be performed at COH, MD Anderson Cancer Center, and Fred Hutchinson Cancer Research Center.

17.8 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain

permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. Source documents provided to the coordinating center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and patient initials.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

17.9 Financial Obligations and Compensation

The investigational drug, nivolumab, will be provided free of charge by BMS. The insurance carrier will be asked to pay for the cost of ICE since these drugs are commercially available

The standard of care drugs and procedures provided will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. However, neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant; however, financial compensation will not be available.

The research participant will not be paid for taking part in this study.

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Appendix A: Registration Coversheet

COH 16403: A MULTI-CENTER PHASE II TRIAL OF NIVOLUMAB PLUS ICE IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA AS BRIDGE TO AUTO-HCT

Please include this coversheet with every registration package that is submitted from your site.

Data Coordinating Center: City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: 626-218-7904 x 87904
Email: DCC@coh.org (use #secure# in subject line)

CRA/Study Coordinator: _____ Contact Number: _____

Patient's Initials: (F M L):

Patient's DOB:

Patient's Zip Code:

Sex: _____Male _____Female

Race:

___ Black
___ Caucasian
___ Asian
___ American Indian
___ Native Hawaiian/Pacific Islander
___ Other _____

Ethnicity:

___ Hispanic
___ Non-Hispanic
___ Other _____

Institution:

Investigator/Treating Physician:

IRB approval valid until (date):

Date Informed Consent Signed:

Projected start date of treatment:

Method of payment: _____

Codes:

01 Private
02 Medicare
03 Medicare & private ins.
04 Medicaid
05 Medicaid & Medicare
06 Military or Veterans Adm. sponsored
07 Self-pay (no insurance)
08 No means of payment (no insurance)
09 Unknown

Appendix B: SAE/UP Reporting Coversheet

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT

For Use by Participating Institutions Only (Non-COH)

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500A FORM MUST BE **EMAILED** TO DCC@COH.ORG WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT OR UNANTICIPATED PROBLEM

COH IRB #16043- Participating Site IRB # _____

From:	Date:
Phone No.:	Email:

Reporting Investigator:	
Event:	
Participant ID:	Institution:
Date Event Met Reporting Criteria (as defined in protocol):	

Type of Report: ☐ Initial ☐ Follow-up

CTCAE Grade : ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5

Attribution to **Nivolumab**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite

Attribution to **NIVO + ICE:** ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite

Historical/Known Correlation to **Nivolumab:** ☐ Expected ☐ Unexpected

Historical/Known Correlation to **NIVO + ICE:** ☐ Expected ☐ Unexpected

Meets Definition of Serious AE: ☐ Serious ☐ Non-serious

Meets Definition of Unanticipated Problem: ☐ UP ☐ Not a UP

Has the event been reported to the participating institution's IRB? ☐ No ☐ Yes Date: __ __ / __ __ / __ __

Authorized Investigator Signature:_____Date: __ __ / __ __ / __ __

Appendix C: Correlative Tissue Form (For All Sites)

A copy of this form should <u>accompany the sample shipments</u> to COH Pathology Core.

Non-COH sites: refer to **Section 8.1.5** for shipping instructions to COH Pathology Core.

COH IRB number: 16403	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

CRA/Study Coordinator/Nurse Printed Name:
CRA/Study Coordinator/Nurse Signature:
Contact Number:

Appendix D: Correlative Blood collection form (For non-COH sites)

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

Cohort B only:

Sample #	Timepoint of Collection	Expected Volume	Tube Type Used (Select One)	Collected Volume	Time of Collection	Actual Date of Collection	Indicate which sample was collected
1.	Cycle 1, Day 1	~ 21 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		~ 20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	Cycle 2, Day 1	~ 21 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		~ 20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
3.	Cycle 3, Day 1	~ 21 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		~ 20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

Peripheral blood will be collected prior to study treatment/procedures at the indicated time points.

A copy of this form should accompany the sample shipments to APCF.

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

Appendix E: Supplemental Materials

These documents are relevant to the protocol; however, they are not considered part of the protocol. They are stored and modified separately; therefore, modifications to these documents do not require protocol amendments.

City of Hope Data and Safety Monitoring Plan

City of Hope's Institutional policy: 05/14/14] Titled: Reviewing and Reporting Unanticipated Problems and Adverse Events Involving Risk to Research Participants or Others

Clinical Research Protocol Deviation policy

Charter for the Data And Safety Monitoring Committee (DSMC)

COH IRB 16043Clinical Monitoring Plan

COH Office of Clinical Trial Auditing and Monitoring SOP

COH DCC Operations Manual – this document will serve as guidance as to the responsibilities of the Data Coordinating Center, as well as those of the participating sites (for this study specifically).