SWOG CANCER RESEARCH NETWORK

Version Date: September 2, 2023

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS AND NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM (NCORP) AFFILIATES AND SUBAFFILIATES; CTSU

FROM: SWOG Operations Office (protocols@swog.org)

RE: **S1826** "A Phase III, Randomized Study of Nivolumab (Opdivo) Plus AVD or Brentuximab Vedotin (Adcetris) Plus AVD in Patients (Age >/= 12 Years) with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma" Study Chairs: Drs. A. F. Herrera, J. Friedberg, S. M. Castellino, S. Parsons, S. C. Rutherford, A. M. Evens, A. Punnett, K. Davison, D. Hodgson, L. S. Constine, L. Kostakoglu Shields, J. Y. Song.

REVISION #6

Study Chair: Alex F. Herrera, M.D.
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Action Codes
(√) Expedited review allowed

Key Updates
(√) Eligibility changes*
*Patient notification not required
(√) Data Submission changes
(√) Editorial / Administrative changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of distribution of this notice through the CTSU Bi-Monthly Broadcast email.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice through the CTSU Bi-Monthly Broadcast email. The changes are effective upon approval by the local IRB; however, any changes to eligibility are effective 30 days after distribution of this notice. If local IRB approval is not granted within 30 days, new registrations must meet any revised eligibility criteria included in the revision or accrual must be suspended until approval is obtained.

REVISION #6

The above referenced study has been revised to: (1) primarily ask sites to submit two additional, previously collected, scans based on protocol specifications; (2) Expand eligibility. The changes are as follows:

Protocol Changes

1. The version date has been updated.

2. Throughout the protocol, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

3. **Section 5.6a:** This section has been expanded upon to include, “Patients who do not complete PRO instruments prior to registration but are otherwise eligible will remain eligible for the primary analysis and other secondary analyses” to maintain eligibility for patients.

4. **Section 9.2:** Footnote “e” was edited to emphasize CT scan requirements.

5. **Section 13.5g:** The request for Patient SSN information was removed.

6. **Section 14.4a:** The location of the Imaging Adjunctive Data Sheet link was updated.

7. **Section14.4f:** This section has been inserted to include, “All contrast-enhanced CT images involved at baseline or contraindicated from scans performed to assess disease as specified in Section 15.4. Submit to IROC Ohio (via TRIAD strongly preferred) for retrospective central imaging review.”

    - The location of the Imaging Adjunctive Data Sheet links were updated.
    - For patients who have had 1-year and 2-year after registration contrast-enhanced CT (or if contra-indicated, PET-CT, CT, MRI, or MR-PET) scan performed prior to activation of S1826 Protocol Revision 6, submit images to IROC Ohio within 60 days after participating site activation of S1826 Protocol Revision 6 (Version Date 9/2/2023).

    - If CT scan is contraindicated and PET-CT scan is submitted, S1826 Imaging Adjunctive Data Sheet for PET scans is required. This form is submitted electronically via the IROC website.

8. **Section 15.4a:** Under Image Collection and Submission Time Points:

    - “If performed” was removed from criterion 4.

    - Criteria 5 and 6 were inserted to indicate the required scan submissions as 1 and 2 years after registration, respectively.

Consent Changes

1. The version date has been updated.

2. Throughout the consent, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

3. The reading scores were updated.

4. “**What exams, tests, and procedures are…”: Under the subheader, “For both Groups 1 and 2,”:**
    - In the seventh bullet regarding Patient Reported Outcomes, language requiring patient reported outcomes for participation in the overall study was removed.

    - **In the eighth bullet regarding patient scans, patients are informed that scans from their 1st and 2nd years after registration will be submitted to the study for review.**

Patient Notification and use of Consent Addendum:

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG’s minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

SWOG has determined that the changes above that are **bolded** may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes.

Who must be informed?

- All patients who have been consented to the study and received treatment.

How must patients be notified?

- Notification must take place either via the attached Consent Addendum or via amended consent form by next study visit. After the change has been discussed with the patient, the patient must sign and date either the Consent Addendum or the [Publish Date] version of the consent form.

What is the notification deadline and process?

- Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.

- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.
- Sites not using the NCI CIRB as their IRB of record: If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved. Important: Any changes to eligibility criterion are effective 30 days after distribution of this notice. If local IRB approval is not granted within 30 days, new registrations must meet any revised eligibility criteria included in the revision or accrual must be suspended until approval is obtained.

Regulatory Considerations:

Do local consent forms need to be updated?

- Yes, local consent forms must be updated to include all the changes in this revision.

The updated protocol and model informed consent form can be accessed from the CTSU website (www.ctsu.org). Please discard any previous versions of the documents and replace with the updated versions. Please contact lymphomaquestion@crab.org or 206/652-2267 with any questions.

This memorandum serves to notify the NCI, and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
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Sharon M. Castellino, MD, MSc - COG
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Informed Consent Addendum Model for S1826

S1826, "A Phase III, Randomized Study of Nivolumab (Opdivo) Plus AVD or Brentuximab Vedotin (Adcetris) Plus AVD in Patients (Age >/= 12 Years) with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma"

The following information should be read as an update to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated below, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

The consent form has been updated to include two additional scan reports you've already had as part of your care. We are requesting the two new reports from one and two years after you joined the study. There will be no extra appointments as these scans are already done.

Patient Signature and Date

By signing this form, I acknowledge that I have read the information above or had it read to me. I have discussed it with a member of the study team and my questions have been answered. I understand that I will be given a copy of this form.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG CANCER RESEARCH NETWORK

A PHASE III, RANDOMIZED STUDY OF NIVOLUMAB (OPDIVO) PLUS AVD OR BRENTUXIMAB VEDOTIN (ADCETRIS) PLUS AVD IN PATIENTS (AGE >/= 12 YEARS) WITH NEWLY DIAGNOSED ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA

NCT# 03907488

This study is being conducted under DCTD, NCI IND

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by SWOG with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology; Children's Oncology Group; ECOG-ACRIN Medical Group; NRG Oncology; and Canadian Cancer Trials Group.

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AGENTS:

NCI Supplied Investigational Agents:
BMS-936558 (Nivolumab, MDX-1106)
(NSC-748726) (IND #)

Commercially Available Agents:
SGN-35 (Brentuximab Vedotin)
(NSC- 749710)
Doxorubicin hydrochloride
(NSC-123127)
Dacarbazine (NSC-45388)
Vinblastine sulfate (NSC-49842)
Filgrastim (r-metHuG-CSF) (Neupogen®)
(NSC 614629)
Pegfilgrastim (Neulasta™) (NSC 725961)

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*** Please see the S1826 Protocol Contact Information page for additional contacts.***

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ALLIANCE/Alliance for Clinical Trials in Oncology
COG / Children's Oncology Group
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG Cancer Research Network

International Participants:

CCTG/Canadian Cancer Trials Group

TABLE OF CONTENTS

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QOL/PRO questions:	Email: sparsons@tuftsmedicalcenter.org or call: Dr. Susan Parsons at: Phone: 617/636-5168

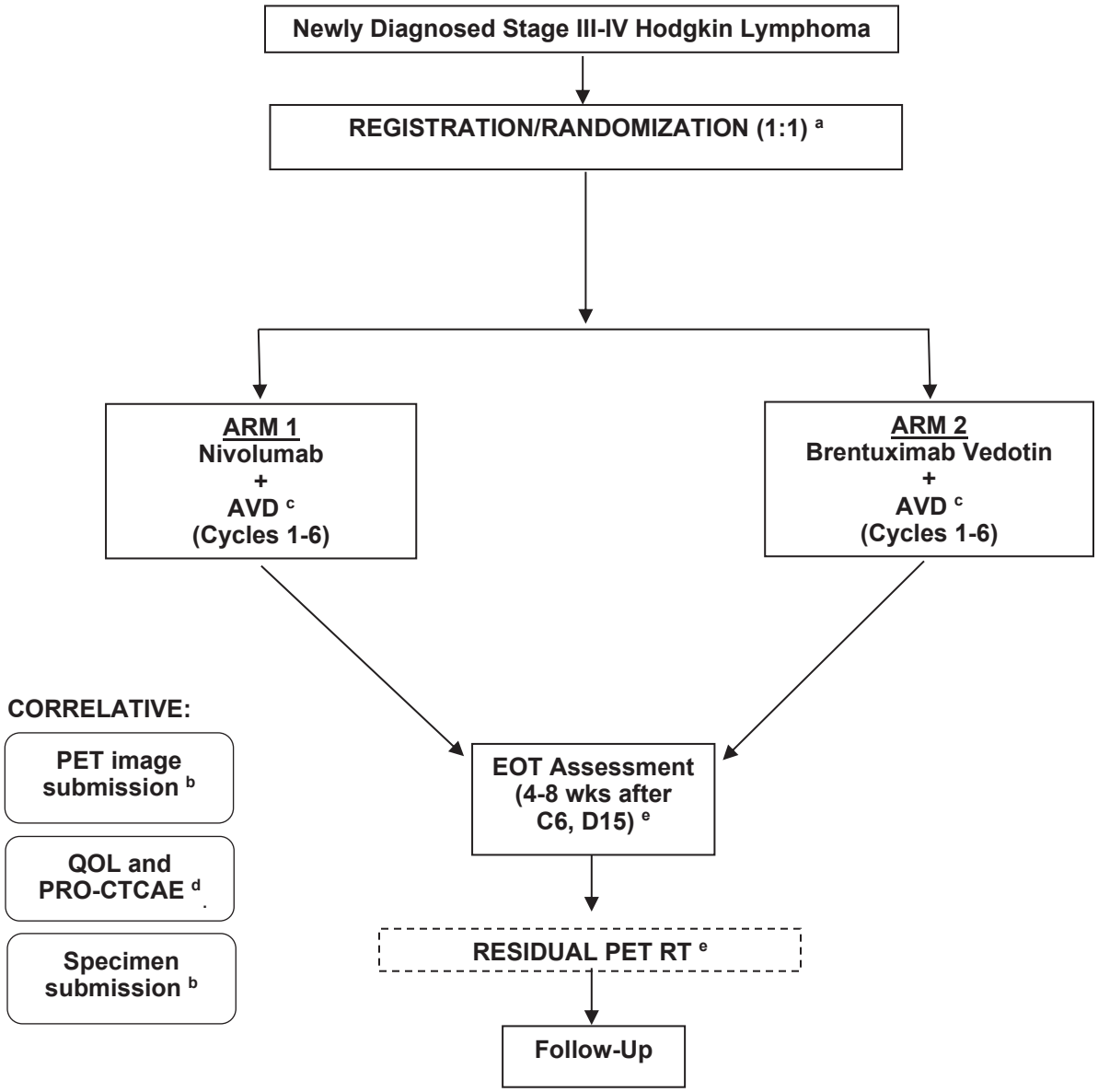
S1826 PROTOCOL CONTACT INFORMATION CONTINUED

Investigational Drug questions:	See Protocol Section 3.1 or PMBAfterHours@mail.nih.gov
Requests for Investigator's Brochures:	See Protocol Section 3.0 or http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm
Access issues for the PMB Online Agent Ordering Processing (OAOP) application:	IBCoordinator@mail.nih.gov
Other Pharmaceutical questions:	Pediatric: Email: Olga Militano at: omilitano@childrensoncologygroup.org Adult: Email: protocols@swog.org
Specimen Tracking System (STS) errors or connectivity issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Protocol and Consent Documents at:	www.ctsu.org
Investigator / Site Registration:	See Protocol Section 13.2 or https://ctep.cancer.gov/investigatorResources/default.htm Email: RCRHelpDesk@nih.gov
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM):	To check CTEP-IAM account: To reset password or request new accounts: https://ctepcore.nci.nih.gov/iam/ApplicationLoginPage.do
Access to iMedidata Rave	See Protocol Section 14.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Section 13.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Streck Tube Kit Orders:	https://ricapps.nationwidechildrens.org/KitManagement
Patient Transfers:	patienttransfer@crab.org
Serious Adverse Event Reporting questions:	See Protocol Section 8.6 Email: adr@swog.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench via the SWOG website (www.swog.org).
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center by phone or email: 206/652-2267 lymphomaquestion@crab.org **For treatment or toxicity related questions** contact the Study Chair by phone or email: US Adults: E-mail: S1826USAdults@swog.org or call: Dr. Alex Herrera (SWOG) at Phone: 626/256-4673 ext. 62405 or Dr. Sarah Rutherford (Alliance) at Phone: 646/962-2064 or Dr. Andrew Evens (ECOG-ACRIN) at Phone: 732-235-9289. Pediatrics: E-mail: S1826pediatrics@swog.org or call: Dr. Sharon Castellino at Phone: 404/785-3616 or Dr. Angela Punnett at: Phone: 416/813-5394. CCTG Adults: Dr. Kelly Davison at: E-mail: kelly.davison@mcgill.ca or Phone: 514/934-1934, ext 31558. or Dr. Michael Crump at: Michael.Crump@uhn.ca or Phone: 416/946-4567.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA



[a] Residual PET Radiation Therapy (Residual PET RT), at time of completion of 6 cycles of protocol therapy, is allowable as indicated in Section 7.5 provided that: 1) Investigator declared (at time of patient registration) patient as intent-to-treat with Residual PET RT, 2) Patient received Cycle 2 PET, and 3) Patient meets criteria indicated in Section 7.5 at time of completion of 6 cycles of protocol therapy.

[b] See Section 12.0 for Central Pathology Review, Central Radiology, and Central Radiation Therapy Review Requirements. See Sections 15.1 and 15.4 for specimen and image submission instructions.

[c] Doxorubicin, vinblastine, and dacarbazine.

[d] See Sections 15.5 and 15.6 for QOL and PRO-CTCAE Questionnaire administration and submission timepoints.

[e] See Section 15.4.

1.0 OBJECTIVES

1.1 Primary Objective:

To compare the progression-free survival (PFS) in patients with newly diagnosed advanced stage classical Hodgkin lymphoma randomized to N-AVD (nivolumab, doxorubicin, vinblastine, dacarbazine) versus that obtained with BV-AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine).

1.2 Secondary Objectives:

a. To compare overall survival (OS) in patients randomized to N-AVD versus BV-AVD.

b. To compare event-free survival (EFS) in patients randomized to N-AVD versus BV-AVD.

c. To compare the metabolic complete response (CR) rate at the end of treatment in patients randomized to N-AVD versus BV-AVD.

d. To compare the physician-reported treatment-related adverse event rates between arms stratified by age groups.

e. To compare patient-reported symptoms using selected PRO-CTCAE items between arms stratified by age groups.

f. To compare the safety and tolerability of N-AVD versus that of BV-AVD.

1.3 Quality of Life Objectives

To compare between arms patient-reported fatigue, neuropathy and health-related quality of life over time (baseline, beginning of Cycle 3, 4-8 weeks after the last dose of protocol therapy (following last dose of study drug or radiation therapy, whichever is later), and 1 and 3 years after randomization) using the PROMIS-Fatigue, the FACT/GOG-Ntx , and the PROMIS Global, respectively.

1.4 Banking Objectives

a. To bank specimens for future correlative studies.

b. To bank PET-CT images for future correlative studies.

2.0 BACKGROUND

2.1 Overview of Study Components

This is a randomized Phase III study comparing the addition of nivolumab or brentuximab vedotin to a backbone of AVD chemotherapy for the initial treatment of advanced stage Hodgkin lymphoma (HL). In addition to the primary therapeutic objective, we will conduct a series of quality of life analyses to assess the impact of each treatment regimen on patient well-being. We will also study the prognostic impact of imaging-based biomarkers like pre-treatment metabolic tumor volume and we will study outcomes based on novel response assessment criteria (i.e. LYRIC and RECIL) that specifically address atypical responses observed with immunotherapy. Finally, we will bank tumor tissue and blood for future translational medicine studies.

2.2 Introduction: Hodgkin Lymphoma

Hodgkin Lymphoma (HL) is a lymphoid neoplasm that is diagnosed in approximately 8190 Americans annually and results in approximately 1070 deaths each year in the USA. *(1)* HL typically affects young adults and presents with painless lymphadenopathy with or without splenomegaly, fevers, drenching night sweats, weight loss and pruritus. The diagnosis is best established by an excisional lymph node biopsy demonstrating large, atypical lymphoblasts surrounded by a heterogeneous infiltrate of non-neoplastic inflammatory and accessory cells. The World Health Organization's classification of lymphomas distinguishes two major subtypes of HL, namely, "classical HL" and "nodular lymphocyte predominant HL".

Classical HL is characterized pathologically by the presence of bizarre monoclonal lymphoid cells that may be either mononuclear (Hodgkin cells) or multinucleate (Reed-Sternberg cells). The malignant Hodgkin and Reed Sternberg cells (HRS) cells of classical HL express CD15 and CD30 surface antigens, but usually not typical B cell markers such as surface immunoglobulin, CD20, CD79a, or the common leukocyte antigen, CD45. *(2)* The B-cell origin of HRS cells is nevertheless demonstrable by the expression of the B-cell specific activator protein (BSAP) derived from the PAX 5 gene in 90% of cases. *(3)* Immunoglobulin genes are rearranged in 98% of HRS cells but are not transcribed due to the absence of the transcription factor Oct-2 and its co-activator BOB-1. The malignant (HRS) cells are typically surrounded by a heterogeneous infiltrate of reactive T- and B-lymphocytes, eosinophils, macrophages, fibroblasts, and variable amounts of collagen deposition (sclerosis). *(4)* Four discrete histologic subtypes of classical HL are currently recognized by the WHO classification including lymphocyte rich classical HL (LRCHL), nodular sclerosing HL, mixed cellularity HL, and lymphocyte depleted HL. After completion of the diagnostic workup, the extent of involvement with HL is designated using the Ann Arbor staging criteria (see Section 4.0). Patients with Stage I-II disease are considered to have "early stage" HL and are generally treated with short courses (2-4 cycles) of combination chemotherapy followed by involved field radiotherapy for some which affords a cure rate of 90-95%. Historically, classification and treatment of patients with Stages IB, IIB, and bulky Stage II is variable in pediatric and adult HL trials and will not be addressed in the current protocol. *(5)* Patients with Stages III-IV disease are considered to have advanced stage HL and are generally treated with 6-8 cycles of combination chemotherapy (with or without radiation therapy, particularly in pediatric patients) as outlined below.

a. History of Therapy for Advanced Stage Hodgkin Lymphoma

Although HL is one of the most curable of all human neoplasms, approximately 15-30% of patients in the United States with Stage III-IV HL still fail treatment of the disease with current management. *(6)* Since HL typically afflicts patients between the ages of 15-40, many years of productive life are tragically lost to this lymphoma each year. The development of the MOPP (mechlorethamine, Oncovin, procarbazine, prednisone) regimen in the 1960s permitted hematologists/oncologists to cure a significant proportion of patients with advanced stage Hodgkin disease for the first time and represented a major milestone in medical oncology. *(7)* After the introduction of MOPP, a number of MOPP-like chemotherapy regimens based on alkylating agents were developed to reduce acute toxicity. These "MOPP-variant" regimens were equivalent to MOPP in efficacy and were associated with less early treatment-related toxicity; however, the major late morbidities of MOPP, sterility and an increased incidence of acute myeloid leukemia, persisted with the derivative regimens. *(8)* The ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) was developed by Bonadonna and colleagues in Milan in the 1970s containing drugs considered to be non-cross resistant with those in the MOPP regimen. *(9)* Early studies by this group demonstrated the ability of ABVD to successfully treat patients with recurrence after MOPP and the efficacy of ABVD as primary therapy. Randomized

trials subsequently proved that ABVD was more effective and less toxic than MOPP. *(10)* Alternating (MOPP-ABVD) and hybrid (MOPP-ABV) regimens were developed but proved to be no more effective than ABVD alone and were more toxic. *(11,12,13,14)* Based on these studies, ABVD became the standard of care for adult patients in the United States and most other countries in the world. Administration of full doses of ABVD without treatment delays, dose reductions, or growth factors appears to optimize cure rates with this regimen. *(15,16)*

Over the years, alternative, brief duration regimens were developed for the treatment of advanced HL, including Stanford V and BEACOPP. Despite promising preliminary efficacy results with this regimen, a randomized US cooperative group Phase III trial of ABVD versus Stanford V with or without radiation therapy in patients with locally extensive or advanced stage HL (ECOG E2496) showed no difference in remission rates, or failure-free survival or overall survival at 5 years. Similarly, in a randomized trial conducted by the EORTC that randomized advanced stage HL patients to either ABVD or 4 cycles of BEACOPPescalated followed by 4 cycles of BEACOPPstandard, there was no statistically significant difference in disease-free or overall survival between the study arms (DFS with ABVD 86% vs 91%, OS 87 vs 90%). Based on these data, and due to concerns about the acute and late toxicities associated with BEACOPP, ABVD has remained the standard of care treatment for adults with advanced stage HL in the US.

More recently, based on the consistent finding that interim PET positivity after 2-3 cycles of ABVD is associated with disease recurrence and is a stronger predictor of patient outcome than traditional clinical prognostic factors like the IPS, PET-adapted therapy of advanced stage HL has been studied. *(17,18,19,20,21)* A Phase II US Intergroup study (S0816) evaluated PET-adapted escalation of therapy in 336 patients with a positive interim PET (PET2) scan, with PET2- patients completing a full 6 cycles of ABVD while patients who were PET2+ after 2 cycles of ABVD underwent escalation of therapy to BEACOPPescalated. The overall 2-year PFS in the entire study population was 79%. In the 271 patients who were PET2-negative and received ABVDx6, the 2-year PFS was 82% as compared to a 2-year PFS of 64% in the 60 patients who were PET2+ after ABVDx2 and were subsequently escalated to BEACOPPescalated. Notably, the majority of the treatment failures in the study were in paitents with a negative interim PET scan, with 58 of 271 PET2-negative patients having progression events. The RATHL study was a study in 1214 patients with advanced stage HL (also included Stage IIA unfavorable and Stage IIB patients) evaluating PET-adapted therapy escalation to BEACOPP in PET2+ patients with a randomized evaluation of therapy de-escalation with omission of bleomycin (AVD) in PET2-negative patients. Similar to the S0816 study, the 3-year PFS was 67.5% among PET2+ patients escalated to BEACOPP. The omission of bleomycin after 2 cycles of ABVD was demonstrated to be non-inferior to continuation of a full 6 cycles of ABVD with 3-year PFS in the AVD group of 84.4% versus 85.7% in the ABVD group. The 3-year PFS and OS in the overall study cohort were 82.6% and 95.8%.

b. Treatment of Pediatric Patients with Advanced Stage Hodgkin Lymphoma

While contemporary combined modality therapy in children and adolescents and young adults results in 5-10 year survival rates of more than 90% when patients of all stages are evaluated, there remain subgroups of HL patients for whom initial cure rates are suboptimal. Among these high-risk patients, intensification of treatment with current conventional agents is inadequate. While the peak age for Hodgkin Lymphoma is 20-34 years of age, younger adolescents (12-18 years) may also benefit from the study of novel agents and approaches used in young adult and adult Hodgkin’s populations. *(22)*

Risk and response-adapted combined modality therapy has been the cornerstone of the pediatric treatment paradigm with the goal of improving treatment outcomes while minimizing late effects of therapy. *(23)* Differences in treatment between adult and pediatric protocols have largely related to age-specific concerns regarding the late effects of alkylating agents (infertility, second malignancy), anthracycline (cardiac toxicity), and radiation (bone and soft tissue growth, second malignancy, cardiopulmonary sequealae) with an early evolution to protocols limiting the cumulative doses of the above chemotherapies and limiting radiation doses to 15 to 25Gy of involved lymph node regions only.

In North America, the Children's Oncology Group (COG) moved from ABVD with extended field radiation therapy to the risk adapted dose-dense ABVE-PC regimen (doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide) in 1997. *(24)* ABVE-PC modified ABVD by (a) substituting vincristine for the more myelosuppressive vinblastine, (b) replacing dacarbazine with etoposide, (c) adding cyclophosphamide and prednisone to enhance efficacy, and (d) increasing dose density by giving chemotherapy every 3 weeks with use of filgrastim to prevent prolonged marrow nadir. *(25)* The P9425 study for patients with intermediate and high risk HL demonstrated an 84% 5 year EFS and 95% OS for high-risk patients using ABVE-PC and involved field radiotherapy. *(*26*)* On that study, 63% of patients were rapid early responders requiring only 3 cycles (9 weeks) of chemotherapy and IFRT; slow responders received 2 additional cycles of chemotherapy. The more recent AHOD0031 trial for intermediate risk (Stage IIB bulk, IIIA, IVA) pediatric HL used the ABVE-PC backbone and established early response assessment using CT and PET response as a means to tailor therapy and reduce radiation therapy for select groups. *(*27*)* AHOD0031 included 1712 children, and the 4 year EFS was 85% and OS 97.8%. The cyclophosphamide dose was 800 mg/m2/cycle and the cumulative anthracycline dose was 200 mg/m2. Notably, there was no benefit to the addition of IF-RT (21Gy) for those patients deemed rapid early responders after 2 cycles who were in complete response at the end of 4 cycles of chemotherapy. Patients with bulky Stage IIB and Stage IVA disease were noted to have inferior outcomes (EFS 80.8%). *(28)* AHOD0831 addressed patients with Stage IIIB and IVB disease with 4 cycles of ABVE-PC augmenting therapy with non-cross reacting chemotherapy for slow early responders and response-adapted RT. The initial results estimate 4y EFS 80.2% *(29)* and the approach is not recommended as standard of care. On all these studies interim response was assessed after 2 cycles of chemotherapy and used a combination of anatomic and FDG-PET criteria. The currently enrolling AHOD1331 in children and adolescents up to age 21 includes patients with IIB bulk, IIIB, IVA and IVB. The study gives 5 cycles of ABVE-PC with a higher alkylator dose (cyclophosphamide 1200 mg/m2/cycle) than delivered in AHOD0031, and is studying the substitution of brentuximab vedotin (Adcetris) for bleomycin with the goal of enhancing rapid response rates (evaluated by FDG-PET after 2 cycles) and thereby limiting RT exposure. Residual PET RT (21 Gy) is given to individual lesions with slow early response (Deauville 4,5) and to all large mediastianl adenopathy (LMA) regardless of response. This was based on the concern of high failures in patients with mediastinal bulk /LMA on AHOD0031. To date the toxicity of the combination of brentuximab vedotin in combination with AVEPC (BV-AVEPC) has not differed from that of the standard experience of ABVE-PC. The overall anticipated RT use on AHOD1331 will be 60% of this high risk population, due to the inclusion of Stage IIB with bulk. Accrual is anticipated to be complete in the fall of 2019 and results will not be available until late 2022.

There are limited data using ABVD in pediatric patients. In a small legacy CCG trial where Fryer et. al. *(30)* administered 12 cycles ABVD to children with advanced-stage HL (n=64), the pulmonary toxicity rate was high at 9%, predominantly occurring before RT was given. The overall survival of this study was 87% at 3 years, suboptimal by today's standards. In a contemporary report from the British Columbia Cancer Agency, ABVD in children and adolescents was associated with very limited pulmonary toxicity, which is more likely associated to bleomycin and not to dacarbazine. *(*31*)* Patients were assigned to risk groups based on adult criteria, and advanced stage patients received 6 cycles of ABVD chemotherapy with a recommendation for IFRT for CT or PET residual disease at the end of therapy. RT was limited to 18% of patients. For those advanced stage patients <18 years of age, 5 year PFS for was 77% and OS 90%, again underscoring the need for more intensive and novel therapies and/or judicious application of consolidative RT for this group. *(*32*)*

While the recent decade of COG AHOD trials has utilized an ABVE-PC chemotherapy backbone and a risk adapted, response based (per the initial 2 cycles of therapy) radiation approach for advanced stage HL with valuable lessons learned, outcomes for children and adolescents with advanced stage disease remain suboptimal with 25-35% needing salvage therapy which often includes HSCT. Additionaly, the current approach in children/adolescents has contrasted to that in adults and contiuned to utilize radiotherapy to maintain EFS: in patients with Stage IIIA and IVA patients on AHOD0031, an estimated 73.5% of patients received RT, while among statge IIIB and IVB patients on AHOD0831, 76.4% received RT.

A pooled analysis of COG legacy HL trials (AHOD0431, AHOD0031 and AHOD0831) indicates that compared to patients < 12 years fo age, adolescents $\geq$ 12 years of age have inferior outcomes. The 5-year cumulative incidence of relapse is higher in older children using either age 12 years or 15 years as the threshold for evaluation. *(33)* Five-year cumulative incidence of relapse in patients < 12 years compared to ≥ 12 years: 12% vs. 17% (p=0.03); in patients < 15 years compared to ≥ 15 years: 13% vs. 19% (p=0.003). When this analysis is limited to advanced stage patients from AHOD0031 and AHOD0831 (Stage IIB with bulk; IIIA; IIIB; IV A; IVB and MC/NS histology), 5-year event-free survival (EFS) was inferior for those ≥ 15 years of age (< 15 yrs. 85% vs. ≥ 15 yrs. 78%; p=0.0255). Multivariable modeling in the pooled analysis of all 3 legacy studies indicates that adolescent age is an independent risk for EFS (≥ 12 years HR 1.52 [95% CI 1.06, 2.19; ref < 12 years]; ≥ 15 years HR 1.43 [95% CI 1.12, 1.83; ref < 15 years]). Age ≥ 15 years is an independent risk for overall survival (≥ 15 years HR 2.58 [95% CI 1.24, 5.38]). *(34)*

2.3 Brentuximab Vedotin for the Treatment of Advanced Stage Hodgkin Lymphoma

Brentuximab vedotin (BV) is a chimeric CD30-specific IgG1 antibody conjugated to the microtubule-disrupting agent, monomethyl auristatin E (MMAE), by an enzyme-cleavable linker. Upon the binding of BV to CD30 on the Hodgkin Reed-Sternberg cell, the ADC is internalized and lysosomal enzymes cleave the linker allowing for the release of MMAE inside the cell. MMAE then binds to tubulin, resulting in cell cycle arrest and subsequent apoptosis of CD30-expressing cells *(35, 36)*. In an initial Phase I, dose escalation study of 45 patients with relapsed/refractory CD30 positive lymphoma, 93% with HL and 7% with anaplastic large-cell lymphoma (ALCL), 50% of patients showed an objective response (OR). Eighty-eight percent of responses occurred within the first 2.8 months (or 4 cycles) and responses lasted a median of 9.6 months. The maximum tolerated dose of BV was 1.8 mg/kg given intravenously every 3 weeks. The most common adverse events (mostly Grade 1 or 2) were fatigue, pyrexia, gastrointestinal symptoms, neutropenia, and peripheral neuropathy. The reported dose-limiting toxicities were grade 4 thrombocytopenia, grade 3

hyperglycemia and febrile neutropenia. *(37)* In another Phase I trial, BV was given weekly for 3 weeks, followed by a week break to 38 patients with HL and 5 patients with ALCL. Fifty-four percent of the patients with HL had an objective response and dose-limiting toxicities in this study included grade 3 gastrointestinal symptoms and grade 4 hyperglycemia. *(38)*

These promising results prompted a multicenter, open label, pivotal Phase II study of BV for the treatment of rel/ref HL. In this study, 102 patients with were treated with BV at 1.8mg/kg every 3 weeks for a maximum of 16 cycles. Patients had received a median of 3.5 prior regimens, and all patients had received prior autologous hematopoietic stem cell transplant (autoHSCT). Seventy-five percent of patients responded, including 35% who had a complete response (CR). *(39)* Based on these results, in 2011 the FDA granted BV accelerated approval for the treatment of rel/ref HL after failure of at least two prior lines of multi-agent chemotherapy in patients who are not transplant candidates or patients with HL who progressed after autoHSCT. Long term follow-up showed durable remissions, with 41% of patients still alive at 5 years. Additionally, of the patients who achieved a CR, the 5-year overall survival (OS) and progression free survival (PFS) were 64% and 52% respectively. *(40,41)*

BV was also studied as consolidation therapy after autologous HSCT. Although most HL patients are cured with multi-agent chemotherapy, up to 20-25% will relapse after or be refractory to initial therapy. The standard of care for these patients is high-dose chemotherapy followed by autoHSCT. *(42, 43)* Despite a 50% durable remission rate, about 50% will still relapse after autologous HSCT. *(44, 45, 46)* The AETHERA trial examined the use of BV as consolidation therapy to improve PFS post autoHSCT. In this trial, patients with high risk features, including primary refractory disease, relapse within 12 months of initial therapy, or extranodal involvement, were given BV 1.8mg/kg for 16 cycles following autologous HSCT. For those who received BV maintenance, median PFS was 42.9 months compared to 24.1 months for those who received placebo. The estimated 2-year PFS in patients who received BV consolidation was 65% compared to 45% in patients who received placebo. *(47)* As a result, the FDA granted BV additional approval as consolidation therapy after autologous HSCT in patients who are at high risk for relapse.

Based on the promising efficacy and tolerability of BV in patients with rel/ref HL, BV was evaluated in the frontline setting in patients with previously untreated HL. A Phase I trial that included 51 patients with newly diagnosed Stage IIA bulky or Stage IIB-IV HL compared BV added to standard ABVD (A-ABVD) and BV added to AVD without bleomycin (BV-AVD). The CR rate was 95% in patients who received A-ABVD compared to 96% of patients who received BV-AVD. However, in the A-ABVD cohort there was an unacceptably high rate of adverse pulmonary events (44%); Therefore, it is recommended that BV not be given in combination with bleomycin. *(48)* A 5-year follow-up of this study showed a failure-free survival of 92% and OS of 100% *(49)*. Based on these findings, the ECHELON-1 trial, a randomized Phase III trial of frontline BV-AVD compared to non-PET-adapted ABVD was conducted in patients with previously untreated advanced stage HL. The study met its primary endpoint, the 2-year modified PFS (with events defined as death, disease progression, or lack of complete response at the end of therapy followed by administration of a subsequent anti-lymphoma therapy) was 82.1% in the BV-AVD group versus 77.2% in the ABVD group. In the intent-to-treat population, 73% of patients in the BV-AVD arm were in CR at the end of the randomized regimen compared to 70% in the ABVD arm. Using the Deauville score (DS), 86% of patients in the BV-AVD arm had a DS of 1-3 at the end of frontline therapy compared to 82% in the ABVD arm. Notable adverse events included neutropenia in 58% of the patients receiving BV-AVD and in 45% of those receiving ABVD. Febrile neutropenia occurred in 21% of those treated with BV-AVD, prompting the common use of prophylactic granulocyte colony-stimulating factor (GCSF). In those who were then given prophylactic GCSF, the rate of febrile neutropenia decreased to 11%. Peripheral neuropathy occurred in 67% of patients in the BV-AVD group and in 43% of patients in the ABVD group. Grade 2 and 3 peripheral neuropathy occurred in 20% and 11% in the BV-AVD group and in 9% and 2% of the ABVD group respectively. Of those

who developed peripheral neuropathy in the BV-AVD group, 67% had resolution of symptoms and 24% had improvement by at least one grade at the time of last follow-up. At the time of last follow-up, 92% of ongoing peripheral neuropathy was grade 1 or 2. *(50)*

Of note, updated data regarding outcomes based on interim PET (PET2) response to BV-AVD on the ECHELON-1 trial were presented at the 2018 ASCO Annual Meeting by Chen and colleagues. Among 664 patients treated with BV-AVD in the intent to treat population, 588 patients had a negative interim PET scan and 47 were interim PET positive (DS 4-5). The 2-year mPFS in PET2+ patients was 57.5% as compared to 85.2% in patients who were PET2-. These data highlight both the fact that the majority of PET2+ patients continued to have disease control at 2 years as well as the relatively high proportion of treatment failures even in patients who have a negative interim PET scan.

a. BV in pediatrics

Brentuximab vedotin is generally well tolerated in pediatric patients at a dose of up to 1.8 mg/kg every 3 weeks. The pivotal Phase II trial that led to FDA approval of the drug included 5 patients with relapsed cHL aged 12-17 with cHL and there were no common severe toxicities or premature discontinuation of therapy related to an AE. *(51)* The combination of brentuximab vedotin with gemcitabine was investigated in a COG Phase I/II trial for relapsed/refractory cHL up to age 30 years (NCT01780662) with preliminary results confirming that the combination is generally well tolerated, and highly effective. *(52,53)* In addition, brentuximabn vedotin combined with chemotherapy in de novol high risk pediatric is currently being investigated in COG AHOD1331 as described above and as a substitute for vincristine in the St. Jude Children's Research hospital trial using OEPA/COPDac regimen (NCT01920932) which recently met accrual.

In pediatrics, brentuximab vedotin has proven to be well-tolerated to date. AHOD1221, a retrieval trial using brentuximab vedotin with gemcitabine [n=42], *(54)* established 1.8 mg/kg every 3 weeks as the treatment dose in children. Overall complete response rate (CR) was 67% [95% CI 51–80]). The most common Grade 3–4 adverse events were neutropenia [36%]), rash [36%], transaminitis [21%], and pruritus [10%]. There were no treatment-related deaths, no ≥ Grade 3 neuropathy, and 1 case of pulmonary toxicity. In the ongoing AHOD1331 using brentuximab vedotin in combination with the AVEPC in the COG (NCT02166463) targeted toxicities being monitored include neuropathy and myelosuppression, with protocol mandated GCSF use. BV-AVD is also being studied in a Phase I/II study of pediatric patients (ages 5-18) with Stage II-IV Hodgkin lymphoma (NCT02979522), wherein patients are receiving up to 6 cycles of 48mg/m2 of BV combined with standard doses of AVD. As of the time of reporting, (in NCT02979522) 8 patients were enrolled onto the study and 6 patients were evaluable for dose limiting toxicities (DLT). No patient experienced a DLT, and the recommended Phase II dose of BV-AVD was determined to be 48mg/m2. Toxicities were as expected with BV-AVD, including neutropenia, vomiting, and mucositis. *(55)* In addition, AHOD1331 (NCT02166463) recently completed accrual (April 30,2019) of 600 pediatric patients < 21 years of age, with n=300 randomized to the brentuximab (+ AVEPC) arm. The AHOD1331 study has met no stopping rules. Myelosuppression was as expected with the dose dense chemotherapy regimen, and has not differed between the BV and non-BV containing arms to date where granulocyte stimulating factor has been applied in both arms a priori.

2.4 The rationale for PD-1 blockade in HL

HL is histologically defined by a small proportion of neoplastic Hodgkin Reed Sternberg (HRS) cells in a polymorphous inflammatory infiltrate. However, this inflammation does not appear to represent an effective host anti-tumor immune response. *(56)* Nearly universal genetic alterations of chromosome 9p24.1, which includes the PD-L1/PD-L2 loci, have been identified in HL, supporting the concept that the PD-1 pathway plays a key role in the host immune evasion that is central to HL pathogenesis. *(57)* The genetic alterations in 9p24.1 are directly linked with increased expression of the PD-1 ligands, PD-L1 and PD-L2, on HRS cells. *(58,59)* In addition, the JAK2 locus is also contained within the 9p24.1 region, and JAK2 activation upregulates PD-L1 transcription and expression.4 Furthermore, Epstein-Barr virus infection, which is frequently observed in HL, has also been identified as a mechanism of PD-L1 upregulation and expression in HL. *(60)* In addition to the PD-1 ligand expression observed on HRS cells, tumor-associated macrophages (TAMs) in the HL tumor microenvironment (TME) frequently express PD-L1. In fact, as might be expected due to the rarity of HRS in the HL TME, TAMs express the majority of PD-L1 in the TME. The topology of PD-L1 expression in the HL TME suggests that TAMs may play an important role in the ineffective immune response observed in HL, since PD-L1+ TAMs are geographically located in close proximity to PD-L1+ HRS cells as well as PD-1+ T-cells (especially CD4+ cells) in the HL TME. *(61)* Based on the multiple ways in which the PD-1 pathway appears to serve an important role in the pathogenesis of HL, there is a strong biologic rationale for PD-1 blockade in the treatment of HL.

In fact, not only is the PD-1 pathway alteration a key facet of the pathogenesis of HL, more significant PD-1 pathway derangement in an HL tumor confers a negative prognosis in patients treated with standard therapies. In a cohort of 108 newly diagnosed patients with HL treated according to the Stanford V regimen, an increasing degree of PD-L1/PD-L2 genetic alteration assessed by FISH (9p24.1 amplification > copy gain > polysomy vs disomy) was associated with inferior PFS. *(62)* Taken together with the near universal PD-1 pathway alterations observed in HL these data suggest two enticing hypotheses for the potential role of PD-1 blockade in HL – the high levels of PD-1 pathway derangement in HL may predict increased susceptibility to PD-1 blockade and perhaps the use of anti-PD-1 therapy could abrogate the negative prognostic impact of PD-1 pathway derangement seen in patients treated with standard therapies.

a. Anti-PD-1 monotherapy in relapsed or refractory HL

Anti-PD-1 antibody monotherapy has been evaluated in patients with relapsed or refractory HL and produced a high rate of objective responses in early phase studies. A Phase I study of nivolumab in patients with rel/ref hematologic malignancies demonstrated an 87% overall response rate (ORR), 17% complete response (CR) rate, and 100% clinical benefit rate in 23 patients with rel/ref HL. *(63)* The majority of patients enrolled on the study (78%) had failed prior autologous stem cell transplantation (autoSCT) and prior brentuximab vedotin (BV). A subsequent Phase II study (CheckMate 205) of nivolumab for rel/ref HL treated 243 patients who had failed prior autoSCT into 3 cohorts of patients, patients in Cohort A were BV naïve (n = 63), patients in Cohort B had failed BV that was administered after autoSCT (n = 80), and patients in Cohort C had received prior BV before and/or after autoSCT failure (n = 100). The ORR with nivolumab therapy among all treated patients was 69% with a CR rate of 16% as assessed by an independent review committee. The median time to response was 2.1 months, and the median duration of response (DOR) across cohorts was 16.6 months. The median progression-free survival (PFS) according to best response was 22.2 months in patients who achieved CR, 15.1 months in patients with a partial response, and 11.2 months in patients with a best response of stable disease, suggesting that even patients without an objective response benefitted from therapy.*(64,65)*

Pembrolizumab was evaluated in a Phase Ib study (KEYNOTE-013) of patients with rel/ref HL who failed prior BV (71% with prior autoSCT). More than half of patients (55%) had received 5 or more lines of prior therapy. Among 31 patients enrolled, the ORR was 65% and CR rate was 16%. The response duration was at least 24 weeks in 70% of responding patients, and, in the overall cohort, the PFS at 52 weeks after initiation of pembrolizumab was 46%. *(66)* A Phase II study (KEYNOTE-087) of pembrolizumab in patients with rel/ref HL enrolled 210 patients into 3 cohorts: Cohort 1 included patients who failed autoSCT and post-autoSCT BV, Cohort 2 included patients who received prior salvage chemotherapy and BV but were refractory and ineligible for autoSCT, and Cohort 3 included patients who failed autoSCT but did not receive BV after ASCT. The ORR and CR rate across all cohorts by independent review were 69% and 22%, respectively. Similar to the Phase II nivolumab study, the response rates across the cohorts were similar and were similar regardless of number of prior therapy lines or whether or not the patient had received prior BV. The majority of patients (76%) had a duration of response of 6 months or greater, and the 9-month PFS was 63%.

Checkpoint blockade, including anti-PD-1 antibody therapy, is associated with characteristic immune-related adverse events (AE) triggered by reversing the immunosuppressive effects of inhibitory checkpoints. Immune-related AEs (irAE) significant enough to require high-dose corticosteroids and preclude prevent further administration of anti-PD-1 antibodies are uncommon, but treating physicians should be aware of these potentially dangerous toxicities and how they should be managed. *(67, 68)* In the Phase I and II studies of pembrolizumab and nivolumab in patients with rel/ref HL, treatment has been well-tolerated, with very few grade 3 or 4 AEs reported and only 5-7% of patients discontinuing treatment due to treatment-related AEs. The most common irAE were hypo/hyperthyroidism (12-16%), rash (9%), hepatitis (5%), pneumonitis (3-4%), but most were grade 1 or 2 and Grade 3 or higher irAEs were rare. *(69, 70)*

b. Incorporation of PD-1 blockade into frontline therapy for HL

Higher degrees of PD-1 pathway derangement (i.e. 9p24.1 amplification or copy gain) are associated with a higher likelihood of treatment failure with standard initial therapy for HL.5 Therefore, the incorporation of PD-1 blockade into initial therapy of HL is a logical strategy to attempt to overcome the negative prognostic impact of PD-1 pathway alteration. The preliminary findings of a study evaluating the addition of nivolumab to doxorubicin, vinblastine, dacarbazine (AVD) as initial therapy in patients with newly diagnosed advanced stage (stage IIB, III, IV) HL (CheckMate 205, cohort D) were reported at the ASH annual meeting in 2017. Fifty-one patients were enrolled and treated with nivolumab monotherapy for 4 doses every 2 weeks followed by combination nivolumab plus AVD (N-AVD) for 12 doses every 2 weeks. Forty-nine patients completed nivolumab monotherapy and ultimately 44 patients completed the full course of N-AVD. Aside from neutropenia (49%) and febrile neutropenia (10%), grade 3 or higher AEs were uncommon. There were few patients who discontinued treatment due to toxicity (4 patients, 8%) and the profile of IrAEs was similar to what has been observed with single agent PD-1 blockade, with endocrinopathy (all thyroid-related) being common (26%, all grade 1-2) and only 1 patient requiring high-dose corticosteroids (for hepatitis). At the end of nivolumab monotherapy, the ORR and CR rates were similar to what has been observed in patients with advanced rel/ref HL (ORR 69%, CR 18% by independent review). In the intent to treat population, at the end of combination therapy, the ORR was 84% and the CR rate was 67% (ORR 93%, CR 74% in evaluable patients). Of note, there were moderate discrepancies between investigator and independently-assessed responses – the end of treatment CR rate per investigators was 80%. Only 2 patients not in CR at the end of treatment received subsequent therapy. These data may speak to the difficulty of assessing

responses to PD-1 blockade using standard criteria and the potential utility of newer response criteria that account for indeterminate findings in patients receiving immunotherapy. *(71, 72)* The modified PFS in the overall cohort at 9 months was 94%, but follow-up is too short to draw any definitive conclusions about the durability of responses as of yet. *(73)*

c. Nivolumab in pediatrics

To date the only published studies on Nivolumab in children include case reports in refractory settings. However PD-1 blockade has been shown to be safe and efficacious in early phase trials. The FDA recently granted accelerated approval for pembrolizumab for the treatment of adult and pediatric patients who have refractory classical Hodgkin lymphoma, or those whose disease relapsed after ≥3 prior lines of therapy. This approval was based on the non-randomized, open-label, multicenter phase 1/2 KEYNOTE-051 study which demonstrates an overall response rate of 50% in refractory/relapsed pediatric HL by RECIST criteria; the median age among 144 patients enrolled was 13 years (range 1-17), with 67% of patients being 10 to < 18 years of age. *(74)* Nivolumab and pembrolizumab both target epitopes on the PD-1 molecule with high affinity and specificity.

Given the excellent response rates to PD1 blockade described in relapsed and refractory HL in adults, nivolumab is currently under study through COG in combination with ipilumumab for refractory lymphoma (ADVL1412; median age 14 years (range 1-25 years) and in combination with BV for relapsed cHL (Checkmate 744 : AHOD1721; NCT02927769) in patients > 5 years age. Dosing is set at 3mg/kg every 2 weeks. Both studies continue to accrue patients.

While 3 mg/kg is the initial labeling dose of nivolumab for hodgkin lymphoma, flat dosing (240 mg q 2 weeks) is now FDA approved for adults. With the recent emphasis on the earlier inclusion of adolescent patients into clinical trials, the PK of nivolumab in this population based on body weight > 40kgs (the average weight of a 12 year old male) has been investigated. These PK data have also been compared to PK in patients with weights < 40kg. Patients with weight > 40kg demonstrated an expected increased exposure (~33%) when receiving 240mg compared to 3mg/kg iv every 2 weeks The geometric means of Cmin, Cmax and Cavg at steady state are predicted to be 95.7, 185 and 122 ug/mL, respectively, with nivolumab i.v. 240 mg Q2W treatment, compared to the geometric means of Cmin, Cmax and Cavg at steady state 71.7, 139 and 91.3, respectively, with nivolumab i.v. 3 mg/kg Q2W treatment.

Ongoing early phase pediatric studies (ADVL1412; NCT02304458) using nivolumab at 3 mg/kg (with no dose cap) indicate the safety profile in subjects 12 to 18 years of age is similar to that seen with adult subjects. The half life of nivolumab with this schedule is 10.2 (+ 1.7) days. *(75)* Based on these data the pediatric dosing of nivolumab proposed in this trial is 3 mg/kg q 2 weeks upto age 18 years of age. A max dose of 240 mg q 2 weeks will be used for consistency with adult dosing and based on the steady state data above.

2.5 Rationale for Current Study

With the advances made in the treatment of advanced stage HL, from the introduction of ABVD, to PET-adapted treatment, and now the introduction of BV into initial treatment, a majority of patients with advanced stage HL will be cured with initial therapy. However, despite these advances, about 20-25% of patients treated for advanced stage HL will have relapsed or refractory disease. *(76)* Even though the recent RATHL study demonstrated that in patients with a negative interim PET scan, the omission of bleomycin after 2 cycles is non-inferior with regards to survival as compared to a full course of ABVD, a significant proportion of patients (16-18%) have a positive interim PET scan and require escalation to

BEACOPP, is a highly effective but toxic regimen associated with secondary malignancies and infertility – a large burden to bear in a disease that disproportionately impacts young patients. *(77)* The addition of BV to initial chemotherapy (AVD) demonstrated improved 2-year modified progression-free survival (mPFS, with events defined as death, disease progression, or incomplete response with administration of subsequent anti-lymphoma therapy) compared to ABVD. However, the BV-AVD regimen was associated with higher rates of neutropenia, sepsis, and peripheral neuropathy compared to ABVD, and there still was an unacceptable ~20% failure rate. *(78)* Clearly, there remains room to improve outcomes in patients with newly diagnosed advanced stage cHL.

In adolescents and older children in North America the Children's Oncology Group (COG) has continued to use radiation therapy (RT) in 60-70% of patients in combination with ABVE-PC (regimen comprised of: doxorubicin, bleomycin, vincristine, etoposide, prenisone, and cyclophosphamide) as the chemotherapy backbone. The 5-year event-free survival (EFS) on AHOD0831, the landmark COG trial in advanced stage HL is 79% overall with Stage IV disease having EFS 77%. *(79)* Hence, pediatric and adolescent patients with advanced stage disease could benefit from novel therapies and efforts to decrease radiation use while maintaining or potentially improving efficacy.

The PD-1 pathway plays a critical role in the pathogenesis of cHL, as demonstrated by nearly universal chromosomal alterations in 9p24.1 and PD-L1 expression in Hodgkin Reed-Sternberg cells. *(80)* cHL is exquisitely sensitive to PD-1 blockade, as demonstrated in Phase I and II studies of nivolumab and pembrolizumab in patients with heavily treated relapsed/refractory cHL. *(81;82)* Interim results of a Phase II trial evaluating the addition of nivolumab to initial chemotherapy (N-AVD) demonstrated promising safety and efficacy. *(83)* The incorporation of PD-1 blockade into front-line therapy represents a clear opportunity to attempt to improve the outcomes and tolerability of initial therapy for patients with newly diagnosed advanced stage cHL.

The primary endpoint of this trial is to evaluate the PFS in patients with advanced stage HL who receive nivolumab added to AVD (N-AVD) as compared to BV-AVD. If the primary endpoint of this trial is met, it would establish N-AVD as a new standard of care for the initial treatment of advanced stage HL in North America, improving outcomes and establishing a new treatment paradigm for a disease where progress has been more or less stagnant with only marginal improvement (i.e. BV-AVD) since ABVD was developed over 40 years ago. In addition, the study could have a considerable potential impact on the treatment of newly diagnosed cHL through the correlative studies that will be performed. We will perform correlative studies that could greatly inform treatment selection for this population by defining and prospectively validating the genetic and cellular predictors of response to initial therapy of cHL, thereby identifying subgroups of patients who are most likely to benefit from treatment with either the experimental (N-AVD) or control arm (BV-AVD). Lastly, the integrated QoL studies will provide the opportunity to assess whether N-AVD is associated with more favorable long term tolerability and QoL than BV-AVD, which, especially if PFS outcomes are similar, may inform practice and suggest a role for considering N-AVD as a new standard of care or the preferred approach in certain subgroups based on QoL outcomes.

2.6 Rationale for Consolidative Targeted Radiation Therapy

As it is an accepted standard of care, particulary in the pediatric population, a modification of Residual PET Radiation Therapy (Residual PET RT) will be used to consolidate systemic treatment for eligible patients in either arm who do not achieve a metabolic complete response. In adults with cHL, RT does not significantly improve outcome among patients with advanced stage HL who achieve a complete response to adequate systemic therapy. For example, an EORTC randomized trial found that adjuvant RT did not improve outcome among patients with advanced stage HL who had achieved a complete anatomic response to 6-8 cycles of MOPP-ABV *(84)*, Approximately 35% of the patients in that trial were assigned RT, however, primarily due to failure to achieve a CR. In the PET-era, the

GITIL/FIL HD 0607 trial found that consolidative RT to sites of initial bulk ≥ 5cm did not significantly improve outcome for patients who had a negative PET scan after 2 cycles and were in metabolic CR after six cycles of ABVD (3-year PFS rate of 97% for RT vs 93% for no further therapy, P = .29). *(85)*

However, among patients not achieving a CR, RT can effectively consolidate primary treatment and significantly reduce the risk of relapse, potentially avoiding the need for salvage chemotherapy and autologous stem cell transplant. The GHSG HD12 found that following 8 cycles of BEACOPP-based chemotherapy, patients with advanced stage HL and a residual mass > 1.5 cm who were randomized to consolidative RT had significantly better freedom from treatment failure compared to those treated with chemotherapy alone *(86)*. This finding is consistent with results from the UKLG LY09 study demonstrating a significant improvement in both progression-free and overall survival associated with consolidative RT (not randomly assigned) in advanced stage HL patients. *(87)*

The optimal time to assess PET response in order to guide RT use is uncertain. Although interim PET has been used to guide consolidative RT use in some trials, the anticipated difference in early PET response between BV-AVD and N-AVD could cause a substantial imbalance in RT exposure between treatment arms. Hence, interim PET will not be used to determine RT use in this trial.

Consequently, response at the end of six cycles of systemic therapy will be used to guide the use of RT in this trial. Specifically, localized Residual PET Radiation Therapy (Residual PET RT) will be used for patients with limited residual PET-avid sites who have achieved a partial response (as per the 2014 Lugano Classification) at the completion of 6 cycles of systemic therapy on either arm. This indication for RT to reduce the rate of relapse in this high-risk population is consistent with available evidence and with recent German Hodgkin Study Group trials. *(88)* This approach is anticipated to reduce the rate of RT in childhood HL patients from 60% to 15% in advanced stage HL.

In advanced-stage or high-risk patients, involved field radiotherapy (IFRT) has traditionally encompassed a large volume of normal tissue due to anatomically widespread sites of multiple disease and extra-lymphatic spread.

One of the aims of this study is to reduce the volume of radiotherapy in order to reduce potential acute and late toxicities, while maintaining disease control.

This will be done in two ways:

1) omitting radiotherapy (RT) among patients who have a complete response to systemic therapy (defined as Deavuville 1-3 after six cycles of systemic therapy), and

2) limiting the volume of RT among patients who receive this treatment by employing Residual PET Radiation Therapy (Residual PET RT).

2.7 Rationale for RT Dose for PET-positive (Deauville 4-5) lesions at EOT

The optimal dose of radiation in this context of course has not been determined in randomized trials. There is variation in practice among expert oncologists with respect to prescribed RT dose for patients with a positive PET scan following chemotherapy.

In the United States and Canada, the common practice is to prescribe >30Gy in this scenario. For example, median dose prescribed to patients with post-chemotherapy Deauville score 4-5 was 37.8Gy in the MD Anderson series, *(89)* and 34.8Gy in the Dana Farber series. *(90)* Local control and progression-free survival is not consistently reported

but is in the range of 65%-85% (i.e. acceptable, but not sufficient to support a lower radiation dose).

The European practice for post-chemotherapy RT in advanced stage HL is based on GHSG protocols, in which 30Gy is the prescribed dose *(91)*. Importantly, in these protocols, Deauville score = 3 is considered a "positive" scan, (and likely accounts for a substantial fraction if not the majority of positive scans on these trials). In S1826, however, RT will only be provided to patients with DS4-5 scans, who are at higher risk of relapse than those with DS3 scans.

Finally, given the substantial competing risk of HL relapse in patients who have not achieved a metabolic CR to six cycles of systemic therapy, and the small volume of malignant nodal tissue that will be boosted, it seems improbable that the additional 6Gy will produce any meaningful increase in the lifetime risk of late toxicity among patients treated on this trial.

So, in summary, the use of a 6Gy boost to the PET-avid abnormality

a. consistent with current North American practice

b. appropriate for the DS4-5 patients on the trial who are at higher risk of relapse than DS3-5 patients who get RT on GHSG trials, and

c. unlikely to produce additional long-term toxicity in the in the context of high-risk HL with poor response to systemic therapy, where control of HL is likely the issue that will determine outcome.

2.8 Rationale for Correlative Studies

The planned future translational objectives of this clinical trial are to identify biomarkers that allow for accurate risk stratification and personalized treatment selection in patients with advanced stage cHL. Specifically, the goal of planned future translational medicine objectives would be to identify tumor-derived molecular markers at baseline and dynamically during treatment that are prognostic of treatment outcome after BV-AVD or N-AVD, predictive of response to nivolumab-based initial therapy (N-AVD), and have greater sensitivity and specificity than PET-CT scans, which are difficult to interpret in the setting of immunotherapy-based treatment. Sections 2.8a and 2.8b (below) describe planned future translational medicine objectives.

Traditional clinical factors like age and stage, among others, have been used for many years as part of the International Prognostic Score (IPS) to risk stratify patients with newly diagnosed advanced stage HL. More recently, three of the IPS factors were used to develop a simpler, IPS-3 score for newly diagnosed advanced stage cHL which was still able to identify high, intermediate, and low risk groups. *(92)* However, the applicability of these traditional clinical prognostic scores across treatment regimens and data cohorts is variable. For example, in the SWOG S0816 study (PET-adapted ABVD with escalation to BEACOPP in interim PET+ patients), patients with a high-risk score (4-7) according to the IPS did not have a statistically significant higher risk of disease progression. Similarly, although gene expression profiles (GEP) have been shown in retrospective cohorts of adult patients with newly diagnosed advanced stage cHL to be associated with treatment outcomes, the applicability of these GEP-based predictor tools to prospectively treated patients has been limited. *(93)* Therefore, better biomarkers in patients with newly diagnosed advanced stage cHL are urgently needed.

a. Tissue-Derived Prognostic and Predictive Biomarkers in cHL – Planned future integrated translational medicine objective

More specifically, in the setting of this clinical trial, in which we will be comparing the addition of novel, targeted agents to standard chemotherapy, there may be a forthcoming unique and important opportunity to define the molecular determinants of response and outcome to these individual regimens. Nivolumab counteracts the PD-1 pathway derangements that are essentially pathognomonic in cHL. In relapsed/refractory cHL, the degree of PD-1 pathway derangement present in a cHL tumor (based on immunohistochemistry and/or FISH) is associated with response to single-agent nivolumab. *(94)* A higher degree of 9p24.1 molecular alteration was associated with improved response and PFS to nivolumab. Notably, as compared to patients with 9p24.1 polysomy and copy gain, no patients with 9p24.1 amplification had primary PD after nivolumab. Similar to 9p24.1 alterations, a higher degree of PD-L1 expression by immunohistochemistry was associated with improved response and PFS in rel/ref HL patients treated with nivolumab. Patients who experienced primary PD with nivolumab treatment all had the lowest degree of PD-L1 expression while nearly all patients who achieved CR had higher degrees of PD-L1 expression (Figure 3). These data suggest that a higher degree of PD-1 pathway derangement in a particular HL patient's tumor may be predictive of response and DOR with anti-PD-1 antibody therapy.

In addition to PD-L1/PD-L2 genetic alteration and PD-L1 expression on HRS and in the TME, another unique biologic feature of HL is altered antigen presentation machinery on HRS cells associated with molecular alterations in B2M and CIITA. There is no expression of MHC-I on HRS cells in about half of HL tumors and MHC-II expression on HRS cells is absent in a sizable minority (30%), while the majority of HL tumors have either absence or significant decrease of MHC-I and MHC-II expression. While no association between clinical features such as bulky disease, stage, or age has been found with expression of the antigen presentation proteins at diagnosis, important prognostic implications associated with lack of expression have emerged. The absence of or decrease of MHC-I (and beta-2 microglobulin) expression on HRS cells is a negative prognostic factor in HL patients treated with standard initial therapy, while MHC-Class II expression was not associated with outcome with chemotherapy. Importantly, the negative prognostic impact of B2M/MHC-I expression with standard chemotherapy was independent of PD-L1 derangement (i.e. 9p24.1 alterations) and derangement of 9p24.1 was not associated with expression of either Class I or Class II MHC. In fact, there was additive prognostic value in the evaluation of B2M/MHC-I/MHC-II expression, since patients with decreased/absent B2M/MHC-I expression AND 9p24.1 amplification had markedly inferior outcomes compared to patients with decreased/absent B2M/MHC-I expression without 9p24.1 amplification – though these patients still had inferior PFS compared to patients with intact B2M/MHC-I. With MHC-I and B2M absent or decreased on HRS cells in most cases of HL, it appears that the mechanism of action of anti-PD-1 antibodies in HL does not rely on CD8+ cytotoxic T-cell based responses. As expected, response to nivolumab and post-nivolumab PFS in patients with rel/ref HL are not associated with the presence of MHC-I or B2M expression on HRS cells. Rather, response to nivolumab and PFS after nivolumab (in patients more distant from prior autoSCT) are associated with at least some degree of expression (positive or decreased vs negative) of MHC-II on HRS cells. Given the important prognostic value of antigen presentation machinery proteins both as prognostic markers of outcome with standard chemotherapy in previously untreated patients it will be important to assess the impact of these markers in the setting of BV-AVD. Likewise, it will be critical to understand the impact of these molecular derangements in patients treated with nivolumab added to standard chemotherapy, and whether these tumor-specific features can be utilized to identify patients who are most likely to benefit from the N-AVD regimen.

NOTE: Planned integrated biomarker testing of specimens banked for planned future research will not occur until an amendment to this protocol (or separate

correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

b. Cell Free Circulating Tumor DNA in cHL – Planned future integrated translational medicine objective

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 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 (e.g. 2/3 of the total PFS events in the SWOG S0618 study were in PET-negative patients). 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 plan to submit a future revision proposing evaluation of 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.

NOTE: Planned integrated biomarker testing of specimens banked for planned future research will not occur until an amendment to this protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

c. Quality of Life and PRO-CTCAE Correlatives

Patients with advanced stage HL are at risk for poor quality of life (HRQL) both as a result of their underlying disease and its treatment. While novel therapies, including the antibody-drug conjugate Brentuximab vedotin (BV) and anti-PD-1 antibodies, such as Nivolumab (Nivo) offer the promise of improved disease-free and overall survival, these agents, are associated with their own symptom burden, such as peripheral neuropathy (BV), rashes, colitis, pneumonitis, and endocrinopathies (Nivo). An integrated aim of the trial will be evaluating the impact of novel therapy through patient-reported outcomes (PROs) of HRQL in advanced stage HL overall and by treatment arms. Adverse symptoms and poor HRQL can limit full delivery of novel agents, which in turn, may alter disease outcomes.

In this study we rely on validated measures (PROMIS Global, PROMIS fatigue, PRO-CTCAE, and FACT/GOG-Ntx) to be completed by patients in a 15-minute period at key clinical time points during the trial. All of these instruments are available for both youth and adult self-report in English, French, and Spanish, allowing for broad participation across the age span of the trial population. Please see also Section 18.2.

2.9 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Adult Patients (age 18 or older)

ADULT (Age 18 or Older): DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	5	10	5	9	29
Asian	3	9	0	0	12
Native Hawaiian or Other Pacific Islander	0	5	0	0	5
Black or African American	43	12	0	0	55
White	177	262	16	17	472
More Than One Race	2	2	2	0	6
Total	230	300	23	26	579

ADULT (Age 18 or Older): INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	1	2
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	2	0	0	7
White	20	30	2	2	54
More Than One Race	0	0	0	0	0
Total	25	34	2	3	64

Pediatric Patients (age 12-17)

PEDIATRIC (Age 12-17): DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	7	0	0	8
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	20	18	3	2	43
White	104	102	24	31	261
More Than One Race	3	0	1	0	4
Total	128	128	28	33	317

PEDIATRIC (Age 12-17): INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	16	10	0	0	26
More Than One Race	0	0	0	0	0
Total	16	11	0	0	27

3.0 DRUG INFORMATION

Investigator Brochures
For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, SGN-35 (Brentuximab Vedotin), Doxorubicin hydrochloride, Dacarbazine and Vinblastine sulfate are commercially available; therefore, Investigator Brochures are not applicable to this/these drug/s. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, BMS-936558 (Nivolumab, MDX-1106) is investigational and is being provided under an IND held by the National Cancer Institute. The current version of the Investigator Brochure for the agent will be accessible to site investigators and research staff through the PMB Online Agent Ordering Processing (OAOP) application (http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm). Access to OAOP requires the establishment of a CTEP Identity and Access Managemetn (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via e-mail (IBCoordinator@mail.nih.gov).

IND Exemption
SGN-35 (Brentuximab Vedotin) (in the U.S. for the pediatric population) is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intend to seek a new indication for use or to support any other significant change in the labeling or product advertising for SGN-35 (Brentuximab Vedotin). This investigation will use an approved route of administration and dosage of SGN-35 (Brentuximab Vedotin) and has no factors that increase the risk of the product. This investigation will be in compliance with 21CFR parts 56, 50, and 312.7 and neither the investigator nor the sponsor will promote or represent that SGN-35 (Brentuximab Vedotin) is safe or effective for the context that is under investigation in this study. This investigation will not commercially distribute or test market the study agent and will not unnecessarily prolong an investigation.

3.1 Nivolumab (BMS-936558, MDX1106, Opdivo®) (NSC # 748726) (IND-)

a. PHARMACOLOGY

Mechanism of Action: Nivolumab is human monoclonal antibody which targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. 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.

b. PHARMACOKINETICS

1. Distribution: Nivolumab has linear pharmacokinetics after single and multiple dosing within the range 0.1 mg/kg to 10 mg/kg. The volume distribution (Vd) is 8L.

2. Elimination: Clearance is independent of dose in the range 0.1 mg/kg to 10 mg/kg. The total body clearance is 9.5 mL/hr, and the elimination half-life of is approximately 26.7 days. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for Nivolumab.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, June 10, 2023[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders – Other (lymphatic dysfunction)	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-related hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		(sarcoid granuloma, sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-related nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3] Nivolumab being a member of class of agents involved in the inhibition of “immune checkpoints”, may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency),

sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4] Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5] Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6] Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7] Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation:

Pregnancy: Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of reproductive potential should use highly-effective contraception during therapy and for at least 23 weeks after treatment has been discontinued. Men receiving nivolumab and who are sexually active with women of child bearing potential should adhere to contraception for a period of 31 weeks after the last dose of nivolumab.

Lactation: It is not known if nivolumab is excreted into breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends women to discontinue breastfeeding during treatment with nivolumab.

3. Drug Interactions: Nivolumab is not expected to have any effect on cytochrome P450 or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions. No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Nivolumab injection is to be administered as a 30 minute IV infusion through a 0.2 micron to 1.2 micron pore size, low-protein binding membrane in-line filter. DO NOT administer as IV push or bolus injection. Do not administer other medications through the same IV line. Flush IV line at the end of the infusion.

e. HOW SUPPLIED

1. Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

2. Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Nivolumab will be supplied as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

f. STORAGE, PREPARATION & STABILITY

1. Vials of nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing and shaking. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

2. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP to drug concentrations no less than 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. Note: Mix gently. Do not shake.

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

4. Stability: Shelf-life stabilitiy studies of the intact vials are ongoing.

The administration of undiluted and diluted solutions of nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Starter supplies will not be provided. Order initial supplies once a patient is randomized to the nivolumab arm. If expedited shipment is required,

sites should provide an express courier account through the Online Agent Order Processing (OAOP) application.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

2. Drug Handling and Accountability (NCI logs or other)

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov). Store and maintain separate NCI Investigational Agent Accountability Records for each ordering investigator on this protocol.

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

3. Drug return and/or disposition instruction

   a. All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (*http://ctep.cancer.gov*).

   b. Drug expiration: (If packaging does not have expiration date, check with drug ordering designee and/or PI at site to confirm receipt of ongoing stability testing letter from NCI when internal drug audits are being performed on a quarterly basis. If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first).

4. Useful Links and Contacts

   - CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
   - NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
   - PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
   - PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
   - CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
   - CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
   - IB Coordinator: IBCoordinator@mail.nih.gov
   - PMB email: PMBAfterHours@mail.nih.gov
   - PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

3.2 Brentuximab vedotin (SGN-35, ADCETRIS®) – COMMERCIALLY AVAILABLE FOR U.S. SITES – SUPPLIED BY SEATTLE GENETICS FOR SITES IN CANADA

a. PHARMACOLOGY

Mechanism of Action: Mechanism of Action: SGN-35 (Brentuximab Vedotin) is a CD-30 directed antibody-drug conjugate (ADC) consisting of 3 components: (1) the chimeric IgG1 antibody cA10, specific for human CD30, (2) the microtubule disrupting agent monomethyl auristatin E (MMAE), and (3) a protease-cleavable linker that covalently attaches MMAE to cA10. Its cytotoxic activity occurs when ACD binds to the CD-30 expressing cell, forming an ADC-CD30 complex compound and releasing MMAEs via proteolytic cleavage. Subsequently, MMAE binds to tubulin to disrupt the microtubule network within the cells, resulting in cell cycle arrest and apoptosis.

b. PHARMACOKINETICS

1. Absorption: Maximum concentrations of antibody drug conjugate (ADC) were typically observed close to the end of infusion.

2. Distribution: The mean steady state volume of distribution was approximately 6–10 L for ADC. In vitro, the binding of MMAE to human plasma proteins ranged from 68–82%.

3. Metabolism: MMAE: Minimal, primarily hepatic via oxidation by CYP3A4/5. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. In vitro, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.

4. Elimination: The elimination half-life of ADC is 4 to 6 days. The microtubule disrupting agent cleaved from brentuximab vedotin (MMAE), 3 to 4 days.

c. ADVERSE EFFECTS

1. Possible Side Effects of Brentuximab vedotin:

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 798 patients.* Below is the CAEPR for SGN-35 (brentuximab vedotin).

Version 2.5, February 13, 2019[1]

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Febrile neutropenia
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Constipation	
Diarrhea		
		Enterocolitis
		Gastrointestinal hemorrhage[3]
		Gastrointestinal obstruction[4]
		Gastrointestinal perforation[5]
		Gastrointestinal ulcer[6]
		Ileus
Nausea		
		Pancreatitis
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
	Pain	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (hepatotoxicity)[7]	
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Lung infection	
	Upper respiratory infection	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		
	Alanine aminotransferase increased	

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Aspartate aminotransferase increased	
Neutrophil count decreased		
	Platelet count decreased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperglycemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Muscle cramp	
	Myalgia	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)
	Paresthesia	
	Peripheral motor neuropathy	
Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS		
	Anxiety	
	Insomnia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Oropharyngeal pain	
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity)[8]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Colitis may also include the term neutropenic colitis.

[3] Fatal and/or serious gastrointestinal hemorrhages have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4] Fatal and/or serious gastrointestinal obstructions have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5] Fatal and/or serious gastrointestinal perforations have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. Lymphoma with preexisting GI involvement may increase the risk of perforation.

[6] Fatal and/or serious gastrointestinal ulcers have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

[7] Hepatotoxicity may manifest as increased ALT/AST, bilirubin, alkaline phosphatase, and/or GGT.

[8] Pulmonary toxicity, which may manifest as pneumonitis, interstitial lung disease, or adult respiratory distress syndrome (ARDS), has been observed in patients treated in brentuximab vedotin monotherapy trials as well as in combination with bleomycin. Concomitant use of bleomycin with brentuximab vedotin is contraindicated.

Adverse events reported on SGN-35 (brentuximab vedotin) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that SGN-35 (brentuximab vedotin) caused the adverse event:

Blood and lymphatic system disorders - Blood and lymphatic system disorders - Other (lymphadenopathy)
Cardiac disorders - Myocardial infarction; Pericardial effusion; Sinus tachycardia
Gastrointestinal disorders - Dyspepsia; Esophagitis
General disorders and administration site conditions - Non-cardiac chest pain
Infections and infestations - Meningitis; Pharyngitis; Sepsis; Shingles; Sinusitis; Skin infection; Soft tissue infection; Thrush; Urinary tract infection
Investigations - Blood lactate dehydrogenase increased; Carbon monoxide diffusing capacity decreased; Creatinine increased; Lipase increased; Lymphocyte count decreased
Metabolism and nutrition disorders - Dehydration; Hypercalcemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
Musculoskeletal and connective tissue disorders - Bone pain; Generalized muscle weakness; Myositis; Neck pain
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Myelodysplastic syndrome
Nervous system disorders - Dysesthesia; Encephalopathy; Nervous system disorders - Other (demyelinating polyneuropathy); Seizure; Syncope
PSYCHIATRIC DISORDERS - Depression
Renal and urinary disorders - Acute kidney injury; Renal and urinary disorders - Other (pyelonephritis)
Reproductive system and breast disorders - Irregular menstruation; Reproductive system and breast disorders - Other (groin pain)
Respiratory, thoracic and mediastinal disorders - Adult respiratory distress syndrome[8]; Pleural effusion[8]; Pneumothorax[8]; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (bronchitis)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin
Vascular disorders - Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: SGN-35 (brentuximab vedotin) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation:
Pregnancy: Based on animal studies, brentuximab vedotin causes miscarriages, birth defects, and affects the testes. Advise men and women of childbearing potential to use effective contraception during the study and 6 months after last dose of brentuximab vedotin.

Lactation: It is not known whether brentuximab vedotin excretes in breast milk. Because of the potential risk to harm a nursing baby, breastfeeding is not allowed while receiving brentuximab vedotin.

3. Drug Interactions:
In vitro data indicate that brentuximab vedotin is oxidized primarily via CYP3A4/5. Co-administration of brentuximab vedotin with a strong CYP3A4 inhibitor such as ketoconazole resulted in moderately increased monomethyl auristatin E (MMAE) exposure by approximately 34%. Therefore, patients who are receiving strong or moderate CYP3A4 inhibitors concomitantly with brentuximab vedotin must be closely monitored for adverse reactions. Co-administration of brentuximab vedotin with a strong CYP3A4 inducer such as rifampin has the potential to affect the exposure to MMAE, moderately reducing MMAE exposure by approximately 46%.

In vitro studies show that MMAE is not a substrate of BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3 or OCT2 transporters. However, in vitro data indicate that MMAE is a substrate of the efflux transporter P-glycoprotein (P-gp). Co-administration of brentuximab vedotin with P-gp inhibitors may increase exposure to MMAE. Patients should be closely monitored for adverse reactions when concomitantly administered P-gp inhibitor with brentuximab vedotin.

Brentuximab vedotin (MMAE) inhibits CYP3A4/5 with an IC50 of 10 μM, and its level peaks to about 7 nM after receiving a dose of 1.8 mg/kg. Co-administration of brentuximab vedotin with midazolam, a CYP3A4 substrate did not affect the exposure of midazolam. SGN-35 is not expected to alter the exposure to drugs that are metabolized by CYP3A4.

Refer to package insert or manufacturer website for the most complete and up to date information. Due to potential drug interactions, a complete patient medication list, including brentuximab vedotin, should be screened prior to, initiation of, and during treatment with brentuximab vedotin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Brentuximab vedotin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.3 Doxorubicin (Adriamycin ®) (NSC-123127)

a. PHARMACOLOGY

Mechanism of Action: Doxorubicin is an anthracycline, topoisomerase II inhibitor. It is isolated from cultures of Streptomyces peucetius var. caesius. The cytotoxic effect of doxorubicin is related to nucleotide base intercalation and cell membrane lipid binding activities. It blocks nucleotide replication and the action of DNA and RNA polymerases. The interaction between doxorubicin and topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of its cytocidal activity.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Steady-state volume of distribution: 809-1214 L/m2; protein binding: 74-76%; doxorubicin does not cross the blood brain barrier.

3. Metabolism: Primarily hepatic

4. Elimination: Half-life for distribution is approximately 5 minutes. The terminal half-life is 20-48 hours.

c. ADVERSE EFFECTS

1. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

   The listed black box warning include: cardiomyopathy, secondary malignancies, extravasation and tissue necrosis, and severe myelosuppression. The most common reported adverse events of doxorubicin are nausea, vomiting, and alopecia.

2. Pregnancy and Lactation: Pregnancy Category D. Doxorubicin HCl can cause fetal harm when administered to a pregnant woman. Doxorubicin HCl was teratogenic and embryotoxic in rats and rabbits at doses approximately 0.07 times (based on body surface area) the recommended human dose of 60 mg/m2. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

   Doxorubicin has been detected in the milk of at least one lactating patient. Nursing is not recommended while receiving doxorubicin therapy because of the potential for adverse events in a nursing child.

3. Drug Interactions: Refer to package insert or manufacturer website for the most complete and up to date information.

   Due to potential drug interactions, a complete patient medication list, including doxorubicin, should be screened prior to initiation of doxorubicin. Of note, doxorubicin is a substrate for CYP2D6, CYP3A4, and P-glycoprotein.

d. DOSING & ADMINISTRATION

Dosing – See Section 7.0 Treatment Plan

Refer to FDA-approved package insert for drug administration

e. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Doxorubicin is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for additional information.

3.4 Dacarbazine (NSC- 45388)

a. PHARMACOLOGY

Mechanism of Action: Dacarbazine is an alkylating agent which is converted to the active alkylating metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide] via the cytochrome P450 system. MTIC alkylates DNA leading to DNA double strand breaks and apoptosis.

b. PHARMACOKINETICS

1. Distribution: Exceeds total body water; suggesting binding to some tissue (probably liver)

2. Metabolism: Extensively hepatic to the active metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide]

3. Elimination: Half-life elimination is biphasic. Initial: 19 minutes, 55 minutes (renal and hepatic dysfunction); Terminal: 5 hours, 7.2 hours (renal and hepatic dysfunction). Excreted in the urine (~40%, as unchanged drug)

c. ADVERSE EFFECTS

1. Possible Side Effects of Dacarbazine:
Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% of subjects treated with dacarbazine include: hypotension, headache, nausea, vomiting, anorexia, muscle weakness, flu-like symptoms, alopecia.

Adverse effects reported in 4% to 20% of subjects include: cerebral hemorrhage, seizure, venous thromboembolism, infection, bone marrow depression, anemia, increased liver enzymes, anaphylaxis, infusion-site pain.

Serious adverse effects reported in ≤ 3% of subjects include: skin photosensitivity.

2. Pregnancy and Lactation: Studies have demonstrated dacarbazine to be carcinogenic and/or teratogenic when used in animals. Women of reproductive potential should avoid becoming pregnant during treatment.

It is not known if dacarbazine is present in breast milk. Due to the potential for serious adverse reactions in the breasted infant, a decision should be made to discontinue dacarbazine or to discontinue breastfeeding.

3. Drug Interactions: Dacarbazine is a major substrate of CYP1A2 and a minor substrate of CYP2E1.

Due to potential drug interactions, a complete patient medication list, including dacarbazine, should be screened prior to initiation of and during treatment with dacarbazine. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

Dosing – See Section 7.0 Treatment Plan

Refer to FDA-approved package insert for drug administration

e. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Dacarbazine is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for additional information.

3.5 Vinblastine sulfate (NSC- 49842)

a. PHARMACOLOGY

Mechanism of Action: Vinblastine sulfate is an alkaloidal antineoplastic agent that inhibits microtubule formation in the mitotic spindle resulting in an arrest of dividing cells at the metaphase stage. It may also interfere in cell-energy production in mitosis and nucleic acid synthesis.

b. PHARMACOKINETICS

1. Distribution: Volume of distribution: 70% of body weight. Protein binding: 98 - 99.7%. Vinblastine blinds extensively to tissues. It does not penetrate CNS or other fatty tissues.

2. Metabolism: Vinblastine sulfate is metabolized by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily to an active metabolite, deacetylvinblastine.

3. Elimination: After rapid IV administration, a triphasic serum decay pattern followed. The respective half-lives were 3-7 minutes, 1.6 hours, and 24.8 hours. About 13.6 to 23.3% of the administered dose was excreted in urine and 10% in the feces, the remaining activity was not accounted for.

c. ADVERSE EFFECTS

1. Possible Side Effects of vinblastine

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Commonly reported adverse events include: myelosuppression, diarrhea or constipation, and peripheral neuropathy (e.g. jaw pain).

CAUTION: Vinblastine sulfate injection is for intravenous use only. The intrathecal administration of vinblastine, a vesicant, can results in death. Syringes containing vinblastine sulfate should be labeled, “FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUSLY USE ONLY.”

2. Pregnancy and Lactation: *Pregnancy category D* Information on the use of vinblastine sulfate during human pregnancy is very limited. Animal studies suggest that teratogenic effects may occur. Women of childbearing potential should be advised to avoid becoming pregnant.

Aspermia has been reported in man. Animal studies show metaphase arrest and degenerative changes in germ cells.

It is not known whether vinblastine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from vinblastine sulfate in nursing infants, a decision should be made whether

3. Drug Interactions:

Refer to the current FDA-approved package insert.

Concurrent oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vinblastine sulfate has been reported to have reduced blood levels of the anticonvulsant and to have increase seizure activity. The contribution of vinblastine sulfate to this interaction is not certain. Dosing adjustment of phenytoin should be based on serial blood level monitoring.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily, or in patients with hepatic dysfunction. An earlier onset and/or an increased severity of side effects of vinblastine can occur.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan.

2. Refer to FDA-approved package insert for drug administration.

e. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Vinblastine sulfate is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for additional information.

3.6 Filgrastim (r-metHuG-CSF) (Neupogen®) (NSC 614629)

a. PHARMACOLOGY

Mechanism of Action: Filgrastim stimulates the production, maturation, and activation of neutrophils; filgrastim activates neutrophils to increase both their migration and cytotoxicity.

b. PHARMACOKINETICS

1. Absorption: First-order pharmacokinetic modeling with maximum serum concentration reached within 2 to 8 hours after subcutaneous injection.

2. Distribution: Average Vd 150 mL/kg.

3. Metabolism: Unknown.

4. Elimination: Renal and neutrophil receptor-mediated, elimination half-life is approximately 3.5 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of Filgrastim: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

   Most frequent adverse reactions reported are skeletal pain (> 20%).

2. Pregnancy and Lactation: Category C, filgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies have demonstrated adverse effects and fetal loss. Filgrastim has been shown to cross the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Excretion in breast milk unknown/use caution.

3. Drug Interactions: Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

   Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

   Filgrastim should not be administered on the same day with anticancer chemotherapeutic agent(s) with leukocyte suppressive properties.

   Filgrastim is contraindicated in patients with hypersensitivity to *E.coli*-derived proteins, filgrastim, or any component of the product.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan.

2. Refer to the current FDA-approved package insert for drug administration.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Filgrastim is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

3.7 Pegfilgrastim (Neulasta™) (NSC 725961)

a. PHARMACOLOGY

Mechanism of Action: Similar to filgrastim, pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end-cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action.

b. PHARMACOKINETICS

1. Absorption: Similar to filgrastim, first-order pharmacokinetic modeling is expected with maximum serum concentration reached within 2 to 8 hours after subcutaneous injection.

2. Distribution: Similar to filgrastim, volume of distribution of averaged at 150 mL/kg.

3. Metabolism: Unknown.

4. Elimination: Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared with filgrastim. The half-life of pegfilgrastim ranges from 15 to 80 hours after subcutaneous injection.

c. ADVERSE EFFECTS

1. Possible Side Effects of Pegfilgrastim*:* Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Most frequent adverse reactions are skeletal pain (< 20%).

2. Pregnancy and Lactation: Category C, pegfilgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies have demonstrated adverse effects and fetal loss. Pegfilgrastim has been shown to cross the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Excretion in breast milk unknown/use caution.

3. Drug Interactions: Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs such as lithium may potentiate the release of neutrophils; ensure that patients receiving lithium and pegfilgrastim have more frequent monitoring of neutrophil counts. Pegfilgrastim should not be administered on the same day with anticancer chemotherapeutic agent(s) with leukocyte suppressive properties. Pegfilgrastim is contraindicated in patients with hypersensitivity to *E.coli*-derived proteins, filgrastim, or any component of the product

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan.

2. Refer to the current FDA-approved package insert for drug administration.

e. PREPARATION, STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Pegfilgrastim is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

The Ann Arbor staging criteria will be used. Stage is based on extent of disease at the time of diagnosis. Only patients with Stage III or IV disease are eligible for this protocol.

4.2 Staging Criteria

STAGE III Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE).

STAGE IV Diffuse or disseminated involvement of one or more extra lymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement).

International Prognostic Score (IPS) *(95)*

The IPS, developed by Hansclever and colleagues, assesses the total score of several individual risk factors (each assigned a value of 1 point) present in a patient. The IPS score is associated with prognosis following standard therapy for HL. A total score of 0 represents the most favorable risk with increasing scores associated with lower freedom from progression and survival.

Age	≥ 45 years	
Gender	Male	
Stage	IV	Note: Stage IV is defined as diffuse or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.
Hemoglobin	< 105 g/L	
Albumin, serum	< 40 g/L	
WBC	≥ 15.0 x 10^9/L	
Lymphocytes	Count < 0.6 x 10^9/L or percent < 8% of WBC	

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or lymphomaquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. All patients must have histologically confirmed newly diagnosed, previously untreated Stage III or IV classical Hodgkin lymphoma (nodular sclerosing, mixed cellularity, lymphocyte-rich, or lymphocyte-depleted, or not otherwise specified (NOS)). Nodular lymphocyte predominant Hodgkin Lymphoma is not eligible.

b. Patients must have bidimensionally measurable disease (at least one lesion with longest diameter ≥ 1.5 cm) documented on the Lymphoma Baseline Tumor Assessment Form in Rave.

c. Patients must have a whole body or limited whole body PET-CT scan performed within 42 days prior to registration. (A contrast-enhanced (diagnostic) CT, MRI or MR-PET is acceptable in event that PET-CT is contra-indicated, however if it is later possible to administer a PET-CT, then PET-CT is strongly preferred for the interim scan (after Cycle 2) (if performed) and the EOT assessment. Otherwise, if PET-CT is not subsequently possible, then the same modality as baseline must be used throughout the trial.) NOTE: All images from PET-CT, CT, MRI or MR-PET scans performed as standard of care to assess disease (**within 42 days prior to registration**) must be submitted as indicated in Section 15.4 and associated radiology reports must be submitted as indicated in Section 14.4a.

5.2 Age criteria: Patients must be ≥ 12 years of age.

5.3 Prior/Concurrent Therapy Criteria

a. Patients must not have received any prior chemotherapy, radiation, or antibody-based treatment for classical Hodgkin lymphoma. Steroid pre-treatment is permitted as outlined in Section 5.4k

b. Patients must not have had prior solid organ transplant.

c. Patients must not have had prior allogeneic stem cell transplantation.

d. Patients must not have received a live vaccine within 30 days prior to planned Day 1 of protocol therapy (e.g. measles, mumps, rubella, varicella, yellow fever, rabies, BCG, oral polio vaccine, and oral typhoid).

e. **At registration, investigator must declare intent-to-treat with Residual PET Radiation Therapy (Residual PET RT- RPRT) to be administered after patient completes 6 cycles of therapy if, after end of treatment, the patient meets criteria specified in Section 7.5 for receiving RT).** Patients will be stratified by investigator's intent-to-treat with Residual PET RT.
- **All pediatric patients (< 18 years of age) will be considered intent-to-treat with Residual PET RT at time of registration.**

5.4 Clinical/Laboratory Criteria

Please note that eligibility criteria and the timing of documentation prior to registration differ by age.

a. Patients must have a performance status corresponding to Zubrod scores of 0, 1 or 2. Use Lansky for patients ≤ 17 years of age. *The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only. See Sections 10.3 and 18.4.

b. Patients must have adequate renal function as indicated below:

Adults (age 18 or older):

- Creatinine clearance ≥ 30 mL/min, as estimated by the Cockcroft and Gault formula. The creatinine value used in the calculation must have been obtained **within 28 days** prior to to registration. Estimated creatinine clearance is based on actual body weight.

  $$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg } \dagger}{72 \times \text{creatinine}^* \text{ (mg/dl)}}$$

  Multiply this number by 0.85 if the participant is a female.

  † The kilogram weight is the participant weight with an upper limit of 140% of the ideal body weight (IBW).
  * Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

Pediatric Patients (age 12-17):

The following must have been obtained **within 14 days** prior to registration:

- Measured or calculated* creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m^2, or

- Serum creatinine ≤ 1.5 x institutional upper limit of normal (IULN), or a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
< 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
16 -17 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR *(96)* utilizing child length and stature data published by the CDC.
*calculated based on institutional standard

c. Patients must have adequate hepatic function, evidenced by the following*:
- Total bilirubin ≤ 2 x IULN, and
- AST and ALT ≤ 3 x IULN

***** unless due to Gilbert's disease, lymphomatous involvement of liver or vanishing bile duct syndrome

For adults (age 18 or older), above hepatic function must be documented **within 28 days** prior to registration.

For pediatric Patients (age 12-17), above hepatic function must be documented **within 14 days** prior to registration.

d. Patients must have adequate cardiac function defined as follows:

Patients must have an echocardiogram (ECHO), MUGA, or functional cardiac imaging scan with a left ventricular ejection (LVEF) fraction ≥ 50% or a shortening fraction of ≥ 27%. **For all patients,** the ECHO, MUGA, or functional cardiac imaging scan must be performed **within 42 days** prior to registration.

e. Patients with known human immunodeficiency virus (HIV) infection must be receiving anti-retroviral therapy and have an undetectable or unquantifiable viral load at their most recent viral load test within 6 months prior to registration.

f. Patients must not have known active Hepatitis B (HBV) or Hepatitis C Virus (HCV) at date of registration. Patients with previously treated HBV or HCV that have an undetectable viral load within 6 months prior to registration and no residual hepatic impairment are eligible.

g. Patients must not have any known central nervous system lymphoma.

h. Patients must not have a history of or active interstitial pneumonitis or interstitial lung disease.

i. Patients must not have had a diagnosis of inherited or acquired immunodeficiency (unless allowed under Section 5.4e).

j. Patients must not have any known uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, hemodynamically unstable cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

k. Patients must not have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to registration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Steroid use for the control of Hodgkin lymphoma symptoms is allowable, but must be discontinued prior to Cycle1, Day1.

l. Patients with peripheral neuropathy must have < Grade 2 at date of registration.

m. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, immunosuppressive drugs, or corticosteroids with doses higher than prednisone 10 mg or equivalent). Autoimmune diseases include but are not limited to autoimmune hepatitis, inflammatory bowel disease (including ulcerative colitis and Crohn's disease), as well as symptomatic disease (e.g.: rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis or glomerulonephritis). Vitiligo, alopecia, hypothyroidism on stable doses of thyroid replacement therapy, psoriasis not requiring systemic therapy within the past 2 years are permitted.

n. No second prior malignancy is allowed except for adequately treated basal (or squamous cell) skin cancer, any in situ cancer or other cancer for which the patient has been disease free for two years.

o. Females of childbearing potential must not be pregnant or nursing, and have a negative pregnancy test within 28 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method while receiving study drug and for women until 6 months after receiving the last dose of study drug or, for men, until 7 months after receiving the last dose of study drug. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.5 Specimen Submission Criteria

a. Patients must have one formalin-fixed paraffin embedded (FFPE) diagnostic tumor block or at least 1 diagnostic, 4-5 micron, H&E slide collected prior to registration and available for submission, as outlined in Sections 12.1 and 15.1a.

b. Patients must be offered participation in banking for planned translational medicine and future research, as outlined in Section 15.2. With patient consent, any residuals from the mandatory tissue submission will also be banked for future research.

Note: Streck tubes must be ordered in advance, as indicated in Section 15.2c. Allow 5-7 days for shipment of the collection kits.

5.6 Patient-reported outcomes and PRO-CTCAE criteria

a. Patients who can complete Patient-Reported Outcome instruments in English, Spanish, or French must complete the PROMIS Fatigue, the FACT/GOG-Ntx, and the PROMIS Global prior to registration. **Patients who do not complete PRO instruments prior to registration but are otherwise eligible will remain eligible for the primary analysis and other secondary analyses.**

b. Patients who can complete Patient-Reported Outcome instruments in English, Spanish, or French must also agree to complete the PROMIS Fatigue, the

FACT/GOG-Ntx, the PROMIS Global, and the PRO-CTCAE (or Ped PRO-CTCAE) at the scheduled on-study assessment timepoints.

5.7 Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and all patients and/or their parents or legal guardians (for patients <18 years of age) must sign and give informed consent and assent (where appropriate) in accordance with institutional and federal guidelines. For participants with impaired decision-making capabilities, legally authorized representatives may sign and give informed consent on behalf of study participants in accordance with applicable federal, local, and CIRB regulations.

Note: As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be randomized between Arm 1 – nivolumab + AVD and Arm 2 – brentuximab vedotin + AVD in a 1:1 fashion using a randomized dynamic balancing algorithm with stratification based on:

a. Age (years): age 12-17 vs. age 18-60 vs. age > 60

b. International prognostic score: 0-3 vs. 4-7

c. Pre-specified plan to use Residual PET Radiation Therapy (Residual PET RT)*: yes vs. no
* See Section 7.5.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact:

- Adults: E-mail: S1826USAdults@swog.org or call: Dr. Alex Herrera (SWOG) at Phone: 626/256-4673 ext. 62405 or Dr. Sarah Rutherford (Alliance) at Phone: 646/962-2064 or Dr. Andrew Evens (ECOG-ACRIN) at Phone: 732-235-9289.

- Pediatrics: E-mail: S1826pediatrics@swog.org or call: Dr. Sharon Castellino at Phone: 404/785-3616 or Dr. Angela Punnett at: Phone: 416/813-5394.

- CCTG Adults: Dr. Kelly Davison at: E-mail: kelly.davison@mcgill.ca or Phone: 514/934-1934, ext 31558. Dr. Michael Crump at: Michael.Crump@uhn.ca or Phone: 416/946-4567.

For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

Initiation of treatment must be planned to start **no more than 14 calendar days after registration.**

7.1 General Treatment Information

a. Treatment Plan Overview

This is a multicenter, randomized, open-label Phase III clinical trial for participants with previously untreated advanced stage (III-IV) classical Hodgkin lymphoma.

Once a patient meets eligibility criteria, the patient will be randomized to either Arm 1 (N+AVD) or Arm 2 (BV+AVD).

The planned therapy duration is 6 x 28 day cycles, with study treatment administered on Days 1 and 15 of each cycle. See Section 7.3 below for specific details about treatment regimen for each arm.

b. Guidance for trial conduct during the COVID-19 pandemic (and other extenuating circumstances)

1. In order to provide participating sites flexibility in treatment participant population, it is the intent of the **S1826** protocol to allow for laboratory and imaging assessments to be drawn and resulted by local healthcare providers (with appropriate oversight by the Responsible Investigator (local treating investigator)), where administration of the assessment at an off-site facility is in the best interest of the patient and provides for continuity of patient care. Utilization of offsite / local healthcare resources for conduct of participant's laboratory and imaging assessments does not need to be documented as a deviation due to COVID-19 pandemic or other extenuating circumstances, however participating sites must document procedures for oversight (by the Responsible Investigator) of assessments performed offsite.

2. In addition to continuity of care options above, follow-up visits may also be delayed if in the judgment of the Responsible Investigator the benefit of delay of a visit outweighs the risks of exposure of the patient to the virus by coming in for an in-person visit and an alternative method (phone or virtual visit) is not possible.

3. Participating sites are requested to carefully consider each participant's ability to come into the clinic for planned treatments (with respect to the local COVID-19 situation) prior to enrollment. Every effort should be made to avoid treatment delays.

    a. Since **S1826** is conducted under an IND, nivolumab must be administered at an approved/NCI-registered site participating in the **S1826** protocol. Total treatment delays (of all components of the study regimen) of up to 4 weeks / 28 days are allowable per protocol, with documented reason for delay. Total treatment delays (of all components of a study regimen) of longer than 4 weeks (for any reason) will require the patient to be removed from protocol treatment permanently (Section 7.8).

    b. For patients declared at time of registration as intent-to-treat with residual PET radiation therapy (RPRT), the EOT PET-CT scan must be submitted for review and approval by IROC RI one week prior to the planned start of RPRT. RPRT may not begin until subsequent IROC RI review and approval (See protocol Sections 12.3 and 7.5b).

c. FFPE diagnostic tumor tissue is required per protocol and must be submitted to the SWOG Biospecimen Bank, as indicated in protocol Section 15.1.

d. PRO (QOL and PRO-CTCAE) assessments are required at applicable timepoints. Please see Sections 15.5c.4 and 15.6c.5 for instructions on questionnaire administration via phone (with provision of a copy via email or mail) in event that COVID-19 extenuating circumstances preclude on-site administration of the questionnaires within the protocol allowable windows. Assessments completed via phone or telehealth (videoconference) visits must still be submitted within allowable windows at time of collection. See Section 14.4.

e. Following are extended windows for protocol assessments in event of a COVID-19 or related extenuating circumstance. The Responsible Investigator rationale for utilization of the extended windows outlined below must be carefully documented in the patient chart as resultant from the COVID-19 pandemic and extenuating circumstance. Please note the allowable windows indicated in Sections 7.5, 9.0, and 15.0 remain applicable for all patients, where there is not a COVID-19 pandemic-related extenuating circumstance.

4. Extended Radiation Therapy window

A pause of RT timing beyond the allowable 72 hours specified in Section 7.5a.2 due to COVID-19 extenuating circumstances, or the need to stop RT in a patient due to COVID-19 positive status are permitted at the discretion of the investigator. Variances due to COVID-19 extenuating circumstances or patient's COVID-19-positive status must be thoroughly documented and discussed with the **S1826** Study Chairs and Radiation Oncology Chair for guidance. Contact the study-specific email listed on the S1826 Protocol Contact Information page.

5. Extended window for peripheral blood sample collection

To provide additional flexibility, the best practices window for the Cycle 3, Day 1 peripheral blood sample collection is being extended to +/- 14 days, and the window for the End of Cycle 6 (or time of off-protocol) and Time of Progression peripheral blood sample collection is being extended to +/- 30 days. See Section 15.2.

6. Extended window for patient follow-up in event of COVID-19 or related extenuating circumstances

To provide additional flexibility, the best practices windows for follow-up visits (both prior to and after progression), which are to occur every 3 months for the first year, then every 6 months for the second and third years, and then annually until 10 years from the date of registration, are being extended to +/- 30 days, where the Responsible Investigator determines that the delayed assessment helps to assure the safety of the patient, with consideration for the COVID-19 pandemic and related extenuating circumstances.

Off-treatment follow-up CT scans should be conducted as close to the protocol timepoint as is reasonably possible, in the judgment of the Responsible Investigator.

To provide additional flexibility, the best practices window for follow-up CT scans at 12- and 24-months after time of registration, is being extended +/- 90 days, where the Responsible Investigator determines that the delayed assessment helps to assure the safety of the patient, with consideration for the COVID-19 pandemic and related extenuating circumstances.

7.2 Pre-medication, Concomitant Therapy, and Supportive Care Guidelines

a. Pre-medication: Pre-medications including antiemetics and steroids can be administered per institutional practice.

b. Concomitant Therapy

1. Required concomitant medications:
The use of granulocyte-colony stimulating factor (G-CSF) is required for patients receiving BV + AVD. G-CSF is optional for patients receiving N + AVD. See Section 7.3 for G-CSF dose and scheduling.

2. Permitted concomitant medications:
Dexrazoxane use is allowed concomitant with doxorubicin as a cardiac protectant per investigator choice and must be captured on study CRFs if used. Since there may be an increased risk of typhlitis associated with myelosuppression with the use of dexrazoxane, treating investigators are cautioned that evaluation for typhlitis should be kept in mind for patients presenting with severe abdominal pain.

The use of topical, inhalational and ophthalmic steroids is permitted. Corticosteroids are permitted as part of a chemotherapy premedication regimen per institutional standards. In addition, a brief course of corticosteroids for prophylaxis (e.g,: contrast dye allergy) or for treatment of non-autoimmune conditions (e.g,: delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Patients may receive hormonal contraceptives.

3. Prohibited concomitant medications:
   - Any investigational agents other than nivolumab.
   - Any concurrent antineoplastic therapy other than AVD, brentuximab vedotin, or nivolumab (i.e.: chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for those subjects planned to receive radiation as specified in Section 7.5).
   - Immunosuppressive agents (except to treat a drug-related AE).
   - Systemic corticosteroids (defined as equivalent to > 10 mg daily prednisone) except as pre-medications, antiemetics, for prophylaxis, or treatment of non-autoimmune conditions for brief course as noted in preceding section, and as stated in Section 18.3 to treat a drug-related AE).
   - Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Short-term steroid premedication for contrast allergy is also permitted.
   - Use of ritonavir or HIV therapy that uses pharmacologic boosters, such as cobicistat in the control arm for HIV+ patients or HIV, is prohibited.

4. Cautionary concomitant medications:
   - The use of strong inhibitors or inducers of CYP1A2 (dacarbazine interaction) or CYP3A4 (doxorubicin, brentuximab vedotin, vinblastine interactions) should be avoided. See Section 18.9.
   - Multiple CYP3A4 interacting agents of moderate or strong effect in the HIV+ patients should not be used. This includes most HIV protease inhibitors.

c. Supportive Care Guidelines

1. Infusion-related reactions:

   All infusions should be administered at a site properly equipped and staffed for anaphylaxis should it occur.

   Medications for treatment of hypersensitivity reactions, such as epinephrine, antihistamines, and steroids, should be available for immediate use in the event of a reaction during administration.

   See Section 8.2c.2 for dose modification guidelines.

2. Nausea and/or vomiting:

   Although the study does not require prophylactic antiemetics, there is no prohibition against their use. Treating investigators should follow institutional guidelines for administration of antiemetics.

3. Suspected Progressive Multifocal Leukoencephalopathy (PML):

   Signs and symptoms of PML may include altered mental status; motor deficits, such as hemiparesis or ataxia; visual disturbances; or higher cortical dysfunction, such as dysphasia or agnosia. Seizures have also been reported in patients with PML (approximately 20%). The onset of neurological deficits may occur over weeks to months.

   See Section 8.2b for dose modification guidelines.

4. Suspected immune reaction to nivolumab:

   See Section 8.2c.2 for dose modification guidelines and Section 18.3 for detailed algorithms for Immuno-Oncology management of the following groups of AEs:

   - Gastrointestinal
   - Renal
   - Pulmonary
   - Hepatic
   - Endocrinopathies
   - Skin
   - Neurological

5. Antimicrobial prophylaxis

   Pneumocystis pneumonia (PCP) is known to occur in patients with compromised immune systems and has been reported in patients receiving ABVD-based therapy, including BV+AVD. PCP prophylaxis should be considered at the discretion of the treating investigator for both arms, particularly in patients treated on Arm 2 (BV+AVD).

   Antimicrobial prophylaxis (such as fluconazole, acyclovir, levofloxacin) is allowed at the discretion of the treating investigator and should be administered per standard of care and institutional procedures.

6. Additional monitoring recommended for patients with pericardial effusion at time of registration

   It has been noted that exacerbation of pericardial effusion/pericarditis may occur in patients with a pre-existing pericardial effusion. Treating investigators should carefully monitor patients who have pericardial effusion at time of enrollment for worsening pericardial effusion and for pericarditis.

   Pericarditis adverse events can be managed according to the “Other treatment-related adverse events” category specified at the end of the dose modifications table in Section 8.2c.2.

7.3 Protocol Treatment

a. **Arm 1 – Nivolumab + AVD [a]**

AGENT	Age/Weight	DOSE	ROUTE	DAY	SCHEDULE [a, b, c]
Doxorubicin [d, g, h]	All patients	25 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Vinblastine [d, h]	All patients	6 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Dacarbazine [d, h]	All patients	375 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Nivolumab [e]	Age 18 or older	240 mg	IV	Days 1 and 15	Every cycle x 6 cycles
Nivolumab [e, h]	Age 12-17 [f]	3 mg/kg (up to 240 mg max)	IV	Days 1 and 15	Every cycle x 6 cycles

[a] N-AVD combination therapy should be administered after all procedures and assessments have been completed. Treatment may be administered up to 3 days before or after the protocol-specified days due to administrative reasons. Treatment delay (≤ 4 weeks) or dose reduction due to adverse events/toxicity is allowed, as indicated in Sections 8.2a and 8.2c.

[b] One cycle = 28 days.

[c] G-CSF administration is allowable, in accordance with institutional procedure.
- If G-CSF is given, it should begin no sooner than 24 hours after completion of chemotherapy.
- Pegfilgrastim:
  - For adult patients and pediatric patients ≥ 45kg: 6mg subcutaneously on Days 2 and 16. (On-body injector kit is allowable).
  - For pediatric patients < 45kg: 0.1 mg/kg subcutaneously on Days 2 and 16 (On-body injector kit is allowable) or dose per institutional standards.
  - For all patients: Biosimilars are also allowable.
- Filgrastim:
  - Suggested to administer 5mcg/kg per day for 5 days (e.g.: Days 6-10 and Days 21-25) but can be adjusted if more or less is needed, should be no less than 2 days between study treatment days, or in accordance with institutional procedure.
  - Filgrastim should be stopped 24 hours prior to Day 15 treatment and may resume 24 hours after the Day 15 treatment.
  - Biosimilar forms of recombinant filgrastim (tbo-filgrastim or filgrastim-sndz) are permitted at institutional discretion.

[d] AVD is to be administered prior to nivolumab per institutional guidelines. Administration method and sequence of each component of AVD (doxorubicin, vinblastine, and dacarbazine) will be according to local and institutional standards.

[e] Nivolumab will be administered after AVD. Nivolumab infusion should start after the conclusion of the dacarbazine. Nivolumab will be administered intravenously over approximately 30 minutes.

[f] Age at date of registration. Patients who turn 18 while on protocol but do not reach max weight, will remain on the 3 mg/kg dose for the duration of protocol treatment.

[g] Dexrazoxane use is allowed concomitant with doxorubicin as a cardiac protectant per investigator choice and must be captured on the **S1826** Concomitant Medication Form, if used. See also Section 7.2b.2.

[h] For dosing based upon the patients' weight, dosing calculations should be based on the body surface area (BSA) and calculated using the body weight for the first dose. However, if the patient's weight later changes by ≥ 10% from the previous weight used to calculate BSA, then BSA should be recalculated and next dose corrected accordingly. All doses should be rounded in accordance with institutional procedure.

Recommended Cardiac Monitoring

Patients who have evidence of CHF, MI, cardiomyopathy, or myositis cardiac evaluation (NYHA I/II) (subsequent to the start of protocol therapy) should have additional consult by a cardiologist, including review of EKG, CPK, troponin, echocardiogram, as clinically indicated, prior to start of each cycle.

b. **Arm 2 – Brentuximab Vedotin + AVD [a]**

AGENT	DOSE	ROUTE	DAY	SCHEDULE [a, b]
Doxorubicin [c, g, h]	25 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Vinblastine [c, h]	6 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Dacarbazine [c, h]	375 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Brentuximab vedotin [d, h]	1.2 mg/kg (max dose 120 mg)	IV	Days 1 and 15	Every cycle x 6 cycles
G-CSF: [e, h] Pegfilgrastim OR Filgrastim	**Pegfilgrastim:** Adults or pediatric patients ≥ 45 kg: 6 mg Pediatric patients < 45 kg: 0.1 mg/kg or dose per institutional standards OR **Filgrastim:** 5mcg/kg per day	**Pegfilgrastim:** SubQ OR **Filgrastim:** SubQ or IV * For patients age 12-17: SubQ is preferred.	**Pegfilgrastim:** All patients: **D2 & D16.** On-body injector kit is allowable. OR **Filgrastim:** See Footnote (e)	Every cycle x 6 cycles See Footnote (e)

[a] BV-AVD combination therapy should be administered after all procedures and assessments have been completed. Treatment may be administered up to 3 days before or after the protocol-specified days due to administrative reasons. Treatment delay (≤ 4 weeks) or dose reduction due to adverse events/toxicity is allowed, as indicated in Sections 8.2a and 8.2d. If BV is discontinued due to toxicity, G-CSF is no longer required.

[b] One cycle = 28 days.

[c] AVD is to be administered first per institutional guidelines. Administration method and sequence of each component of AVD (doxorubicin, vinblastine, and dacarbazine) will be according to local and institutional standards.

[d] Brentuximab vedotin is to be administered after AVD. BV infusion should start after the conclusion of the dacarbazine. BV will be administered intravenously over approximately 30 minutes.

[e] G-CSF administration is required unless BV is discontinued due to toxicity.

- Begin G-CSF no sooner than 24 hours after completion of chemotherapy.
- Pegfilgrastim:
  - For adult patients and pediatric patients ≥ 45kg: 6mg subcutaneously on Days 2 and 16. (On-body injector kit is allowable).
  - For pediatric patients < 45kg: 0.1 mg/kg subcutaneously on Days 2 and 16 (On-body injector kit is allowable) or dose per institutional standards.
  - For all patients: FDA-approved biosimilars are also allowable.
- Filgrastim:
  - Suggested to administer 5mcg/kg per day for 5 days (e.g.: Days 6-10 and Days 21-25) but can be adjusted if more or less is needed, should be no less than 2 days between study treatment days, or in accordance with institutional procedure.
  - Filgrastim should be stopped 24 hours prior to Day 15 treatment and may resume 24 hours after the Day 15 treatment.
  - FDA-approved biosimilar forms of recombinant filgrastim (tbo-filgrastim or filgrastim-sndz) are permitted at institutional discretion.

[g] Dexrazoxane use is allowed concomitant with doxorubicin as a cardiac protectant per investigator choice and must be captured on the **S1826** Concomitant Medication Form, if used. See also Section 7.2b.2.

[h] For dosing based upon the patients' weight, dosing calculations should be based on the body surface area (BSA) and calculated using the body weight for the first dose. However, if the patient's weight later changes by >/= 10% from the previous weight used to calculate BSA, then BSA should be recalculated and next dose corrected accordingly. For BV, actual weight will be used except for patients weighing greater than 100kg; dose will be calculated based on 100kg for these individuals. All doses should be rounded in accordance with institutional procedure.

7.4 PET-CT response assessment

Primary response assessment by PET-CT must occur 4-8 weeks after the last dose of study drug.

Responses will be assessed based on the local radiology review according to the 2014 Lugano classification using the 5-point Deauville score (See Section 10.1).

Central review of PET scans will not be performed in real time; therefore, therapy should proceed as per the initial randomization arm without awaiting central review results. This is not PET response adapted therapy.

For patients who do undergo interim PET-CT scanning as part of standard of care testing, or because they have been declared eligible for radiation, specific guidelines are provided below, pertaining to each study arm about management and decision-making.

a. Baseline

Per Section 12.0, unless otherwise contraindicated, patients must receive a baseline PET-CT scan. While a contrast-enhanced (diagnostic) CT, MRI or MR-PET is acceptable in event that PET-CT is contra-indicated, if it is later possible to administer a PET-CT, then PET-CT is strongly preferred for the interim scan (after Cycle 2) (if performed) and the EOT assessment. Otherwise, **if PET-CT is not subsequently possible, then the same modality as baseline must be used throughout the trial.**

NOTE: All images from PET-CT, CT, MRI or MR-PET scans performed as standard of care to assess disease (**within 42 days prior to registration**) must be submitted as indicated in Section 15.4 and associated radiology reports must be submitted as indicated in Section 14.4a.

b. Interim PET-CT Scans

If PET-CT is contra-indicated at baseline, and it is later possible to administer a PET-CT, then PET-CT is strongly preferred for the interim scan (after Cycle 2) (if performed) and the EOT assessment. Otherwise, the same modality as baseline must be used throughout the trial.

Although it has been a standard of care to perform interim PET-CT scans (e.g. after Cycle 2), in patients with HL undergoing initial treatment, **S1826 protocol treatment is NOT intended to be PET response-adapted therapy**.

Since the historical standard indication for radiation use in pediatric patients includes criteria regarding interim response, the study team intends to collect interim PET-CT data in patients who are declared at time of patient registration as intent-to-treat with radiation therapy accordinto to protocol guidelines. Interim PET-CT data are not intended for use in real-time treatment decision making (see Sections 7.4b.1 and 7.4b.2 for guidance on interim PET-CT information according to treatment arm). Integrated imaging objectives are planned for incorporation into the protocol with a future protocol revision. For this reason, ***interim PET-CT scans are not required per protocol unless*** the investigator declared (at the time of patient registration) intent-to-treat with radiation therapy according to protocol guidelines.

For patients who are declared a intent-to-treat with radiation therapy, interim PET-CT must be performed after 2 cycles of therapy (Day 53 ± 3 days) and prior to start of Cycle 3. Images must be submitted, as indicated in Section 15.3. (See also Sections 7.5, and 12.0). The interim PET-CT data will allow future analysis of the impact of narrowing the RT indications.

1. Arm 1: N+AVD

   Due to the often indeterminate PET-CT results observed in patients with HL treated with PD-1 blockade, **N+AVD treatment is not intended to be PET-response adapted**.

   A treatment change based on interim PET-CT in the absence of formal disease progression defined in Section 10.1b.4 is not recommended and will be considered a protocol violation.

   If a therapy switch is planned based on interim scanning (i.e. Deauville 4 or 5 in the absence of formal disease progression), biopsy confirmation of active lymphoma is required to avoid a protocol violation (as long as the biopsy is safe/feasible). If biopsy is not feasible, contact the Study Chair for guidance.

2. Arm 2: BV+AVD

   BV+AVD therapy is not intended to be response-adapted, and interim PET-CT scanning is not a protocol-specified study activity.

   If interim PET-CT is performed and treatment is changed based on interim PET-CT results in the absence of disease progression (i.e. Deauville 4 or 5 in the absence of formal disease progression), this will not be counted as an PFS event.

   However, if a therapy switch is planned, biopsy confirmation of active lymphoma is strongly encouraged (as long as the biopsy is safe/feasible).

   If biopsy is not feasible, contact the Study Chair for guidance.

c. End-of-Treatment Assessments

If PET-CT was previously contra-indicated for the patient, and it is later possible to administer a PET-CT, then PET-CT is strongly preferred for the EOT assessment. Otherwise, the same modality as baseline must be used throughout the trial.

Interpretation of PET-CT in patients with HL treated with PD-1 blockade can be challenging due to the indeterminate PET-CT results that are often observed. In the CheckMate 205 study, only 2 out of 12 patients who were not in CR at the end of N+AVD by independent review were treated with subsequent salvage therapy.

Moreover, the positive predictive value for end-of-treatment PET-CT scans (in the setting of nivolumab) is unknown. **When interpreting interim and EOT PET-CT results for patients in Arm 1, treating investigators should take into consideration that the false positive rate may be high.**

It is generally good clinical practice to confirm the presence of relapsed or refractory HL prior to initiating second line therapy. Especially because of these challenges with PET-CT interpretation in patients with HL treated with PD-1 blockade, in the absence of a formal disease progression event (and even in the setting of PD), **it is strongly recommended that patients undergo biopsy confirmation of residual HL (as long as the biopsy is safe/feasible) at the end of treatment (or thereafter) prior to the initiation of second line therapy for suspected relapsed or refractory HL**.

In the event of indeterminate PET-CT results at the end of treatment (see LYRIC criteria, Section 18.1), the patient should be observed without additional treatment and repeat imaging should be performed after an additional 12 weeks (or sooner if clinically indicated) to determine whether there is true progressive disease. Biopsy confirmation should be sought (if safe/feasible) prior to initiation of second line therapy if repeat imaging is concerning for relapsed or refractory HL.

Please see also Section 9.1 for required laboratory assessments to be performed at the EOT visit. Peripheral blood must be submitted, with patient's consent, as indicated in Section 15.2.

7.5 Radiotherapy Indications, Dosage, Timing and Credentialing

End-of-treatment Residual PET Radiation Therapy **may be administered at the discretion of the treating physician**, provided that the intent to deliver RT was declared at study enrollment and the criteria below are met. Of note, as described above, indeterminate PET-CT scan findings are common with nivolumab treatment.

Patients who are declared eligible for RT are not required to receive RT - if the treating physician feels like residual PET-avid lesions are consistent with indeterminate response (see LYRIC criteria, Section 18.1), it is allowable to observe the patient without additional treatment and perform repeat imaging after an additional 12 weeks (or sooner if clinically indicated) to determine whether there is true progressive disease.

In advanced-stage or high-risk patients, involved field radiotherapy (IFRT) has traditionally encompassed a large volume of normal tissue due to anatomically widespread sites of multiple disease and extra-lymphatic spread. **One of the aims of this study is to reduce the volume of radiotherapy in order to reduce potential acute and late toxicities, while maintaining disease control.** This will be done in two ways: 1) omitting radiotherapy (RT) in patients who have a complete response to systemic therapy (defined as Deauville 1-3 after six cycles of systemic therapy), and 2) limiting the volume of RT among patients who receive this treatment only to residual PET+ lesions.

a. Eligibility for protocol-specified radiation therapy Residual PET RT

1. The treating investigator must have declared intent for use of Residual PET RT at the date of registration to the protocol (and patient must meet criteria for RT indications in Section 7.5b).

2. Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care.

   Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

   See also Section 7.1b for extended allowable windows in event of COVID-19 extenuating circumstance.

3. All investigators registering pediatric patients are required to agree to intent to apply RT per the disease and response characteristics defined below. Investigators at all other (non-COG) participating institutions will be required to have declared their intent to apply RT prior to patient registration and randomization (per Section 5.3e).

4. IROC Rhode Island will verify patient eligibility for protocol-specified RT. To allow for IROC Rhode Island review prior to RT, images must be submitted to IROC Ohio (via TRIAD preferred) as indicated in Sections 12.3 and 15.4.

b. Indications for Radiotherapy

1. The indication for RT will be based on the end-of-treatment imaging evaluation performed upon completion of 6 cycles of systemic therapy (4-8 weeks after the last dose of study drug). In general terms, RT will be delivered when patients have 1-2 sites initially involved with HL that achieve only a partial response. Specifically, RT will be indicated when the patient has persistent sites upon completion of 6 cycles of systemic therapy that meet all of the following criteria:

   a. Residual nodal mass ≥ 2.5cm in axial diameter, or residual extranodal lesion >1cm in axial diameter (e.g. lung nodule or splenic nodule), and

   b. Deauville score = 4 or 5 (See Section 10.1a), and

   c. ≥ 30% reduction in maximal transverse diameter compared to pre-treatment imaging.

2. RT may be given to one or two nodal sites. RT to more than two nodal sites is not allowed.

c. Contraindications for RT:

1. Deauville score 5 due to development of new PET avid sites during systemic therapy.

2. Three or more persistent PET-avid (Deauville score 4-5) sites at completion of systemic therapy.

3. An end-of-treatment PET-avid lesion contained within a mass that is measurable by CT scan and has not achieved at least 30% reduction in transverse diameter since initiation of therapy.

   Patients with the above features are unlikely to be cured with RT, and *biopsy with alternative management should be considered.*

d. Radiotherapy Dose and Schedule for SRL Lesions

Radiotherapy will consist of 3000-3600 cGy in fractions of 150-200 cGy per day.

1. The treatment will be given 5 days per week.

2. All fields should be treated once each day.

3. The total elapsed treatment time will be approximately 4 weeks.

e. Timing of Radiotherapy and Starting Criteria

Treatment should begin 5-12 weeks from Cycle 6, Day 15 of chemotherapy or when blood counts have recovered.

Criteria include an ANC > 750/μL and platelets > 75,000/μL prior to treatment for each site.

f. Credentialing Requirements

See Section 18.6d for credentialing requirements.

7.6 Follow-up and Disease Evaluation Off-Protocol Treatment

The last dose of protocol therapy is defined as either the last dose of study drug or the last dose of radiation therapy (administered per protocol), whichever is later.

The End-of-Treatment assessment is defined as the visit occurring 4-8 weeks after the last dose of study drug.

The End-of-RT assessment is defined as the visit occurring after the last dose of radiation therapy, for patients who were registered with intent-to-treat with RPRT and go on to receive RT per protocol.

a. Prior to Progression

All patients will have the following every 3 months for the first year after registration, then every 6 months for years 2 and 3, then annually until 10 years after registration.

- History and Targeted Physical exam
- Toxicity notation
- Completion of QOL Questionnaires at 4-8 weeks after the last dose of protocol therapy (following last dose of study drug or radiation therapy, whichever is later), 1 year after registration and 3 years after registration.
- Completion of the PRO-CTCAE Questionnaire after last dose of study drug, after last dose of radiation therapy (if applicable), and then 3-6 (if off-treatment early), 9, 12, 18, 24, 30, and 36 months (after date of registration) visits.

All patients will have a contrast-enhanced CT scan of chest, abdomen and pelvis (+ neck or other involved areas, if involvement at baseline) (or if contra-indicated, PET-CT, CT, MRI, or MR-PET) at 1 and 2 years after registration.

b. For patients receiving residual PET Radiation Therapy

Patients must have a PET-CT (or if contra-indicated, CT, MRI, or MR-PET) within 8-12 weeks after completion of radiation therapy.

c. Time of Progression

FDG-PET-CT scan: Patients who are removed from protocol treatment must receive a PET-CT scan before starting subsequent therapy.

For patients contra-indicated for FDG-PET-CT, a MRI, MR-PET or a contrast-enhanced CT scan of chest, abdomen, and pelvis (+ neck, if involvement at baseline) is allowable.

d. Follow-up After Progression

Following disease progression, patients will be followed annually for survival and note of subsequent therapy which is typically performed by medical record review.

7.7 Patient-Reported Outcomes

a. Quality of Life Assessments

Patients who can complete Patient-Reported Outcome instruments in English, Spanish, or French must complete the baseline PROMIS Fatigue questionnaire, FACT/GOG-Ntx, and the PROMIS Global. The PROMIS Fatigue questionnaire, FACT/GOG-Ntx, PROMIS Global questionnaires will also be administered to these patients at Day 56 (corresponding to the beginning of cycle 3), 4-8 weeks after the last dose of protocol therapy (following last dose of study drug or radiation therapy, whichever is later), and at years 1 and 3 after randomization. The scheduled follow-up PRO assessments should be completed even if the patient goes off protocol treatment early for any reason (including progression). The **S1826** PRO Cover Sheet for Patient Questionnaires is required to be submitted at each PRO assessment time. See Section 15.5 for PRO (QOL) administration procedures. PRO assessments at baseline and follow-up should be completed even if a patient is later deemed clinically ineligible after enrollment. If a patient is removed from protocol therapy prior to an indicated administration timepoint, the indicated assessment tools should still be administered at that timepoint. It will take approximately 15 minutes for the patient to complete the questionnaires at each time point.

b. PRO-CTCAE Assessments

Adult patients who can complete PRO-CTCAE instrument in English, Spanish, or French and Pediatric patients who can complete the PRO-CTCAE instrument in English must complete the PRO-CTCAE questions at the beginning of treatment and weekly during radiation treatment, corresponding to the following time points indicated in Section 15.6a. The administration timing of the PRO-CTCAE questionnaire should coincide with the physician-directed toxicity assessment for the respective visit. If a patient is removed from protocol therapy prior to an indicated administration timepoint, the scheduled PRO-CTCAE assessments must continue to be administered until such time that the patient starts a subsequent non-protocol systemic anti-cancer therapy. See Section 15.6 for PRO-CTCAE questionnaire administration procedures.

7.8 Criteria for Removal from Protocol Treatment

a. Completion of protocol treatment (ether completion of 6 cycles of study drug or (where applicable) completion of radiation therapy, whichever is later).

b. Progression of disease or symptomatic deterioration (as defined in Section 10.1).

c. Unacceptable toxicity per treating physician or study chair recommendation.

d. Treatment delay of all components of study regimen (BV or nivolumab AND AVD) for any reason > 28 days.

e. Unplanned radiation therapy (that was not declared as intent-to-treat with Residual PET RT at date of registration and/or does not meet criteria in Section 7.5).

f. The patient may withdraw from the protocol treatment at any time for any reason.

7.9 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.10 Follow-Up Period

All patients will be followed until death or 10 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Dose Modifications

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

a. Dose interruption or delay is permitted for toxicity or administrative reasons. If toxicity is deemed attributable to any single agent, then dose delay or missed dose of any single agent is allowable (ie, nivolumab, BV, A, V, or D alone may be delayed or missed or the entire regimen (N-AVD or B-AVD) may be delayed or missed at the discretion of the treating investigator.

1. If all drugs are held > 3 and ≤ 28 days after the protocol-scheduled date, the total treatment is considered delayed.

a. The next treatment after a delayed dose should occur as soon as possible (per the treatment schedule) once all toxicities resolve per the adverse event tables below or once the administrative delay is addressed.

b. The reason for delay must be documented.

c. When treatment is resumed, the treatment should be counted as the treatment cycle that was originally due at the earlier protocol-scheduled date, and the calendar will reset for subsequent visits.

- For example, if C2/D15 dose is delayed by 10 days and is administered on D25 of Cycle 2, then the calendar will reset on Day 25 and the next scheduled dose will be scheduled to be administered 14 days later on what would have originally been Cycle 3/Day 11 (and will be counted as C3/D1).

2. If an individual drug is held for >3 days, then respective dose of the individual drug (e.g. vinblastine) will be considered a missed dose, and when the individual drug is resumed (once all toxicities have improved per the adverse event tables), it will be counted as the next scheduled dose.

   a. Missed doses may not be made up.

   b. Data submission for the missed dose will reflect the reason for missed dose.

3. A total treatment interruption [i.e. stopping all study drugs nivolumab and AVD or BV and AVD) of > 28 days will require the patient to go off-protocol therapy].

b. Hematologic Toxicity:

Although it has been common practice in adult oncology settings in the United States to attenuate doses or delay treatment due to cytopenias alone, recent studies have shown that this policy is unneccessary and inadvisable for patients receiving ABVD and results in suboptimal treatment outcomes. *(97,98)* Patients should receive full doses of AVD on schedule on Days 1 and 15 of each 28 day cycle without treatment delays, unless neutropenic fever or documented infections are present. In nearly all cases, counts will recover despite administration of the next course of full dose chemotherapy administered on time. *(99, 100)*

c. Arm 1: N-AVD

The following tables summarize the criteria for nivolumab dose delays. The dose of nivolumab should not be modified. If dose delay criteria are met, the entire dose of nivolumab is held until the patient meets criteria for nivolumab re-initiation and then the patient should resume full dose nivolumab. In the event of a nivolumab-related AE that requires hold or discontinuation of nivolumab, AVD may be continued (dose reductions may be necessary according to Section 8.2 above). If nivolumab is withheld for > 6 weeks due to nivolumab-related toxicity, nivolumab should be permanently discontinued.

If patient is unable to receive *ALL components* of study therapy (i.e: Nivolumab as well as A, V, and D) > 4 weeks (for any reason), then patient must go off protocol treatment.

1. Dose Modification and Management for Myocarditis

   - Nivolumab will be held for Grade 2 cardiac dysfunction pending evaluation.
   - Nivolumab will be permanently discontinued for Grade 3 or 4 cardiac dysfunction and Grade 2 events that do not recover to normal parameters or that reoccur.
   - Treatment with steroids as clinically indicated.
   - For cardiomyopathy without evidence of myocarditis, please call the Study Chair to determine management (e.g. doxorubicin dose modification).

Cardiac [a, c]	**Management/Next Dose for BMS-936558 (Nivolumab) Cardiac Toxicities**
Grade 1	Hold nivolumab pending evaluation and observation.[b] Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below.
Grade ≥2 with suspected myocarditis	Hold nivolumab.[b] Admit to hospital. Cardiology consult. Rule out MI or other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, antithymocyte globulin (ATG) or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Discontinue nivolumab. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit, if appropriate). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off protocol treatment.

[a] Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin.

[b] Patients with evidence of myositis without myocarditis may be treated according as "other event". See "All other treatment-related events" in Section 8.2c.2.

[c] Pericarditis events should be managed according to the "Other treatment-related adverse events" category at the end of the table in Section 8.2c.2.

Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.

2. Dose Modification and Management for all other Adverse Events

Treatment-related Adverse Event	Grade of Event	Management for Nivolumab
Nephritis	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 2.
	Grade 3	Hold nivolumab until < Grade 2.
	Grade 4	Permanently discontinue nivolumab.
	See also: Section 18.3 for Renal Adverse Event Management Algorithm.	
Diarrhea (immune-related enterocolitis)	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 2
	Grade 3	Hold nivolumab until < Grade 2.
	Grade 4	Permanently discontinue nivolumab.
	See also: Section 18.3 for GI Adverse Event Management Algorithm.	
Endo-crinopathy (hypophysitis, adrenal insufficiency, Type 1 diabetes	≤ Grade 1	No change.
	Grade 2	Hold until < Grade 2.
	Grade 3	Hold until < Grade 2.
	Grade 4	Permanently discontinue nivolumab.
	Note: Asymptomatic hypothyroidism does not require dose modification. See also: Section 18.3 for Endocrinopathy Management Algorithm.	
Pneumonitis, broncho-spasm, pulmonary toxicity or interstitial lung disease	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until event resolves to baseline.
	Grade 3	Permanently discontinue nivolumab.
	Grade 4	Permanently discontinue nivolumab.
	Above does not include infusion reactions. See also: Section 18.3 for Pulmonary Adverse Event Management Algorithm.	
Neurologic (encephalitis, encephalopathy, seizure, Guillain-Barre syndrome, myelitis, excludes peripheral neuropathy)	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until event resolves to baseline. If event is felt to represent immune-related neurologic toxicity, the Study Chair should be consulted before re-initiation of nivolumab.
	Grade 3	Permanently discontinue nivolumab.
	Grade 4	Permanently discontinue nivolumab.
	See also: Section 18.3 for Neurological Adverse Event Management Algorithm.	
Peripheral Neuropathy	Grade 1-2	No change.
	Grade 3	• Reduce the dose of vinblastine by 50% for all further cycles of AVD. • If nivolumab-related, hold nivolumab until improves to Grade 2
	Grade 4	• Vinblastine will be omitted from all future cycles of AVD. • If nivolumab-related, discontinue nivolumab permanently
	See also: Section 18.3 for Neurological Adverse Event Management Algorithm.	

Treatment-related Adverse Event	Grade of Event	Management for Nivolumab
Skin drug-related AE	≤ Grade 1	No change.
	Grade 2	No change.
	Grade 3	Hold nivolumab until < Grade 3.
	Grade 4	Permanently discontinue nivolumab.
	See also: Section 18.3 for Skin Adverse Event Management Algorithm.	
Ocular toxicities (uveitis, iritis)	≤ Grade 1	No change.
	Grade 2	• Consider holding nivolumab, treat with topical steroids such as 1% prednisolone acetate suspension. • Evaluation by ophthalmologist strongly recommended.
	Grade 3	• Hold nivolumab. • Treat with systemic corticosteroids such as 1-2mg/kg of prednisone. • Evaluation by ophthalmologist strongly recommended.
	Grade 4	• Permanently discontinue nivolumab. • Treat with systemic corticosteroids such as 1-2mg/kg of prednisone.
Abnormal liver function (AST/ALT, Total bilirubin, immune-related hepatitis)	≤ Grade 1	No change.
	Grade 2	• Nivolumab management: hold nivolumab until < Grade 2 or baseline. • AVD management: If the bilirubin rises to > 2 x ULN (but ≤ 5 x ULN), the doxorubicin and vinblastine doses must be reduced by 50% of last dose received to avoid undue hepatic toxicity. Full doses should be given once the bilirubin is ≤ 2 x ULN.
	Grade 3	• AVD management: If the bilirubin rises to ≥ 5x ULN, then hold doxorubicin and vinblastine. • Nivolumab management: hold nivolumab until < Grade 2 or baseline. If AST/ALT>8x ULN or bilirubin >5x ULN, permanently discontinue nivolumab.
	Grade 4	Permanently discontinue nivolumab.
	If patient has concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN, then permanently discontinue nivolumab. See also Section 18.3 for Hepatic Adverse Event Management Algorithm.	

Treatment-related Adverse Event	Grade of Event	Management for Nivolumab
Amylase or lipase, associated with GI symptoms	≤ Grade 1	No change.
	Grade 2	No change.
	Grade 3	No change if asymptomatic. If GI symptoms, hold nivolumab until asymptomatic and < Grade 3.
	Grade 4	Permanently discontinue nivolumab. Note: Isolated Grade 4 abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis may not require nivolumab delay or discontinuation, but there should be discussion with the Study Chair[1]
	[1] Contact the Study Chair for consultation on asymptomatic Grade 4 amylase or lipase abnormalities. See also: Section 18.3 for GI Adverse Event Management Algorithm.	

Infusion / hypersensitivity reactions (manifestation may include: fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, **bronchospasm)**	≤ Grade 1	• Remain at bedside and monitor subject until recovery from symptoms.
		
		• Following prophylactic premedication is recommended for future infusions:
		
		  • Diphenhydramine 50 mg (1 mg/kg up to 50 mg in pediatric patients) PO/IV or equivalent
		
		  and/or
		
		  • Acetaminophen/ paracetamol 325 to 1000 mg (10-15 mg/kg up to 650 mg in pediatric patients) PO at least 30 minutes before additional administration.
		
		  • No change in dose for future administration.

Treatment-related Adverse Event	Grade of Event	Management for Nivolumab
Infusion / hypersensitivity reactions (manifestation may include: fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, **bronchospasm)**	Grade 2	• Stop infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (1 mg/kg up to 50 mg in pediatric patients) PO/IV or equivalent and/or acetaminophen /paracetamol 325 to 1000 mg (10-15 mg/kg up to 650 mg in pediatric patients) PO; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid (e.g. hydrocortisone 50-100 mg IV (1-2 mg/kg up to 100 mg in pediatric patients)) and/or bronchodilator therapy may also be administered as appropriate if reaction is severe or patient not responding to diphenhydramine or acetaminophen. • 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 drug will be administered at that visit. • Administer diphenhydramine 50 mg IV, (1 mg/kg up to 50 mg in pediatric patients) 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). • For future infusions, following prophylactic pre-medications are recommended: diphenhydramine 50 mg (1 mg/kg up to 50 mg in pediatric patients) or equivalent and/or acetaminophen /paracetamol 325 to 1000 mg (10-15 mg/kg up to 650 mg in pediatric patients) should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of methylprednisolone or equivalent) may be used if premedication with diphenhydramine and acetaminophen is not sufficient to prevent infusion reactions.

Treatment-related Adverse Event	Grade of Event	Management for Nivolumab

Infusion / hypersensitivity reactions
 	
(manifestation may include: fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, **bronchospasm)**
	Grade 3 or Grade 4	• Immediately discontinue infusion. Begin an IV infusion of normal saline and treat the subject as follows:
		  • Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1 mg/mL solution for subcutaneous administration (pediatric patients: 0.01 mg/kg [0.01 mL/kg/dose of **1 mg/mL** solution].
		  • IM also allowed per institutional standards.
		  • SubQ not to exceed 0.5 mg/dose) or 0.1 to 0.25 mg of a 0.1 mg/mL solution injected slowly for IV administration in adults, and/or diphenhydramine 50 mg IV (1 mg/kg up to 50 mg in pediatric patients) with methylprednisolone 100 mg IV (1 mg/kg up to 100 mg in pediatric patients) (or equivalent), as needed.
		  • Subject should be monitored until the investigator is comfortable that the symptoms will not recur.
		
		• For Grade 3, rechallenge of nivolumab can be considered with approval of the Study Chair via email to: S1826pediatrics@swog.org (for pediatric patients) or to: S1826USAdults@swog.org (for adult patients).
		
		• For Grade 4, permanently discontinue drug. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.
		
		• In case of late-occurring hypersensitivity symptoms, symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

	Note: Treatment guidelines may be modified based upon local SOPs, as appropriate. See also: Section 18.3 for Skin Adverse Event Management Algorithm.	

Treatment-related Adverse Event	Grade of Event	Management for Nivolumab
Hematologic (excluding lymphopenia)	Grade 1-2	No change.
	Grade 3-4	• No change required • G-CSF use for subsequent cycles is recommended. If already using daily filgrastim, additional doses should be considered. • For anemia, manage per institutional guidelines. Erythrocyte transfusion is allowable. • For thrombocytopenia, consider platelet transfusion and/or manage per institutional guidelines. Delay of nivolumab for Grade 4 thrombocytopenia may be considered at the investigator's discretion.
Febrile Neutropenia, Sepsis, infections, or Infestations	Grade 1-2	No change. *(only pertains to infection/infestation)*
	Grade 3-4	• Hold protocol therapy until ≤ Grade 2. • After recovery to ≤ Grade 2, continue N-AVD at same dose level. • Must use G-CSF with subsequent cycles. • Consider prophylaxis with antibacterial therapy for subsequent cycles. • For repeated occurrences, it is allowable to decrease the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician.
Any other laboratory abnormality (except AST/ALT, Total bilirubin, thrombocyte-penia, neutropenia, lymphopenia)	≤ Grade 1	• No change.
	Grade 2	No change.
	Grade 3	If clinically significant, hold nivolumab until < Grade 2. If not clinically significant, no change.
	Grade 4	Hold nivolumab. If clinically significant, nivolumab may need to be discontinued. Consult with Study Chair to discuss restarting nivolumab. If not clinically significant, hold nivolumab until < Grade 2. [1, 2, 3]
	[1] Grade 4 lymphopenia or leukopenia or does not require drug discontinuation. [2] Resolved, well-controlled, or asymptomatic hypothyroidism does not require approval by Study Chairs prior to restarting therapy. [3] Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.	

Treatment-related Adverse Event	Grade of Event	Management for Nivolumab
All other treatment-related events	≤ Grade 1	No change.
	Grade 2	No change.
	Grade 3	Hold nivolumab until < Grade 2.
	Grade 4	Permanently discontinue nivolumab. [1]
	[1] With exception of laboratory abnormalities, as noted above. See also: Section 18.3 for Skin Adverse Event Management Algorithm.	

d. Arm 2: BV

Dose delay or modification is allowable for toxicities related to brentuximab therapy if it is determined by the treating physician that it is in the best interest of the patient for safety reasons taking into consideration the overall clinical status of the subject. In the event of a BV-related AE that requires hold or discontinuation of BV, AVD may be continued (dose reductions may be necessary according to Section 8.2 above). If patient is unable to recieve *ALL components* of study therapy (i.e: BV as well as A, V, and D) > 4 weeks (for any reason), then patient must go off protocol treatment.

For toxicity-related modifications beyond Cycle 1, suggested dose modifications of brentuximab vedotin are as follows:

Intrapatient Dose Modification for Brentuximab

Dose Level	Brentuximab vedotin Dose
1	1.2 mg/kg (max 120 mg)
–1	0.9 mg/kg (max 90 mg)

Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption. For toxicities that can be treated or prevented, such as nausea, vomiting, diarrhea and neutropenia, treatment may be resumed at the previous dose once supportive measures have been instituted and toxicity recovers to Grade 2 or less.

For additional information on dose management, please see also Dosing and Administration Guide for brentuximab vedotin in cHL at: http://www.seattlegenetics.com/application/files/6515/4238/3292/adcetris_USPI.pdf.

The following table summarizes brentuximab vedotin dose modifications.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Allergic reactions **or** **Acute infusional reactions/ cytokine release syndrome**	Grade 1-2	For first reaction: • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity). • Treat reactions with diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. Depending on the reaction severity, dexamethasone 0.2 mg/kg (max 10 mg) IV, or other systemic corticosteroid per institutional standard, should be used. • Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered. Dosing of brentuximab vedotin should be administered at half of the previously administered rate. For subsequent doses: • Utilize diphenhydramine with or without acetaminophen as pretreatment for all subsequent infusions. • Dosing should be administered over the shortest period that was well tolerated. If Grade 1-2 infusion reactions recur despite the above measures, either during re-challenge or subsequent treatments: • Take the measures outlined above. • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10mg) IV or equivalent to medications above prior to infusion.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Allergic reactions **or** **Acute infusional reactions/ cytokine release syndrome**	Grade 3	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. • Once symptoms recover, brentuximab vedotin should not be resumed for that course. • Subsequent courses of brentuximab vedotin may be considered at physicians' discretion, after approval by the Study Chair. • All subsequent infusions should use the following pre-medications prior to infusion, diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent). In addition, the infusion should be administered at 50% of the previous infusion rate. If necessary, corticosteroids (up to 25 mg of methylprednisolone or equivalent) may be used if premedication with diphenhydramine and acetaminophen is not sufficient to prevent infusion reactions.
	Grade 4	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated. • Epinephrine or bronchodilators should be administered as indicated. • Hospital admission for observation may be indicated. • Discontinue brentuximab vedotin.
Anaphylaxis	Any Grade	If anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy.
Peripheral Neuropathy	Grade 1	No change.
	Grade 2	• Reduce dose to 0.9mg/kg (max 90 mg) and resume treatment; if already at 0.9mg/kg continue dosing at that level.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Peripheral Neuropathy	Grade 3	• Treatment should be delayed until neuropathy improves to Grade 2 or lower. • Once improved to grade 2 or lower, brentuximab vedotin should be reduced to 0.9mg/kg and treatment should be resumed. • Patients who develop grade 3 neuropathy after dose reduction of brentuximab vedotin to 0.9mg/kg should have brentuximab vedotin discontinued. • In the setting of Grade 3 peripheral neuropathy (e.g., obstipation, weakness), that persists/occurs despite discontinuation of BV, the dose of vinblastine will be reduced by 50% for all further cycles of AVD
	Grade 4	• Discontinue brentuximab vedotin. • In the setting of Grade 4 peripheral neuropathy (e.g., obstipation, weakness), that persists/occurs despite discontinuation of BV, vinblastine will be omitted from all future cycles of AVD.
Pneumonitis	Grade 1	No change.
	Grade 2	If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. Upon occurrence of pneumonitis, study therapy should be held, and notify the Study Chair within 48 hours.
	Grade 3-4	If suspected, strongly consider administration of 100 mg of oral prednisone or intravenous methylprednisolone (1 mg/kg IV every 12 hours) in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. **Discontinue brentuximab vedotin.** Upon occurrence of pneumonitis, study therapy should be held, and notify the Study Chair within 48 hours.
Abnormal liver function (AST/ALT, Total bilirubin, immune-related hepatitis)	≤ Grade 1	No change.
	Grade 2	• If the bilirubin rises to > 2 x ULN (but ≤ 5 x ULN), the doxorubicin and vinblastine doses must be reduced by 50% of last dose received to avoid undue hepatic toxicity. Full doses should be given once the bilirubin is ≤ 2 x ULN.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Abnormal liver function (AST/ALT, Total bilirubin, immune-related hepatitis)	Grade 3-4	• AVD management: If the bilirubin rises to ≥ 5x ULN, then hold doxorubicin and vinblastine. • Withhold doxorubicin and vinblastine dose until ≤ Grade 2 or has returned to baseline. • BV management: Dose reduction of brentuximab vedotin to 0.9mg/kg can be considered. • If recurs after BV dose reduction, discontinuation of brentuximab vedotin can be considered.
Progressive Multifocal Leukoence-phalopathy (PML)	Any Grade	If PML is suspected, a diagnostic work-up should be performed. The workup may include, but is not limited to the following: • Neurologic examinations and neurology consultation, as warranted. · • Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect. • PCR analysis. JCV DNA, detectable in CSF or in a brain biopsy, is suggestive of PML. Brentuximab vedotin dosing should be held if PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued.
Febrile Neutropenia, Sepsis, Infections or infestations	Grade 1-2 (only pertains to infection/infestation)	No change.
	Grade 3	• Hold protocol therapy until ≤ Grade 2. • If using daily filgrastim (rather than pegfilgrastim), additional doses beyond days 6-10 should be administered in subsequent cycles. • Consider prophylaxis with antibacterial therapy for subsequent cycles. • First occurrence - continue at same dose level. • Second occurrence – Consider dose reduction to 0.9mg/kg (max 90 mg) of brentuximab vedotin. • Additional occurrence – – If brentuximab vedotin has already been dose reduced, consider discontinuation of brentuximab vedotin. • If febrile neutropenia recurs despite brentuximab vedotin dose reduction or discontinuation, it is allowable to decrease the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician. •

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Febrile Neutropenia, Sepsis, Infections or infestations	Grade 4	• Hold protocol therapy until ≤ Grade 2. • If using daily filgrastim (rather than pegfilgrastim), additional doses beyond days 6-10 should be administered. • Consider prophylaxis with antibacterial therapy for subsequent cycles. • First occurrence - consider dose reduction to 0.9mg/kg (max 90 mg) of brentuximab vedotin. • Second/repeated occurrence – if brentuximab vedotin has already been dose reduced, discontinuation of brentuximab vedotin is recommended. • If febrile neutropenia recurs despite brentuximab vedotin dose reduction or discontinuation, it is allowable to decrease the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician.
Hematol-ogic (excluding lympho-penia)	Grade 1-2	No change.
	Grade 3-4	• No change required. • For neutropenia, if using daily filgrastim (rather than pegfilgrastim), additional doses beyond days 6-10 and 21-25 can be considered. • For anemia, manage per institutional guidelines. Erythrocyte transfusion is allowable. • For thrombocytopenia, consider platelet transfusion and/or manage per institutional guidelines. Delay of brentuximab vedotin for Grade 4 thrombocytopenia may be considered at the investigator's discretion.
Non-hematol-ogic events (not including electrolyte abnormaliti es or others not specifically outline above, e.g. neuropathy)	Grade 1-2	No change.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline. • Dose reduction of brentuximab vedotin to 0.9mg/kg (max 90 mg) can be considered. • If non-hematological Grade 3-4 toxicity recurs after one dose reduction, discontinuation of brentuximab vedotin should be considered.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Electrolyte abnormal-ities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected. • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption but should receive appropriate medical therapy.

8.3 Dose Modification Contacts

For treatment or dose modification questions, please contact:

- Adults: E-mail: S1826USAdults@swog.org or call: Dr. Alex Herrera (SWOG) at Phone: 626/256-4673 ext. 62405 or Dr. Sarah Rutherford (Alliance) at Phone: 646/962-2064 or Dr. Andrew Evens (ECOG-ACRIN) at Phone: 732-235-9289.

- Pediatrics: E-mail: S1826pediatrics@swog.org. or call: Dr. Sharon Castellino at Phone: 404/785-3616 or Dr. Angela Punnett at: Phone: 416/813-5394.

- CCTG Adults: Dr. Kelly Davison at: E-mail: kelly.davison@mcgill.ca or Phone: 514/934-1934, ext 31558 or Dr. Michael Crump at: Michael.Crump@uhn.ca or Phone: 416/946-4567.

8.4 Adverse Event Reporting /Serious Adverse Event Reporting Guidance

Please Note: This protocol utilizes Rave® / Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration for expedited reporting of serious adverse events. The CTEP-AERS integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and

- AEs are recorded and complete (no missing fields) and the form is query free (fields added to the form during study build do not need to be query free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

If you have questions about this process, please contact the SAE Program Manager 210-614-8808 or email adr@swog.org.

The CTEP-AERS electronic reporting system “Help” feature has detailed instructions in the section "Submitting Reports for RAVE Users".

8.5 COVID-19 Adverse Event Reporting Requirements:

Per the NCI “Guidance for Collection of Adverse Events Related to COVID-19 Infection,” accessible from: https://ctep.cancer.gov/content/docs/Adverse_Event_Guidance_COVID-19_Final_3-25-20.pdf, any known COVID-19 infection should be reported as an adverse event (and if applicable via CTEP-AERS).

8.6 Serious Adverse Event Reporting Requirements

a. Purpose

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (FDA, 21 CFR 312.32). See Table 8.1 for definition of a Serious Adverse Event (SAE) and reporting requirements.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported to the SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.1.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 8.1) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report via CTEP-ARS within the number of calendar days of learning of the event specified in Table 8.1.

Some adverse events require 24-hour notification (refer to Table 8.1) via CTEP-AERS.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

d. Other recipients of adverse event reports

CTEP will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 8.1.

The investigational agent used in Arm 1 of this study is Nivolumab (BMS-936558, MDX1106, Opdivo®).

If there is any question about the reportability of an adverse event or if internet connectivity is disrupted, please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.1.

Table 8.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] [Nivolumab (BMS-936558, MDX1106, Opdivo®)] [Arm 1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 8.6f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:**

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested by the SAE Program Manager, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006.

2. **PRO-CTCAE**

Clinician-graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items, but no protocol directed action will be taken. The study-specific S1826 PRO-CTCAE items can be found on the forms section of the CTSU S1826 protocol webpage.

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 8.2. The commercial agent(s) used in Arms 1 and 2 of this study are Doxorubicin hydrochloride, Dacarbazine and Vinblastine sulfate.

The commercial agents used in Arm 2 of this study are filgrastim, pegfilgrastim, and SGN-35 (brentuximab vedotin).

If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.2.

Table 8.2. Expedited reporting requirements for adverse events experienced by patients on study Arm 1 and Arm 2 who have received the commercial drug(s) listed in Section 8.6g above within 30 days of the last administration of the commercial agent(s).

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event [b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.
   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP by fax at 301-897-7404 in accordance with instructions provided by the CTEP-AERS system. Supporting documentation must also be submitted to SWOG Operations Office by fax to 210-614-0006.

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy.** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss.** Pregnancy Loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy Loss" under the Pregnancy, puerperium and perinatal conditions SOC**.

   A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal.** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as Grade 4 **"Death neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

9.0 STUDY CALENDAR

9.1 Treatment Calendar

REQUIRED STUDIES	PRE REG	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		After last dose of study drug [m]	End of Tx Assess 4-8 wks after last dose of study drug	4-8 wks after either the last dose of study drug or last dose RT, whichever is later
		D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15			
History and Targeted Physical [p] (including wt.)	X	X		X		X		X		X		X			X	
Performance Status	X	X		X		X		X		X		X			X	
Disease Assessment	X														X	
Toxicity Notation [q]		X		X		X		X		X		X		X	X	
PRO-CTCAE [a]		X		X		X		X		X		X		X		
LABORATORY																
TSH [b]		X				X				X					X	
CBC/Differential/Platelet [c]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
CMP [d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Pregnancy Test	X														*(X)* [o]	
HIV viral load and CD4 count [e]	*(X)*															
X-RAYS AND SCANS																
PET-CT [f]	X					*(X)*[i]									X	
ECHO, MUGA, or functional cardiac imaging scan [g]	X															
IMAGING SUBMISSION																
PET-CT [h]	X					*(X)*[i]									X	
SPECIMEN SUBMISSION																
FFPE diagnostic tissue [j]	X															
Peripheral Blood (Streck) [k]		X				X								X		
QOL SUBMISSION [l]																
PROMIS-Global	X					X										X
PROMIS-Fatigue	X					X										X
FACT/GOG-Ntx	X					X										X
TREATMENT [n]																
ARM 1:																
Nivolumab		X	X	X	X	X	X	X	X	X	X	X	X			
AVD		X	X	X	X	X	X	X	X	X	X	X	X			
ARM 2:																
Brentuximab Vedotin		X	X	X	X	X	X	X	X	X	X	X	X			
AVD		X	X	X	X	X	X	X	X	X	X	X	X			

Click here for footnotes.

NOTE: Forms are found on the protocol-specific page of the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in the SWOG Best Practices document accessible from the "Best Practices" link at: https://www.swog.org/clinical-trials/protocol-workbench.

[a] PRO-CTCAE or Ped PRO-CTCAE questionnaire, based on patient age with adult ≥ 18 and pediatric 12-17 years, must be completed on Day 1, prior to beginning treatment (for English-, Spanish- and French- speaking adult and English-speaking pediatric patients). All subsequent PRO-CTCAE questionnaires must be completed within a +/- 7-day window of the indicated timepoint. See also Section 15.6 for administration instructions.

[b] For patients randomized to Arm 1 (N-AVD), TSH must be performed at baseline and then every 4-8 weeks prior to the start of the cycle, as clinically indicated. Results of the baseline TSH test does not determine eligibility but is performed prior to initiating treatment for Arm 1 patients only, in order to obtain baseline measurements.

[c] Allowable window for CBC with differential is within 3 days prior to start of Cycles 1-6 and must include: WBC count, hemoglobin, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC). See also Section 7.1b for extended allowable windows in event of COVID-19 extenuating circumstance.

[d] Allowable window for CMP is within 3 days prior to start of Cycles 1-6 and must include: electrolytes (sodium, potassium, chloride, bicarbonate (CO2)), albumin, serum or plasma creatinine or calculated creatinine clearance, and liver function tests (total bilirubin, SGOT [AST], SGPT [ALT], alkaline phosphatase). See also Section 7.1b for extended allowable windows in event of COVID-19 extenuating circumstance.

[e] Required within 6 months prior to registration for patients who are known to be HIV-positive.

[f] A contrast-enhanced (diagnostic) CT, MRI or MR-PET is acceptable in event that PET-CT is contra-indicated, however if it is later possible to administer a PET-CT, then PET-CT is strongly preferred for the interim scan (after Cycle 2) (if performed) and the EOT assessment. Otherwise, if PET-CT is not subsequently possible, then the same modality as baseline must be used throughout the trial.

[g] For Patients Randomized to Arm1 (N-AVD): Recommended cardiac monitoring includes: EKG, ECHO, CPK & Troponins to be done within 3 days prior to Day 1 of each Cycle, as clinically indicated for patients who: 1) develop CHF, 2) are deemed at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs, or 3) have evidence of CHF or MI, cardiomyopathy, or myositis cardiac evaluation (NYHA I/II). See also Section 7.3a.

[h] See also: Sections 14.4 and 15.4. NOTE: If patient goes off protocol treatment early the EOT PET-CT must still be collected/submitted at 4-8 wks after the last dose of study drug.

[i] All pediatric patients and all patients who were declared (at date of registration) intent to treat with EOT Residual PET RT must have a standard of care PET-CT on Day 53 (+/-3 days) (after Cycle 2/Day 15 and prior to the start of Cycle 3).

[j] 1 FFPE block or 1 H&E slide required per Section 15.1 for pathology review. At same timepoint, with patient's consent, tissue must be collected for banking per Section 15.2.

[k] With patient's consent, peripheral blood must be collected per Section 15.2.

[l] Patient-reported outcome instruments are required at Baseline for patients who can complete the forms in English, Spanish, or French and must also be administered to these patients at the required follow-up time points (timing based on registration date). If a patient refuses or cannot complete the patient questionnaires at any time point, he or she should be asked to do so at the next scheduled assessment time. Note that there are two age-based versions of the PROMIS measures for adults 18+ and for pediatric patients age 12-17 years. See also Sections 14.4 for data submission and 15.5 for administration instructions.

[m] If patient goes on to receive RT, then toxicity and PRO-CTCAE assessments must be performed after administration of both the last dose of study drug and after last dose of radiation therapy.

[n] End of treatment Residual PET RT is allowable for eligible patients, as indicated in Section 7.5.

[o] Females of childbearing potential who will receive radiation therapy per protocol must have a standard of care pregnancy test, prior to start of radiation therapy.

[p] Targeted H&P with systems examined as per the treating physician discretion (must include weight).

[q] See Section 8.6 for SAE reporting requirements. Note: If a patient experienced a severe (Grade ≥3) adverse event that is possibly, probably or definitely related to protocol treatment that was not previously reported in RAVE, report SAE on the **S1826** Late Adverse Events Form (Section 14.4).

9.2 Follow-up After Off-Protocol Treatment

REQUIRED STUDIES	Follow-up Prior to Progression [a]									At Prog	FUP Post-Prog
	3-6 mos after reg (if off-Tx early)	9 mos after reg	End of RT	12 mos after reg	18 mos after reg	24 mos after reg	30 mos after reg	36 mos after reg	Y4 - Y10		
History and Targeted Physical Exam [b] (including weight)	X	X		X	X	X	X	X	X	X	X
Performance Status	X	X		X	X	X	X	X	X	X	X
Disease Assessment				X		X					X
Toxicity Notation [c]	X	X	X	X	X	X	X	X	X	X	
PRO-CTCAE [d]	X	X	X	X	X	X	X	X			
X-RAYS AND SCANS											
PET-CT			*(X)* [h]							X	
CT *(or MRI)* [e]				X		X					
SPECIMEN SUBMISSION											
FFPE diagnostic tissue [f]										X	
Peripheral Blood (Streck) [f]										X	
QOL SUBMISSION [g]											
PROMIS-Global				X				X			
PROMIS-Fatigue				X				X			
FACT/GOG-Ntx				X				X			

NOTE: Forms are found on the protocol-specific page of the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in the SWOG Best Practices document accessible from the "Best Practices" link at: https://www.swog.org/clinical-trials/protocol-workbench.

[a] Every 3 months (+/- 7 days) for the first year, then every 6 months (+/- 7 days) for the second and third year, then annually (+/-14 days) until 10 years from the date of registration or until time of progression. See also Section 7.1b for extended allowable windows in event of COVID-19 extenuating circumstance.

[b] Targeted H&P with systems examined as per the treating physician discretion.

[c] See Section 8.6 for SAE reporting requirements. Note: If a patient experienced a severe (Grade ≥3) adverse event that is possibly, probably or definitely related to protocol treatment that was not previously reported in RAVE, report SAE on the **S1826** Late Adverse Events Form (Section 14.4).

[d] PRO-CTCAE assesssments must be collected within +/- 7 days of timepoints indicated above. **The scheduled follow-up PRO-CTCAE assessments should coincide with the physician-directed toxicity assessment and must be completed even if the patient goes off protocol treatment early for any reason or if a patient is deemed ineligible for any reason until such time that the patient starts a subsequent non-protocol anti-cancer therapy.** See also Section 15.6 for administration instructions.

[e] All patients must have a contrast-enhanced CT scan of chest, abdomen and pelvis (+ neck or other involved areas, if involvement at baseline) (or if contra-indicated, CT, MRI, or MR-PET) at 1 and 2 years after registration (+/- 14 days). See also Section 7.1b for extended allowable windows in event of COVID-19 extenuating circumstance.

[f] With patient's consent, peripheral blood and tissue must be collected per Section 15.2.

[g] **The scheduled follow-up PRO assessments must be completed even if the patient goes off protocol treatment early for any reason or the patient progressed or if a patient is deemed ineligible for any reason.** If a patient refuses or cannot complete the patient questionnaires at any time point, he or she should be asked to do so at the next scheduled assessment time. See also Sections 14.4 for data submission and 15.5 for administration instructions.

[h] Patients who receive Residual PET RT, per Section 7.5, (ONLY) must have a PET-CT (or if contra-indicated, CT, MRI, or MR-PET) within 8-12 weeks after completion of radiation therapy.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

Response and progression will be evaluated in this study using the revised international working group guidelines (Lugano classification) *(101)*.

10.1 Measurement of Treatment/Intervention Effect

a. Target Lesions & Target Lymph Nodes

FDG avid lesions: Up to five of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly FDG avid. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

PET 5-Point Scale / Deauville score:

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

b. Metabolic Response at the end of Cycle 6 or end of treatment.

1. Complete Metabolic Response (CR) (as defined by all the following):

a. Deauville Score of 1, 2, or 3 with or without a residual mass or nodal lesion:

- 1, no FDG uptake above background;
- 2, FDG uptake ≤ mediastinum;
- 3, FDG uptake > mediastinum but ≤ liver.

b. In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.

c. No new lesions.

d. No evidence of FDG avid disease in marrow unless as noted in Section 10.1b.1b.

e. In the event that a bone marrow biopsy is performed at baseline and the patient had evidence of marrow involvement by bone marrow biopsy at baseline, a repeat marrow will be required to confirm CR. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR.

2. Partial Metabolic Response (PR) (as defined by all the following):

   a. Deauville Score of 4 or 5 with reduced uptake compared to baseline and residual mass(es) of any size.

   b. No new lesions.

   c. In the event that a bone marrow biopsy is performed at baseline: Residual marrow uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with a BM biopsy.

3. No Metabolic Response (SD) (as defined by all the following):

   a. Deauville Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment.

   b. No new lesions.

   c. No change in marrow uptake from baseline.

4. Progressive Metabolic Disease (PD) (as defined by any of the following):

   a. Deauville Score 4 or 5 with an increase in intensity of uptake from baseline.

   b. New FDG-avid foci consistent with lymphoma.

   c. New or recurrent FDG-avid foci in the bone marrow.

   * For patients who are contra-indicated for PET-CT, see Section 18.7 for Measurement-based Response Assessment According to the Lugano Classification.

10.2 **Best Response:**

a. CR: One objective status of CR documented before relapse.

b. PR: One objective status of PR documented before progression but not qualifying as a CR.

c. Stable: At least one objective status of stable documented at least 6 weeks after registration, not qualifying as anything else above.

d. Increasing Disease: Objective status of progression.

e. Inadequate assessment, response unknown: No other response category applies.

10.3 Performance Status

See also Section 18.4.

a. Patients ≥ 18 years of age will be graded according to the Zubrod performance status scale:

GRADE	SCALE
0	Fully active; able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

b. Patients ≤ 17 years of age will be graded according to the Lansky play-performance scale for pediatric patients. *The conversion of the Lansky to Zubrod scale is intended for NCI reporting purposes only. See Section 18.4.

This scale is rated by parents based on their child's activity over the past week. Parents fill out the assessment based on the directions on the form, and the form is re-administered over time to assess for changes in performance status.

An excerpt of the relevant directions for parents is as follows:

"Think about your child's play and activity over the past week. Think about both good days and bad days. Average out this period. Now read the descriptions and pick the one that best describes your child's play during the past week."

RATING	DESCRIPTION
100	Fully active, normal
90	Minor restrictions with strenuous physical activity
80	Active, but gets tired more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	Stuck in bed; needs help even for quiet play
20	Often sleeping; play is entirely limited to very passive activities
10	Does not play nor get out of bed
0	Unresponsive

10.4 **Progression Free Survival** (PFS)

From date of registration to date of first observation of progressive disease according to the 2014 Lugano classification, or death due to any cause. Patients last known to be alive and without report of progression are censored at date of last contact. See Sections 10.1b.4 and 18.7 for definition of progressive disease according to 2014 Lugano classification.

10.5 **Event Free Survival** (EFS)

From date of registration to date of first occurrence of EFS event. Patients last known to be alive and without EFS event are censored at date of last contact.

EFS Events are defined as:

- Disease progression/relapse
- Administration of non-protocol specified systemic anti-lymphoma therapy (i.e. salvage therapy) at any time after initiation of protocol therapy.
    - Administration of non-protocol specified systemic anti-lymphoma therapy for residual or relapsed Hodgkin lymphoma (whether or not confirmed by biopsy) in the absence of formal progression of disease according to the Lugano classification

- Administration of any non-protocol specified radiation therapy at any time after initiation of protocol therapy:
    - Administration of radiation therapy in a patient who was not declared eligible for radiation therapy at registration
    - Administration of radiation in a patient who was declared eligible for radiation therapy but does not meet protocol-specified criteria for use of radiation (refer to Section 7.5).

10.6 **Time to Death**

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Analysis and Power Justification

The primary endpoint is progression free survival (PFS).

Based on previous data, the 2-year PFS for the control arm (Arm 2) is estimated to be approximately 84%. Prior PFS data in patients with advanced stage Hodgkin lymphoma indicates that a proportion of patients may be long-term non-progressing patients. An exponential cure rate model is assumed for both arms with 70% long term non-progressing patients on the control arm (Arm 2) and 74% on the experimental arm (Arm 1). In addition, among the fraction of patients with disease progression, a hazard ratio of 1.67 is assumed between the arms. The BV-AVD control arm (Arm 2) PFS model is written that the PFS at year t is equal to 0.70+0.30*exp(-0.38t) and .74+ .26*exp (-.38t/1.67) for the N-AVD experimental arm (Arm 1). The power calculations are based on the log-rank based testing on simulated data sets from the survival cure models described above. At the end of study, this corresponds to an average hazard ratio (based on 10,000 simulated hazard ratios from the Cox model) of 1.58.

940 eligible patients are expected to be accrued over 4 years with a total of 987 patients assuming an expected ineligible rate of 5% (6% of enrolled patients deemed ineligible due to central pathology review on **S0816**). The analysis is event-based and planned after achieving 179 events across arms, that will be reached at approximately 2 additional years of follow-up. The power to detect a change in time-to-event PFS outcomes corresponds to a 2-year PFS in the control arm (Arm 2) of 84% and a 2-year PFS of 90% in the experimental arm (Arm 1) of 86%. The power calculations assume uniform patient entry and a one-sided stratified log-rank test at 2.5% significance level.

Sensitivity analyses of above will be performed where PFS is censored/not-censored at the time of start of non-protocol therapy.

11.2 Interim Analysis

For early reporting, interim analyses will be conducted when 25%, 50% and 75% of anticipated progressions or deaths in the pooled across arms have been observed. This under the alternative hypothesis this approximately corresponds to 58%, 85% of accrual and six months after completing full accrual. Evidence suggesting early termination for of the study would be if the alternative hypothesis of a greater than average hazard ratio control vs. experimental hazard ratio of 1.58 is rejected at a one-sided .5% level at the first interim analysis, and 1% level at second or later of the interim analyses. At the second interim analysis testing would approximately correspond to observing a hazard ratio favoring the control of approximately .96. The conservative first interim analysis acknowledges the potential late therapeutic effect of the experimental arm relative to the control arm. The timing of interim analyses will be based the combined number of PFS events across arms. At full information or the time of primary analysis will occur when 179 PFS events have been observed.

Interim Analysis	Information	One-sided Futility p-value	One-sided superiority P-value
1	25%	.002	NA
2	50%	.01	.005
3	75%	.01	.005

At the second two interim analyses superiority testing will be conducted at the .5% level.

Final Analysis Plan: If the trial is not stopped early, the final analysis will test the null hypothesis (HR=1) for PFS using stratified log-rank test with a one-sided alpha of 0.021. The strata used in the stratified log-rank test are those defined and coded as in Section 6.0 in the dynamic balancing randomization scheme utilized for the study. The variables include: Age (years): age 12-17 vs. age 18-60 vs. age > 60, International prognostic score: 0-3 vs. 4-7 and Pre-specified plan to use Residual PET Radiation Therapy (Residual PET RT)*: yes vs. no. The analysis will be based on modified intent-to-treat and will include all eligible patients as randomized regardless of treatment received. The one-sided alpha of .021 will control of the overall type-one error of the study (including the 2 interim superiority analyses) to be less than .025. The final analysis type-1 error calculations were based simulation studies using the information times specified in the interim analysis schedule and interim analysis specified superiority p-value testing.

RT monitoring: The use of RT will almost exclusively be on the pediatric population, but due to the concern appropriate use in N-AVD arm given the potential of false progressions, it will be monitored closely throughout the study. The DSMB will be provided rates of radiotherapy used in each arm (and within the 12-17 years and ≥ 18 years age groups in each arm) for each meeting. The committee will monitor the rate of radiotherapy in both arms and by age group to ensure that there is no overuse in the experimental arm (Arm 1). Due to variability in early event calculations focus on this analysis will not commence until after 30 patients have completed RT. At that point, if there is greater than 15% difference between arms, then the additional communication to NCI and study team for protocol amendment would be considered. This substantive threshold for action in rates is motivated by limited sample sizes and by a slightly higher expected baseline rate of RT use in the N-AVD arm based on the ECHELON-1 and CheckMate 205 studies. If after 75 patients have received RT, then a smaller difference (10%) would be considered a concern and warrant additional discussion with NCI and the study team. We will apply the same rules to RT differences within each age group in each arm.

11.3 Analysis of Secondary Endpoints

Secondary endpoints include overall survival (OS), event-free survival (EFS), metabolic complete response (CR) rate, safety and tolerability.

A key secondary endpoint for the study is OS. Based on previous data, the estimated 2-year OS in the control arm (Arm 2) was 96%. We assume that overall survival in the experimental arm (Arm 1) will follow an exponential distribution, with 4 years of accrual, 2 additional years of follow-up, a stratified log-rank test at two-sided alpha level of .05 will have 90% power to detect a hazard ratio of 2.8 (corresponds to an improvement of OS from 96% in the control arm (Arm 2) to 98.5% in the experimental arm (Arm 1)). A total of 61 OS events (deaths) are required for the final analysis.

Event free survival (EFS) will be estimated using Kaplan-Meier method and compared between treatment arms using cox regression model. Based on the estimated 2-year modified PFS of 82% in the control arm (Arm 2), and the average hazard ratio 1.54, we anticipate at least 195 events under the alternative hypothesis. With 940 eligible patients, the hazard ratio can be estimated to within ±0.28 (95% confidence).

Metabolic complete response is defined using 2014 Lugano classification. In the previous study, the CR rate was 86% at the end of frontline therapy for BV-AVD, but the estimate might include BEACOPP and/or radiation therapy. We assume that the CR rate is 83% for BV-AVD alone, with 940 eligible patients, a binomial test at one-sided alpha level of .025 will have 92% power to detect an increase in CR rate from 83% in the control arm (Arm 2) to 90% in the experimental arm (Arm 1).

Toxicity will be evaluated using the CTCAE Version 5 items. Eligible patients receiving at least one dose of drug will be included in the assessment of adverse events by treatment arms. The maximum Grade for each toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. With 470 eligible patients in each arm, any toxicity with at least 4% prevalence has at least a 90% chance of occurring within an arm. Toxicity rates in each arm can be estimated to within at least ± 4.5% with 95% confidence. Treatment-related toxicities between arms will be compared using Fisher's exact test stratified by age groups.

Targeted patient-reported toxicities also will be collected at each time point (see Sections 9.1 and 9.2), using the PRO-CTCAE for patients 18 years and older and from youth 12-17 years, using the Ped PRO-CTCAE.

Safety Monitoring: The CTEP IDB Drug Monitor, **S1826** study chairs, statisticians and data coordinator(s) will review aggregate adverse event rates by arms on a monthly basis, and serious adverse events immediately after receiving notification. Additionally, special summary reports will be run more frequently to evaluate adverse events in both arms for the first six weeks of the treatment regimen to ensure that there is no significant increase in adverse events in the combination arm of chemotherapy and immunotherapy. Conference calls will be scheduled to discuss these data as needed.

11.4 Interim Safety Analysis

In addition to ongoing toxicity monitoring and every DSMC meeting, after 6 months after approximately 125 patients have been registered to each arm and again concurrently with each interim efficacy analyses, there will be an additional interim assessment death or discontinuation of all components of BV+AVD or N+AVD prior to the protocol-specified completion of all components of BV+AVD or N+AVD due to an adverse event. If there is an absolute difference of a 5% rate of death or complete discontinuation of all components of BV+AVD or N+AVD due to adverse events in the experimental arm (Arm 1) versus Arm 2, then the consideration of temporarily closing the study to accrual pending a decision by the DSMC as to whether to continue accrual. We note that we will also present data on deaths separate to treatment discontinuation to the DSMC. We will present all deaths to treatment, and deaths within 30 days of completing therapy. If the decision is to re-open accrual, this will require a protocol amendment and will include justification for continued accrual and for any treatment regimen modifications. In addition, due to the absence of published data using N-AVD in the pediatric population, a toxicity review will be conducted after the first 10 patients who are 12-17 years of age are enrolled to Arm 1. A teleconference will be planned to discuss the AEs in this group of patients, the participants are expected to include SWOG and COG Study Chairs, Disease Committee Chair, SWOG executive officer, Study Statisticians and NCI CTEP representation.

11.5 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistics and Data Management Center and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study. PRO-CTCAE data should not be used in adverse event stopping rules.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

All patients registered to this study will undergo retrospective pathology review. The purpose of this review is to verify histologic diagnosis.

See Sections 14.4a and 14.4b for associated forms and pathology report submission instructions. See Section 15.1 for required tissue submission instructions.

Pathology review will be coordinated by SWOG.

In the event that a patient is deemed ineligible due to pathology review results, the patient will not be evaluated for the primary or secondary endpoints.

12.2 Radiology Review

All patients registered are planned to undergo retrospective PET-CT review. The purpose of this planned review will be to retrospectively verify disease stage at study entry, response at Cycle 2 (in patients who undergo interim imaging per standard of care), end-of-treatment response, and to retrospectively confirm patient eligibility for Radiation Therapy per criteria indicated in Section 7.5.

See Section 15.4 for required image submission instructions.

If participating sites would like assistance with interpretation of pediatric radiology results, pediatric courtesy reviews are available by contacting Sandy Kessel at IROC Rhode Island via E-mail at: SKessel@qarc.org.

Radiology Courtesy Reviewers for Pediatric Patients:

Drs. Lai and Mhlanga will be serving as Radiology Courtesy reviewers for pediatric patients enrolled to **S1826**. **To request courtesy review, contact IROC at contact information listed above.**

Hollie A. Lai, MD
Children's Hospital of Orange County,
Department of Radiology,
1201 W. La Veta Ave,
Orange, CA 92868
Phone: 714/509-9160
Email: hlai@choc.org

Joyce Mhlanga, MD
Mallinckrodt Institute of Radiology
510 South Kingshighway Boulevard,
St. Louis, MO 63110
Phone: 314/362-2809
Email: jmhlanga@wustl.edu

12.3 Radiation Therapy Review

Radiotherapy (RT) for patients can only be delivered at approved RT facilities. Pre-treatment Review of Radiation therapy plans will be conducted by IROC Rhode Island.

Data detailed in Section 14.4h below must be submitted to IROC Ohio (via TRIAD preferred) per instructions in Section 15.4 one week prior to the planned start of Radiation Therapy for review and approval.

IROC Rhode Island will verify that the patient meets protocol-specified RT criteria indicated in Section 7.5b and will confirm eligibility for RT with the treating investigator or notify the investigator in the event that the patient does not meet protocol-specified criteria for RT. In the event that IROC Rhode Island RT interpretation differs from local participating site interpretation, the case will be forwarded to at least one of two expert reviewers for final confirmation.

This RT QA review will also confirm sites of partial response which will require radiation.

Any radiation therapy delivered not consistent with the RT QA review response categorization will be considered a major protocol deviation.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Initiation of treatment must be planned to start **no more than 14 calendar days after registration.**

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a participating Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

13.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principle Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

13.4 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

a. **IRB Approval:**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

b. **Protocol-Specific Requirements For S1826 Site Registration**

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process. See also Section 18.6d.

c. **Downloading Site Registration Documents:**

Download the site registration forms from the **S1826** protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password
- Click on ***Protocols*** in the upper left of your screen
  - Enter the protocol # in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select **SWOG** protocol number **S1826.**
- Click on ***Documents*****,** select ***Site Registration***, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

d. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log in to the CTSU members' website (www.ctsu.org), go to the ***Regulatory*** section and select ***Regulatory Submission***

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 in order to receive further instruction and support.

e. **Checking Your Site's Registration Status:**

Site registration status may be verified on the CTSU members' website.

- Click on ***Regulatory*** at the top of the screen
- Click on ***Site Registration***; and
- Enter the site's 5-character CTEP Institution Code and click on ***Go***
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

f. **Delegation of Task Log (DTL)**

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

13.5 OPEN Registration Requirements

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN tab on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID
b. Protocol Number
c. Registration Step
d. Treating Investigator
e. Credit Investigator
f. Patient Initials
g. Patient's Date of Birth
h. Country of Residence
i. ZIP Code
j. Gender (select one):
   - Female Gender
   - Male Gender
k. Ethnicity (select one):
   - Hispanic or Latino
   - Not Hispanic or Latino
   - Unknown
l. Method of Payment (select one):
   - Private Insurance
   - Medicare
   - Medicare and Private Insurance
   - Medicaid
   - Medicaid and Medicare
   - Military or Veterans Sponsored NOS
   - Military Sponsored (Including Champus & Tricare)
   - Veterans Sponsored
   - Self Pay (No Insurance)
   - No Means of Payment (No Insurance)
   - Other
   - Unknown
m. Race (select all that apply):
   - American Indian or Alaska Native
   - Asian
   - Black or African American
   - Native Hawaiian or other Pacific Islander
   - White
   - Unknown

13.6 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. **For COG Credited Enrollments ONLY**: Prior to enrollment on this study, patients enrolling must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

e. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.7 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS AFTER REGISTRATION:

Submit the following:

- Vital Status Form
- **S1826** Onstudy Form
- Baseline Tumor Assessment Form
- Pathology Report
  (NOTE: Upload reports via the Source Documentation Baseline Form in Rave®.)
- Submit radiology reports from all PET-CT, contrast-enhanced CT, MRI, or MR-PET scans performed to assess disease at baseline. (NOTE: Upload reports via the Source Documentation Baseline Form in Rave®.)
- **S1826** Imaging Adjunctive Data Sheet.
  This form is submitted electronically via the IROC website for PET scans; If PET scan is contraindicated and CT or MRI is submitted, the **S1826** Imaging Adjunctive Data Sheet is not required. Go to: https://wrightcenterofinnov.qualtrics.com/jfe/form/SV_cC0Pih8vSYcCnfU, then click on the arrow at the bottom of the screen to move to the screen with form questions, complete the form (clicking on arrows at bottom of screen to get to next page of questions), then click “submit”. Participating sites have the ability to save a copy of the submitted form responses by clicking “Download PDF” after submitting the form.
- All PET-CT images (or if PET-CT contraindicated, then all contrast-enhanced CT, MRI or MR-PET) from scans performed as standard of care to assess disease within 42 days prior to registration. Submit to IROC Ohio (via TRIAD strongly preferred) for retrospective central imaging review.

b. WITHIN 28 DAYS AFTER REGISTRATION:

Submit the following:

- Specimens as outlined in Sections 15.1 and 15.2.
- **S1826** Pediatric PROMIS Global Health 7+2 (Pediatric) or **S1826** PROMIS-Global Health (Adults)
- **S1826** Pediatric PROMIS Fatigue 10a (Pediatrics) or S1826 PROMIS Fatigue 7a (Adults)
- **S1826** FACT/GOG-Ntx (Pediatric and Adult)
- **S1826** Cover Sheet for Patient-Completed Questionnaires or S1826 Cover Sheet for Pediatric Patient-Completed Questionnaires

c. WITHIN 15 DAYS AFTER CYCLE 1, DAY 1:

Submit the Vital Status Form

d. WITHIN 15 DAYS AFTER EACH CYCLE OF TREATMENT

Submit the following:

- Vital Status Form
- **S1826** Treatment Form
- **S1826** Adverse Event Form
- **S1826** Concomitant Medication Form

e. WITHIN 15 DAYS AFTER EACH PRO-CTCAE ASSESSMENT INCLUDING CYCLE 1 / DAY 1 (PRIOR TO BEGINNING OF TREATMENT), BEGINNING OF EACH SUBSEQUENT TREATMENT CYCLE (CYCLE 2 - 6), AFTER LAST DOSE OF STUDY DRUG, AFTER LAST DOSE OF RADIATION THERAPY (where applicable), 3-6 MONTHS AFTER DATE OF REGISTRATION (IF PATIENTS GOES OFF-TREATMENT EARLY), 9, 12, 18, 24, 30 AND 36 MONTHS AFTER DATE OF REGISTRATION.

Submit the following:

- **S1826** PRO-CTCAE (Adults) or **S1826** Pediatric PRO-CTCAE (Pediatrics)

f. WITHIN 15 DAYS AFTER EACH DISEASE ASSESSMENT INCLUDING: CYCLE 2 PET-CT (if done for clinical indication), CYCLE 6 (or at the End of Treatment if prior to Cycle 6), AT THE END OF RT (if patients received protocol-specified residual PET RT), and AT 1 YEAR AND 2 YEARS AFTER REGISTRATION

For after Cycle 2, after Cycle 6 (or at the end of treatment if prior to Cycle 6), and at the end of RT PET-CT

Submit the following:

- Vital Status Form
- Follow-up Tumor Assessment Form
- Radiology reports from PET-CT, contrast-enhanced CT, MRI, or MR-PET performed to assess disease at each time point. (NOTE: Upload reports via the Source Documentation: Disease Assessment form in Rave®.)
- **S1826** Imaging Adjunctive Data Sheet for PET scans; If PET scan is contraindicated and CT or MRI is submitted, the **S1826** Imaging Adjunctive Data Sheet is not required.
  This form is submitted electronically via the IROC website at: https://wrightcenterofinnov.qualtrics.com/jfe/form/SV_cC0Pih8vSYcCnfU. See Section 14.4a for navigation instructions.
- All PET-CT images (or if PET-CT contraindicated, then all contrast-enhanced CT, MRI or MR-PET) from scans performed to assess disease as specified in Section 15.4. Submit to IROC Ohio (via TRIAD strongly preferred) for retrospective central imaging review.

For at 1-year and 2-year after registration contrast-enhanced CT

Submit the following within **30 days** of the above-specified timepoints:

- Follow-up Tumor Assessment Form
- Radiology reports from CT performed to assess disease at each time point. (NOTE: Upload reports via the Source Documentation: Disease Assessment form in Rave®).
- All contrast-enhanced CT images of chest, abdomen and pelvis (+ neck or other involved areas, if involvement at baseline) (or if contra-indicated, PET-CT, CT, MRI, or MR-PET) from scans performed to assess disease as specified in Section 15.4 Submit to IROC Ohio (via TRIAD strongly preferred) for retrospective central imaging review.
  - For patients who have had 1-year and 2-year after registration contrast-enhanced CT (or if contra-indicated, PET-CT, CT,

MRI, or MR-PET) scan performed prior to activation of S1826 Protocol Revision 6, submit images to IROC Ohio within 60 days after participating site activation of S1826 Protocol Revision 6 (Version Date 9/2/2023).

- If CT scan is contraindicated and PET-CT scan is submitted, S1826 Imaging Adjunctive Data Sheet for PET scans is required. This form is submitted electronically via the IROC website at: https://wrightcenterofinnov.qualtrics.com/jfe/form/SV_cC0Pih8vSYcCnfU. See Section 14.4a for navigation instructions. See Section 14.4a for navigation instructions.

g. WITHIN 15 DAYS AFTER CYCLE 3, DAY 1:

Submit the following:
- Specimens as outlined in Section 15.2.
- **S1826** Pediatric PROMIS Global Health 7+2 (Pediatric) or S1826 PROMIS-Global Health (Adults)
- **S1826** Pediatric PROMIS Fatigue 10a (Pediatrics) or S1826 PROMIS Fatigue 7a (Adults)
- **S1826** FACT/GOG-Ntx (Pediatrics and Adults)
- **S1826** Cover Sheet for Patient-Completed Questionnaires or **S1826** Cover sheet for Pediatric Patient-Completed Questionnaires.

h. WITHIN 15 DAYS AFTER LAST DOSE OF PROTOCOL THERAPY (following last dose of study drug or radiation therapy, whichever is later):
Submit the following:
- Vital Status Form
- Off Treatment Notice
- **S1826** Treatment Form
- **S1826** Adverse Event Form
- **S1826** Pediatric PROMIS Global Health 7+2 (Pediatric) or **S1826** PROMIS-Global Health (Adults)
- **S1826** Pediatric PROMIS Fatigue 10a (Pediatrics) or **S1826** PROMIS Fatigue 7a (Adults)
- **S1826** FACT/GOG-Ntx (Pediatrics and Adults)
- **S1826** Cover Sheet for Patient-Completed Questionnaires or **S1826** Cover sheet for Pediatric Patient-Completed Questionnaires.

i. WITHIN 15 DAYS AFTER THE END OF TREATMENT VISIT (4-8 weeks after last dose of study drug):

Submit the following:
- Vital Status Form
- **S1826** Adverse Event Form
- **S1826** Concomitant Medication Form
- Follow-up Tumor Assessment Form
- Radiology reports from PET-CT, contrast-enhanced CT, MRI, or MR-PET performed to assess disease at each time point. (NOTE: Upload reports via the Source Documentation: Disease Assessment form in Rave®.)
- Specimens as outlined in Section 15.2.
- **S1826** Imaging Adjunctive Data Sheet for PET scans; If PET scan is contraindicated and CT or MRI is submitted, the **S1826** Imaging Adjunctive Data Sheet is not required.

This form is submitted electronically via the IROC website at: https://wrightcenterofinnov.qualtrics.com/jfe/form/SV_cC0Pih8vSYcCnfU. See Section 14.4a for navigation instructions.

- All PET-CT images (or if PET-CT contraindicated, then all contrast-enhanced CT, MRI or MR-PET) from scans performed to assess disease as specified in Section 15.4. Submit to IROC Ohio (via TRIAD strongly preferred) for retrospective central imaging review.

j. WITHIN 7 CALENDAR DAYS PRIOR TO THE START OF PLANNED RESIDUAL PET RT (per Section 7.5), as applicable:

Submit the following:

- Copies of reports (radiology, operative, pathology, cytology) and any other information used in defining the target volumes. **Note: Reports and imaging previously submitted to IROC Ohio (via TRIAD strongly preferred) (per Section 15.4) need not be resubmitted.**
- Required data indicated in Section 18.6l to IROC Ohio (via TRIAD strongly preferred) for pre-treatment and approval.

k. WITHIN 7 CALENDAR DAYS AFTER COMPLETION OF PLANNED RESIDUAL PET RT (per Section 7.5), as applicable:

Submit the following:

- **S1826** Adverse Event Form
- **S1826** Protocol-specified Residual PET Radiation Therapy Form.
- Submit the required data indicated in Section 18.6l.3 to IROC Ohio (via TRIAD strongly preferred).

l. WITHIN 15 DAYS AFTER PROGRESSION/RELAPSE:

Submit the following:

- Vital Status Form
- **S1826** Treatment Form (if patient was still on treatment)
- **S1826** Adverse Event Form (if patient was still on treatment)
- Follow-up Tumor Assessment Form
- Radiology reports from PET-CT, contrast-enhanced CT, MRI, or MR-PET performed to assess disease at each time point. (NOTE: Upload reports via the Source Documentation: Disease Assessment form in Rave®.)
- Specimens as outlined in Section 15.2.
- **S1826** Imaging Adjunctive Data Sheet for PET scans; If PET scan is contraindicated and CT or MRI is submitted, the **S1826** Imaging Adjunctive Data Sheet is not required.
  This form is submitted electronically via the IROC website at: https://osu.az1.qualtrics.com/jfe/form/SV_8v1309A87eQOArb. See Section 14.4a for navigation instructions.
- All PET-CT images (or if PET-CT contraindicated, then all contrast-enhanced CT, MRI or MR-PET) from scans performed to assess disease as specified in Section 15.4. Submit to IROC Ohio (via TRIAD strongly preferred) for retrospective central imaging review.
- Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

m. WITHIN 15 DAYS AFTER INITIATION OF NON-PROTOCOL THERAPY

Submit the following:

- Vital Status Form
- **S1826** Non-Protocol Therapy Form

n. AFTER OFF STUDY DRUG OR RADIATION THERAPY (WHERE APPLICABLE), EVERY 3 MONTHS FOR THE FIRST YEAR FROM REGISTRATION, THEN EVERY 6 MONTHS FOR THE SECOND AND THIRD YEAR FROM REGISTRATION, THEN ANNUALLY UNTIL 10 YEARS FROM THE DATE OF REGISTRATION.

Submit the following within **30 days** of the above-specified timepoints:

- Vital Status Form
- Follow Up Form
- Late Adverse Events (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] adverse event that is possibly, probably, or definitely related to protocol treatment, or a Serious Adverse Event [SAE] of any grade/attribution, that has not been previously reported).

Note: After disease progression, above forms must be submitted annually (wherein, patients will be followed annually for survival and note of subsequent therapy which is typically performed by medical record review).

o. AFTER OFF STUDY DRUG OR RADIATION THERAPY (WHERE APPLICABLE) TREATMENT, AT 1-YEAR AND 3-YEARS AFTER DATE OF REGISTRATION:

Submit the following within **30 days** of the above-specified timepoints:

- Vital Status Form
- **S1826** Pediatric PROMIS Global Health 7+2 (Pediatric) or **S1826** PROMIS-Global Health (Adults)
- **S1826** Pediatric PROMIS Fatigue 10a (Pediatrics) or **S1826** PROMIS Fatigue 7a (Adults)
- **S1826** FACT/GOG-Ntx (Pediatrics and Adults)
- **S1826** Cover Sheet for Patient-Completed Questionnaires or S1826 Cover Sheet for Pediatric Patient-Completed Questionnaires

p. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

For all patients:

Submit the following:

- Vital Status Form
- Notice of Death
- **S1826** End of Study Form

If patient was on protocol treatment:

Submit the following:

- **S1826** Treatment Form (final)
- **S1826** Adverse Event Form (final)

If patient completed/ was off protocol treatment:

Submit the following:

- **S1826** Follow Up Form
- **S1826** Non-protocol Therapy form (if non-protocol treatment was initiated and this form was not previously submitted).

q. WITHIN 30 DAYS OF DECLARATION OF LOST TO FOLLOW-UP, REFUSAL OF ANY FOLLOW-UP, OR MAXIMUM FOLLOW-UP OF 10 YEARS:

Submit the **S1826** End of Study Form

15.0 SPECIAL INSTRUCTIONS

The following table provides an overview summary of the specimen submission timepoints. Please review the detailed specimen submission requirements outlined in Sections 15.1 - 15.3 below. All specimen submissions will be shipped to the SWOG Biospecimen Bank (Lab #201).

FFPE Tissue

Timepoint	Reason for Submission	Specimen	Kit Provided?	Required?
Baseline (submitted within 28 days after registration)	Pathology Review	Diagnostic Biopsy **FFPE block (preferred) * OR** **1 high-quality, 4-5 micron, H&E slide**	No	Required for Eligibility
	Banking for Planned future TM research	Diagnostic Biopsy **FFPE block (preferred) * OR** **1 high-quality, 4-5 micron H&E slide ** and** **15 unstained, 4-5 micron, positively-charged slides ****	No	Required with patient consent
			No	Required with patient consent
	* Note: If the patient consents to specimen banking an FFPE block is strongly preferred. If the patient does not consent to specimen banking, then the H&E stained slide is preferred. ** For patients that consent to specimen banking: The baseline tissue submision should include either an FFPE tissue block (strongly preferred) or a total of 2 high-quality, 4-5 micron H&E slides plus 15 unstained, 4-5 micron, positively-charged slides to meet both pathology reivew and banking requirements. (Note: If the patient consents to specimen banking and an FFPE tissue block is submitted, then the FFPE block will be utilized for both the required pathology specimen and the baseline tissue banking specimen for planned future research. Otherwise, a total of 17 tissue slides should be submitted as listed above.).		
Progression (submitted within 15 days after progression)	Banking for Planned future TM research	Where a progression biopsy was performed via standard of care procedure and tissue is available, submit: **FFPE block (preferred) OR** **1 quality, 4-5 micron, H&E slide** **and** **15 unstained, 4-5 micron, positively-charged slides.**	No	Required with patient consent

Peripheral Blood

Timepoint	Allowable Window for Collection	Specimen	Kit Provided?	Required?
Cycle 1, Day 1	Within 3 days prior to start of treatment	Peripheral Blood in **cfDNA Streck tubes**	Yes	Required with patient consent
Cycle 3, Day 1	+/- 3 days	Peripheral Blood in **cfDNA Streck tubes**	Yes	Required with patient consent
After Cycle 6 / Day 15 *	+/- 15 days	Peripheral Blood in **cfDNA Streck tubes**	Yes	Required with patient consent
Time of progression (if applicable)	+/- 15 days	Peripheral Blood in **cfDNA Streck tubes**	Yes	Required with patient consent

* Note: The C6/D15 blood draw should be a fixed timepoint (even if patient comes off treatment early or goes on to receive RT).

See also Section 7.1b for extended allowable collection windows in event of COVID-19 extenuating circumstance.

15.1 Specimens for Pathology Review (**REQUIRED**):

a. Specimens must be submitted at the time points listed below.

1. **Within 28 days after registration, submit**:
Formalin-fixed paraffin embedded (FFPE) ***diagnostic*** tumor tissue, including either: 1 block or 1 quality, 4-5 micron, H&E slide.

NOTE: **If the patient consents to specimen banking an FFPE tissue block is strongly preferred**. If the patient does not consent to specimen banking, then the H&E stained slide is preferred.

b. Specimen Collection and Submission Instructions

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures). If collection/submission instructions differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

c. Specimen collection kits are not being provided for tissue submission; sites will use institutional supplies.

d. See Section 15.3 for Specimen Labelling and Shipping Instructions.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of diagnostic tissue samples for SWOG Biospecimen Submission and Pathology review is identified as follows:

Lab #201: SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division
Phone: 614/722-2865
E-mail: bpcbank@nationwidechildrens.org

15.2 Banking for Planned future Translational Medicine (**REQUIRED with Patient Consent**)

Specimens for translational medicine and banking (submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (Optional for Patient):

a. With patient consent, specimens must be submitted at the following times for planned future translational medicine objectives (see Section 9.0)

1. **20 ml Peripheral blood – collected in two 10ml cell-free DNA Streck tubes** (see Section 15.2c) – at the following timepoints:

a. Cycle 1, Day 1 (within 3 days prior to start of treatment)

b. Cycle 3, Day 1 (+/- 3 days)

c. After Cycle 6 / Day 15 (+/- 15 days); Note: The C6/D15 blood draw should be a fixed timepoint (even if patient comes off treatment early or goes on to receive RT).

d. Time of Progression, if applicable (+/- 15 days)

See also Section 7.1b for extended allowable windows in event of COVID-19 extenuating circumstance.

2. **Formalin-fixed paraffin embedded (FFPE) *diagnostic* tumor tissue** for planned future translational medicine:

At baseline: If an FFPE tissue block was NOT submitted for pathology review (Section 15.1), then **submit 1 high-quality, 4-5 micron H&E slide and 15 unstained, 4-5 micron, positively-charged slides for specimen banking within 28 days after registration.** If 1 FFPE tissue block was submitted for pathology review, then no additional tissue is required at baseline. Include the corresponding pathology report, labeled with the SWOG patient number, in the shipment.

At time of progression, where a biopsy was performed via standard of care procedure and tissue is available, submit: 1 FFPE tissue block or 1 high-quality, 4-5 micron, H&E slide and 15 unstained, 4-5 micron, positively-charged slides within 28 days after biopsy was performed. Include the corresponding pathology report, labeled with the SWOG patient number, in the shipment.

Note: If the patient consents to optional specimen banking and limited tissue is available for the baseline submission, then at least 1 H&E slide must be submitted for eligiblity, as per Section 15.1. If the patient consents to optional specimen banking and limited or no tissue is available for submission at time of progression, then the site must document the reason for the incomplete specimen submission in the participant's medical record and in the SWOG Specimen Tracking System, as follows:

- If limited tissue is available, this must be documented in the Specimen Tracking System under "Comments" at the time of specimen submission.
- If no tissue available, this must be documented in the Specimen Tracking System by choosing "Notify that Specimen Cannot be Submitted".

b. Specimen Collection and Submission Instructions

Streck Cell-Free DNA Collection Tube Collection Guidelines

- Fill tube completely (10 mL)
- Immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in an inadequate specimen.
- **After collection, blood in cfDNA Streck tubes should never be refrigerated**, as this will compromise the specimen. Blood collected in cfDNA Streck tubes is stable at room temperature.

If blood in Streck tube cannot be shipped the day of collection, then it must be kept at **room temperature** and shipped on the next working day to the SWOG Biospecimen Bank (Lab #201). Do not process.

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources). If collection/submission instructions differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

c. Streck tubes for peripheral blood submisison may be ordered by using the SWOG Biospecimen Bank Management Application at https://ricapps.nationwidechildrens.org/KitManagement. Sites must order collection kits in advance of each collection timepoint; A single collection kit will be provided for each collection timepoint. Allow at 5-7 days for shipment of collection kits.

d. Specimen collection kits are not being provided for tissue submission; sites will use institutional supplies.

e. See Section 15.3 for Specimen Labelling and Shipping Instructions

In the online specimen tracking system, the appropriate SWOG laboratory for submission of diagnostic tissue samples for SWOG Biospecimen Submission and Pathology review is identified as follows:

Lab #201: SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201
Phone: 614/722-2865
E-mail: bpcbank@nationwidechildrens.org

NOTE: Planned integrated biomarker testing of specimens banked for planned future research will not occur until an amendment to this protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

15.3 SPECIMEN LABELING AND SHIPPING

a. Label blood tubes with the following:

- SWOG patient number
- Patient initials
- Collection date (date the specimen was collected from the patient)
- Specimen type (i.e., whole blood)

b. Include the following on FFPE tissue labels:

- SWOG patient number
- Patient initials
- Collection date (date the specimen was collected from the patient)
- Site of collection (e.g., Lymph node, left breast, liver, etc.)
- Label the specimen type to be consistent with the specimen chosen in Specimen Tracking (e.g., FFPE tissue)
- The Surgical Pathology ID # (Accession#) and block number (e.g., A2, 3E, 2-1, B, etc.) must be on both the specimen label and the pathology report in order for the Bank to adequately match the specimen with any findings in the pathology report.
- All slides derived from FFPE block(s) should be labeled with thickness (in µm).

c. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)
All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option “SWOG – SWOG – CTSU”). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.qacrab.org/Documents/SpecT%20Instructions-Insts.pdf); or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of diagnostic tissue samples for SWOG Biospecimen Submission and Pathology review is identified as follows:

Lab #201: SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201
Phone: 614/722-2865
E-mail: bpcbank@nationwidechildrens.org

NOTE: The SWOG Biospecimen Bank shipping address is accessible from the SWOG Specimen Tracking System, which must be utilized to log and track each specimen shipment.

2. The cost of shipment of samples to the Biospecimen Bank is offset via the NCTN site payment at each collection timepoint. An overnight courier airbill is not provided. Participating sites are to use their instituional account number (or similar local method of payment) for the shipment.

3. Complete instructions for packaging and shipping specimens are located on the SWOG Specimen submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

15.4 Imaging Submission Requirements **(REQUIRED*)**

*** If PET-CT is contraindicated for Patient, sites are to submit the contrast-enhanced CT, MRI or MR-PET from the same timepoint**

PET-CT images must be locally read and interpreted by the local site radiology service. PET-CT must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio (via TRIAD strongly preferred). TRIAD will manage routing these studies to IROC Ohio for Imaging Submission procedures for central data collection, and quality control (QC) check and retropective review as well as to IROC Rhode Island for the pre-treatment RT QA review as well as central review.

a. Image Collection and Submission Time Points:

Digital image collection is required at the following time points:

1. PET-CT scans must be performed within 42 days prior to registration, as indicated in Section 5.1c and must be submitted to IROC within 15 days after registration, as indicated in Section 14.4a.

2. Interim PET-CT scans that are performed for clinical purposes after Cycle 2, Day 15 and prior to Cycle 3 must be submitted to IROC within 15 days after the assessment, as indicated in Section 14.4f.

3. End of Treatment PET-CT scans must be performed 4-8 weeks after the last dose of study drug and must be submitted to IROC within 15 days after the assessment, as indicated in Sections 14.4f, 14.4i, and 14.4l.

4. Progression/Relapse PET-CT scans must be performed and submitted to IROC within 15 days after progression/relapse, as indicated in Section 14.4l.

5. 1 year after registration contrast-enhanced CT scans of chest, abdomen and pelvis (+ neck or other involved areas, if involvement at baseline) (or if contra-indicated, PET-CT, CT, MRI, or MR-PET) must be performed and submitted to IROC within 30 days after the assessment, as indicated in Section 14.4f.

6. 2 years after registration contrast-enhanced CT scans of chest, abdomen and pelvis (+ neck or other involved areas, if involvement at baseline) (or if contra-indicated, PET-CT, CT, MRI, or MR-PET) must be performed and submitted to IROC within 30 days after the assessment, as indicated in Section 14.4f.

See also Section 7.1b for extended allowable windows in event of COVID-19 extenuating circumstance.

b. Digital Image and Radiation Therapy Submission

1. Image Submission Requirements

Submission of treatment plans as DICOM RT is required. Digital data must include treatment planning CT, structures, plan, and dose files.

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD is the preferred means of image transfer to the IROC. Due to the critical time constraints for submitting data for pre-treatment review, we encourage sites to submit data via TRIAD to ensure that the pre-treatment reviews are completed in a timely manner.

In the event that a site has not completed all steps required for TRIAD data submission in time to meet the timeline for review, data submitted via SFTP will also be accepted. See the instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data (www.irocri.qarc.org).

2. TRIAD Access Requirements:

TRIAD is the preferred means of image transfer to the IROC. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging and radiation therapy data.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see Section 13.2), and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

3. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/ .

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

15.5 Patient-Reported Outcomes: Instructions for Administration **(REQUIRED*)**
***if patient speaks language in which the assessment tool is available (English, Spanish or French for most tools)**

Patients are required to complete PRO forms at baseline and follow-up timepoints. Questionnaires should be completed at the time of the patient's scheduled clinic visit but if this is not possible then the patient should complete them within ± 7 days of the follow-up contact. Please see Section 15.5c.4 for methods of administration in cases where patient visit is not conducted in the participating site's clinic.

a. QOL Instruments

The current CIRB-approved PRO (QOL) patient-facing forms are accessible on the CTSU website (www.ctsu.org) under "Documents" / "CIRB Documents" tab / "Amendment Reviews" subtab.

Patients who are <18 years of age at time of registration and turn age 18 while on protocol will continue to complete the Pediatric QOL assessments for the remainder of the protocol-specified timepoints.

1. Pediatric PROMIS Global (Pediatric) or PROMIS-Global (Adults) (estimated time of completion: 1-2 minutes)

   - Available in English, Spanish, and French

2. Pediatric PROMIS Fatigue 10a (Pediatrics);
   PROMIS Fatigue 7a (Adults)
   (estimated time of completion: 2-3 minutes)

   - Fatigue 10a: Available in English, Spanish
   - Fatigue 7a: Available in English, Spanish, and French.

3. FACT-GOG-NTX (both Pediatric and Adult, modified to remove platinum-related items)
   (estimated time of completion: < 5 minutes)

   - Available in English, Spanish, and French

b. Administration Timepoints for all QOL instruments

1. Baseline (prior to registration)
2. Cycle 3 / Day 1 (prior to beginning treatment on Cycle 3)
3. 4-8 weeks after the last dose of protocol therapy (following last dose of study drug or radiation therapy, whichever is later)
4. 1 year after date of registration

5. 3 years after date of registration

If a patient is removed from protocol therapy prior to an indicated administration timepoint, the indicated assessment tool must still be administered at that timepoint regardless of whether the patient has started a subsequent anti-cancer therapy (after stopping protocol treatment).

c. Administration of Questionnaires

1. The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each section. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment.

2. It is permissible to assist patients with completing the questionnaires, being careful not to influence the patient's response. Note what assistance was required and indicate the reason in the Comments section (e.g., elderly, too sick, etc.). Discourage family members from: 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.

3. If a patient refuses or cannot complete the questionnaire for some reason, then this must be documented in the **S1826** Cover Sheet for Patient-Reported Outcomes.

4. If a patient misses an appointment or is too sick to complete the questionnaires on the scheduled date, a copy of the QOL questionnaires must be provided to the patient (e.g. via e-mail, mail, or sent home with him/her). A telephone (or videoconference) interview must be scheduled and completed within one week of the originally scheduled timepoint. Patient responses to questionnaire items are to be obtained during the telephone (or videoconference) interview while the patient is looking at a copy of the questionnaire. The date of the telephone (or videoconference) interview is to be noted in the Cover Sheet for Patient-Reported Outcomes.

5. If a patient is deemed clinically ineligible after registration but protocol treatment was initiated, he/she should continue the PRO assessments as scheduled. PRO (QOL) assessments continue per scheduled timepoints even if the patient discontinues protocol treatment early and starts a subsequent anti-cancer therapy (after stopping protocol treatment).

d. Administration Quality Control Procedures

When a patient is registered to **S1826**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed before receiving treatment. You may wish to photocopy the Study Calendar, Section 9.0, and include the patient's name and specific dates. A copy of this (if created) should be kept in the patient file.

1. If a patient goes off protocol treatment, continue to administer the patient completed questionnaires according to the protocol-defined assessment schedule (time from registration date).

2. If a patient refuses or cannot complete the patient questionnaires at one time point, he/she should be asked to do so at the next scheduled administration time.

3. The Quality of Life Coordinator will monitor compliance on a regular basis, having been provided with timely reports from the SWOG Statistical Center. The Expectation Report and the MediData RAVE system provides reminders of upcoming quality of life assessments for a patient.

4. Anyone involved in the collection of quality of life data in SWOG trials should review the Patient-Reported Outcome Questionnaires training program available on the SWOG website (under the CRA workbench). The training program is a narrated set of slides designed to standardize the way quality of life data is collected from patients. Questions regarding the quality of life assessments can be addressed to the SWOG Statistics and Data Management Center (206/652-2267).

15.6 Patient-Reported Outcome Common Toxicity Criteria for Adverse Events (PRO-CTCAE) (***REQUIRED*** for English- and Spanish- and French-speaking adult patients and English-speaking pediatric patients)

PRO-CTCAE questions must be administered to English- and Spanish-, and French-speaking patients weekly during the treatment period, as outlined below.

a. Administration Timing

Patients will complete the PRO-CTCAE questions at the following time points:

1. Cycle 1 / Day 1 (prior to beginning treatment)

2. Day 1 of each subsequent treatment cycle (Cycle 2-6) (+/- 7 days)

3. After last dose of study drug (+/- 7 days) and, where applicable, after last dose of radiation therapy, as applicable to the patient) (+/- 7 days)

4. 3-6 months after date of registration (if patient goes off-treatment early) (+/- 7 days)

5. 9, 12, 18, 24, 30 and 36 months after date of registration (+/- 7 days)

The administration timing of the PRO-CTCAE questionnaire should coincide with the physician-directed toxicity assessment for the respective visit.

If a patient is removed from protocol therapy prior to an indicated administration timepoint, the scheduled PRO-CTCAE assessments must continue to be administered until such time that the patient starts a subsequent non-protocol systemic anti-cancer therapy.

b. Administration Instrument

The current CIRB-approved PRO (PRO-CTCAE) patient-facing forms are accessible on the CTSU website (www.ctsu.org) under “Documents” / “CIRB Documents” tab / “Amendment Reviews” subtab.

For adult patients (≥ 18 years of age), a total of 19 questions per timepoint will be answered using the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE). The estimated time of completion for the Adult PRO questionnaire is 10 minutes.

For pediatric patients (12-17 years of age), a total of 33 questions per timepoint will be answered using the Pediatric Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (Pediatric PRO-CTCAE). The estimated time of completion for the Pediatric PRO questionnaire is 15 minutes. Patients who turn age 18 while on protocol will continue to complete the Pediatric PRO-CTCAE assessment for the remainder of the protocol-specified timepoints.

The study-specific PRO-CTCAE items for this protocol can be found in Section 18.10.

c. Questionnaire Administration Instructions

1. The first time the patient completes the questionnaire: Please read the instructions attached to the patient questionnaire to the patient. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations, whether or not they are related to the cancer or its treatment.

2. It is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Discourage family members from: 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.

3. It is very important to review the PRO-CTCAE questionnaire after the patient has completed it to be sure all questions have been answered and that only one answer is marked per question. If the patient has marked more than one answer per question, ask the patient which answer reflects how he/she is feeling. If the patient has skipped a question, tell the patient that a question was not answered and ask if she would like to answer the question. Always give the patient the option to refuse. If the patient declines to answer any question, indicate on the form by the question that the patient did not want to answer this question.

4. If a patient misses an appointment and the physician-directed toxicity assessment is not conducted, then the PRO-CTCAE assessment for that timepoint should be documented as missed on the respective **S1826** PRO-CTCAE form.

5. If the patient appointment is conducted via a telehealth visit within one week of the originally scheduled timepoint, and the toxicity assessment is also conducted via the telehealth visit, then, the PRO-CTCAE questionnaire may also be administered via telephone (or videoconference) at the same timepoint. A copy of the PRO-CTCAE questionnaire must be provided to the patient (e.g. via e-mail or mail), and a telephone (or videoconference) interview may completed at the same telehealth visit as the toxicity assessment or may be scheduled separately as close to possible (and within the 7-day window of the original assessment timepoint) to the physician-directed toxicity assessment. Patient responses to questionnaire items are to be obtained during the telephone (videoconference) interview while the patient is looking at a copy of the questionnaire.

6. If a patient is deemed clinically ineligible after registration but protocol treatment was initiated, he/she should continue the PRO assessments as scheduled. If the patient discontinues protocol treatment early, the PRO-CTCAE assessments continue at the scheduled timepoints until such time that the patient begins new/different systemic anti-cancer therapy off-protocol.

d. Additional Quality Control Procedures:

When an English-, Spanish-, or French-speaking patient is registered on **S1826**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed.

If a patient refuses or cannot complete the PRO questionnaire at any time **point, he or she should be asked complete the next set of patient questionnaires at the next scheduled assessment time**.

Anyone involved in the collection of quality of life data in SWOG trials should review the Patient-Reported Outcome Questionnaires training program available on the SWOG website (under the CRA workbench). The training program is a narrated set of slides designed to standardize the way quality of life data is collected from patients. Questions regarding the quality of life assessments can be addressed to the SWOG Statistics and Data Management Center (206/652-2267).

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent and Assent
The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review
This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability
An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact
The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to: E-mail: ncicteppubs@mail.nih.gov.

   The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring
This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality
Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

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18.0 APPENDIX

18.1 LYRIC Criteria

18.2 Quality of Life

18.3 Management Algorithms Immuno-Oncology (I-O) Therapy for Endocrinopathy, Gastrointestinal, Hepatic, Neurological, Pulmonary, Renal and Skin Adverse Events for Nivolumab (Arm 1) Adverse Event Management

18.4 Performance Status Scales

18.5 FDG-PET-CT Imaging Procedures and Image Acquisition

18.6 Radiation Therapy Guidelines

18.7 Measurement-Based Response Assessment According to the Lugano Classification

18.8 Instructions for the SWOG Biospecimen Bank – Lab #201: Solid Tissue, Myeloma and Lymphoma Division

18.9 CYP1A2 and CYP3A Inhibitors and Inducers

18.10 PRO-CTCAE Common Terminology Criteria for Adverse Events (PRO-CTCAE) Instrument

18.11 Patient Clinical Trial Wallet Card

18.12 AYA Educational Resource Information, COG Participating Site Frequently Asked Questions, NCTN Adult Group Participating Site Frequently Asked Questions

18.1 LYRIC Criteria

Lugano Classification was developed based on treatment with cytotoxic agents. Immunotherapeutic drugs may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as clinical responses after initial increases in tumor burden or even the appearance of new lesions.

Thus, the 2014 Lugano Classification may not provide an accurate assessment of response to immunotherapeutic agents. Provisional modification of the Lugano criteria (LYRIC Criteria) may be used to assess participants who meet progressive disease per Lugano Classification. *(1,2)*

The LYmphoma Response to Immunomodulatory therapy Criteria (LYRIC) has recently been proposed for tumor response assessment after immunomodulatory therapies such as immune checkpoint inhibitors. *(3)* These criteria address possible flare phenomenon or pseudoprogression that may be misclassified as progressive disease (PD) particularly during the first two or three weeks of treatment thus leading to underestimation of the clinical benefit of the treatment.

LYRIC criteria introduced a term “Indeterminate Response (IR)” to be able to distinguish between flare/pseudo-progression and true PD. A mandatory subsequent evaluation within 12 weeks is required to confirm or refute true progressive disease.

Complete Response	Partial Response	Progressive Disease
Same as Lugano	Same as Lugano	As with Lugano with the following **exceptions**: **Indeterminate response (IR)** IR1: ≥50% increase in SPD of up to 6 measurable lesions in first 12 weeks of therapy without clinical deterioration IR2: <50% increase in the overall SPD with a. Appearance of a new lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment IR(3): Increase in FDG uptake without a concomitant increase in lesion size or number Patients with IR should continue on therapy and have repeat imaging after an additional 12 weeks (or sooner if clinically indicated). Progressive disease criteria in these patients will be met if: IR1: An additional increase in the target SPD of ≥ 10% between the first IR1 timepoint and the SPD being assessed; or an increase in ≥ 5mm in either dimension of at least one lesion for lesions ≤ 2cm and 10mm for lesions > 2cm. IR2: the new or growing lesion(s) should be added to the target lesions (total of no more than 6) and there is PD if the SPD if the newly defined set of target lesions has increased ≥50% from their nadir value (which may precede the IR time point). IR3: There is evidence of PD by an increase in lesion size or the development of new lesions.
Abbreviations: SPD, sum of the product of the diameters; PPD, product of the perpendicular diameters.		

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18.2 Quality of Life

a. Quality of Life Objectives

To compare between arms patient-reported fatigue, neuropathy and health-related quality of life over time (baseline prior to registration, at Day 56 (corresponding to the beginning of Cycle 3), 4-8 weeks after the last dose of protocol therapy (following last dose of study drug or radiation therapy, whichever is later), and 1 and 3 years after randomization) using the PROMIS-Fatigue (or Ped PROMIS Fatigue), the FACT/GOG-Ntx, and the PROMIS Global (or Ped PROMIS-Global), respectively

1. Hypothesis: 1: Patients randomly assigned to the N-AVD arm will have worse fatigue scores during initial treatment with resolution by one-year post treatment than patients randomly assigned to the BV arm. Patients receiving both nivolumab and radiation therapy will have worse fatigue than recipients of nivolumab without radiation. Self-reported fatigue and HRQL will be measured by the PROMIS Fatigue scale(s) (adult or pediatric versions) and PROMIS-Global or Pediatric PROMIS-Global, respectively.

2. Hypothesis 2: Patients randomly assigned to the BV-AVD will have worse FACT/GOG-Ntx scores on treatment and by 1 year after the completion of treatment, as compared to patients randomly assigned to the N-AVD arm. Scores will be worse for patients 40 years or older.

b. Background

Patients with newly diagnosed, advanced stage HL are at risk for poor HQRL as a result of their underlying disease and its treatment -- whether dose-dense chemotherapy alone or in combination with planned radiotherapy. Several studies in adults with HL have also demonstrated that a subset of patients report severe fatigue at the time of diagnosis (est. 10%) and that for some fatigue persists long after completion of therapy. The introduction of novel therapies into the upfront treatment of HL, including the antibody-drug conjugate Brentuximab vedotin (BV) and PD-1 inhibitors, such as Nivolumab offer the promise of improved disease-free and overall survival, the potential reduction of radiotherapy, and the associated decrease in late effects. These agents, however, are associated with their own symptoms burden, such as peripheral neuropathy (BV) or rashes, colitis, pneumonitis, and endocrinopathies (Nivo). Recent studies suggest a rate of peripheral sensory neuropathy of 20% or higher with BV, and toxicity that was associated with premature abandonment of the experimental arm on the ECHELON1 trial. The long term impact of Nivo on HRQL after successful immunomodulation of the tumor is not known, although recent studies have demonstrated the relationship between adverse events and poorer HRQL. Hence, we propose the first study to capture longitudinal HRQL, anchored to symptom burden in pediatric and adult patients with advanced stage HL.

Recently validated measures within the constructs of overall HRQL, fatigue, and patient-reported symptoms afford us with an instrument battery that is targeted and brief, spans the full age span of the trial population, and generally available in the needed target languages (i.e., English, Spanish, and French).

In the current Children's Oncology Group (COG) Phase III trial in HL (AHOD 1331; NCT02166463) in which we are evaluating the inclusion of BV into the existing chemotherapy backbone, we have serially measured HRQL, patient-reported CIPN, health care utilization and health utilities from more than 300 children and where appropriate, from their parent proxies. (Proxy report was used in children under 11 years, who could not provide unassisted self-report). We have collected provider grading of targeted toxicities, most notably peripheral neuropathy, at each cycle. More than 97% of eligible patients participated in the study, completing baseline measures prior to the start of planned therapy. At scheduled follow up time points (Cycle 2, D8; Cycle 5, D8; 6-8 weeks off therapy; 12- and 36- months off-therapy), we have collected measures from 95% of participants. Similar to the proposed study, we have begun the analysis with aggregate results (preserving the blinding by study arm) with the plan of ultimately comparing by study arm, following completion of full trial accrual.

c. Quality of Life Instruments

In this study we rely on validated measures (PROMIS Global, PROMIS fatigue, and FACT/GOG-Ntx) to be completed by patients in a 15-minute period at key clinical time points during the trial. All of these instruments are available and have been validated for both youth and adult self-report in English, French, and Spanish, allowing for broad participation across the age span of the trial population. Moreover, the youth and adult versions of the same instruments have been determined to measure the same constructs, enabling us to combine the age groups into unified analyses, stratified by age.

1. <u>PROMIS Fatigue</u>

The PROMIS Fatigue measure is the standard for evaluating cancer-related fatigue in clinical trials. *(1)* The seven item PROMIS-Fatigue short form for adults and the 10 item short form for children < 18 years have been created from validated item banks (adult, 95 total items; pediatric 23 total items). The PROMIS Fatigue instruments evaluate self-reported symptoms ranging from mild subjective feelings of tiredness to a sustained, overwhelming sense of exhaustion that affects one's ability to perform daily activities and function normally [PROMS-Fatigue manual]. PROMIS Fatigue instruments provide a unidimensional assessment of fatigue that captures both the experience of fatigue (frequency, duration, and intensity) and its impact on physical, mental, and social activities. *(2)* A raw summary score of survey results is rescaled into a standardized score (T-score) with a mean of 50 and standard deviation of 10 (i.e., scores above 50 indicate worse than average fatigue) [PROMS-Fatigue manual].

2. <u>FACT/GOG-Ntx</u>

Neurotoxicity will be assessed using the 11-item Neurotoxicity component of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity (FACT/GOG-Ntx) questionnaire. The FACT/GOG-Ntx is the FACT-G plus an eleven-item subscale that evaluates symptoms and concerns associated specifically with chemotherapy-induced neuropathy. The scale contains two items related to platinum-based chemotherapy, which will be deleted for the scale score (thus, a maximum score of 36 vs. 44). Additionally, the scale contains a 4-item peripheral sensory neuropathy subscale, which has been shown by Huang et al. to be sensitive to change over time. A one-point difference in the sensory subscale is clinically important. (Cella, personal communication, October 2018).

The FACT/GOG-Ntx and its peripheral sensory subscale measures the severity on a continuous scale. The FACTGOG-Ntx is a reliable and valid instrument for assessing the impact of neuropathy on health-related quality of life in adults, having demonstrated strong psychometric properties, including sensitivity to meaningful clinical distinctions and responsiveness to change over time patterns were reported by the National Surgical Adjuvant Breast and Bowel Project. *(3,4,5,6)* Scale scores were related to clinical grading scores non-linearly (i.e., 2.4 for clinical Grade 0 to 24.5 for clinical Grade 3). The scale allowed for discrimination among patients with similar clinical grade and highlighted different symptoms as being bothersome at different points during therapy. As a measure of criterion validity, Huang et al. demonstrated that scale scores were able to discriminate the presence or absence of CIPN, based on clinical grading, with an area under the receiver operating characteristics curve (AUC of ROC) of 81%. *(7)* CIPN has been shown to have a negative effect on health-related quality of life (HRQL) in several diverse populations. Large effect sizes, equivalent to two standard deviations, were detected in HRQL comparisons between chemotherapy naïve patients and those with CIPN in a study of women with ovarian cancer. *(8)* Mols et al. demonstrated in a sample of over 1600 patients that those in the top decile of neuropathy symptoms had statistically significant worse HRQL across all measured domains, a finding echoed in the qualitative research of Textor et al. *(9,10)*

The FACT/GOG-Ntx also has been used successfully in the ongoing Children's Oncology Group study AHOD 1331 for both youth self-report (patients ages 11 years and older) and parent proxies. Internal consistency reliability exceeded 0.80 for both raters on the 9-item total neuropathy scale score and on the 4-item sensory neuropathy subscale. (Parsons, personal communication). Additionally, mean scale scores for the FACT-Ntx differed significantly by clinical grading (stratified as any neuropathy vs. no neuropathy) for both raters. Compared to patients without neuropathy, those with neuropathy reported significantly lower HRQL scores, as has been documented in adults with neuropathy.

3. PROMIS Global

The PROMIS-Global is a 10-item measure of general health and functioning, detailing the respondent's perceptions of physical function, pain, fatigue, emotional distress, social health, and overall health. In addition to specific item scores, the measure yields two summary scores for global physical health and global mental health. These summary scores can be compared to general population norms when converted to a T-score metric (mean, 50; SD, 10). Using an established algorithm, this measure can also be used to calculate EQ-5D index scores. *(11)*

d. Timepoints

The quality of life assessments are scheduled to occur at baseline prior to registration, at Day 56 (corresponding to Day 1 of Cycle 3 [assessment window +/- 7 days]), 4-8 weeks after the last dose of protocol therapy (following last dose of study drug or radiation therapy, whichever is later) [assessment window 4 weeks]), at 1 year after registration (assessment window +/- 7 days), and at 3 years after registration (assessment window +/- 7 days).

e. Experimental Research Techniques/tests Employed and Expertise of PI

Research staff members will be trained to administer quality of life forms by viewing a training module available on the SWOG website (www.swog.org); the program can be found at the CRA WorkBench/Training. For example, this training program indicates that research staff should not influence the patient's responses to the questionnaires. Research staff will need to enter the reported data into the online Medidata RAVE system. Efforts to minimize missing data are critical to obtaining interpretable results. The training module addresses methods for reducing missing data.

Susan Parsons, M.D., M.R.P., Tufts Medical Center, is the Principal Investigator on two ongoing embedded studies within AHOD 1331 (study Chair: Sharon Castellino, M.D., MSc., Emory, Children's Hospital of Atlanta) to evaluate chemotherapy-induced peripheral neuropathy, using the FACT/GOG-Ntx and global HRQL.

Statistical analyses will be performed by Joseph Unger, Ph.D., who leads the PRO Core within the SWOG Statistical Center.

f. Recall Period for the measures is as follows:

1. FACT/GOG-Ntx: 7 days
2. PROMIS-Global (adults): 7 questions "in general," 3 questions past 7 days; Pediatric Global: 7 "in general", 2 questions past 7 days
3. Fatigue 7a (adults) OR Fatigue 10a (kids): 7 days

g. QOL Statistical Considerations

Quality of life assessments will occur in conjunction with the clinical follow-up schedule in order to minimize missing data and to link the clinical assessments with patients' self-reported symptom burden. This design should also minimize patient and staff burden. The assessment times are fixed and are scheduled to occur as noted in Section 18.2d. The time points are designed to capture acute toxicity and HRQL impact prior to treatment initiation, during planned therapy (e.g., Cycle 3, Day 1) and at the end of planned therapy (including radiation), as well as the persistence of toxicity and HRQL impact after date of registration (at 12 and 36 months). The assessment at Cycle 3, Day 1 was selected to align with a post 2 cycle disease response that will be done on the trial in the same time frame. The end-of-treatment visit after completion of planned therapy also coincides to the anticipate dose peak level of the tubulin toxins and thus, the potentially greatest risk of CIPN, as has been seen in our ongoing COG study. The 12-month after date of registration time points are important to understanding the potential resolution of acute toxicities and their impact on HRQL for these novel agents. The 36-month after date of registration time point is deliberately chosen both to assess persistence of toxicity (i.e., fatigue and neuropathy), as well as to capture HRQL in cases where salvage therapy may have been necessary in cases of failure of primary treatment on either study arm. In addition, given the unknown temporal course of immune modulation in de novo disease both with regard to control of HL and to the risk of immune-mediated toxicity, a 36-month assessment time point is thought to be important. The specification of fixed assessment times helps limit the potential to induce a dependence between the clinical and QOL outcomes, which could bias the QOL results. Study windows have been created around each of the planned assessments to avoid dependency of the treatment course (e.g., due to treatment delays).

Multiple primary endpoints will be examined, two for fatigue, and two for neuropathy. To examine the four independent endpoints with full power that includes adjustment for multiple comparisons, all 940 eligible patients will be included in the QOL analyses. To adjust for multiple comparisons, we will set alpha=.0125 based on Bonferonni.

Two primary endpoints are specified for fatigue, one 4-8 weeks after the last dose of protocol therapy (following last dose of study drug or radiation therapy, whichever is later) and one at 1 year after randomization. We hypothesize that patients randomly assigned to the N-AVD arm will have worse fatigue scores during initial treatment, although there is uncertainty about the direction of the effect, suggesting that a two-sided design is appropriate. Fatigue is further hypothesized to be mitigated by year 1, although again there is uncertainty regarding the impact of the therapies on the magnitude and direction of the affects at this timepoint. Fatigue will be examined by arm using the PROMIS Fatigue. *(12,13,14,15)* Both a pediatric and adult version of the PROMIS Fatigue have been validated as noted above and have been determined to assess the same constructs in the different patient age groups (pediatric vs. adults). This allows the combining of scores across age, although stratification by age will be conducted given potentially different levels of fatigue. The PROMIS-Fatigue scale has a standardized mean of 50 with a SD of 10 points. *(16,17,18,19)* Representative literature about the trajectory of fatigue over time in a broad range of cancer patients indicates that follow-up scores after treatment initiation have a standard deviation of about 12 points. *(20)* Our goal is to identify an effect size of 0.3, a small to medium effect, with good power. *(21)* This corresponds to a difference of 3.6 points or larger in the PROMIS-Fatigue between arms, which has been shown to be approximately in the middle of the range (3-5 points) of clinically meaningful differences identified for this instrument. *(22)* We assume, conservatively, dropout or non-response of 20% at the first assessment (time of completion of treatment) and 25% at the second assessment (1 year after randomization). Based on these parameters and using a two-sided two-arm normal design, there will be 95% power to detect a difference of 3 points in the PROMIS-Fatigue at last day of protocol therapy and 93% power at 1 year after randomization.

Neuropathy will be analyzed by arm at 1 year and at 3 years after randomization. This instrument is validated for both pediatric and adult patients. We hypothesize that patients assigned to the BV-AVD arm will have worse neuropathy over time compared to patients on the N-AVD arm, although as for fatigue, we allow uncertainty about the direction of the effect and will rely on a two-sided design. Neuropathy will be measured using the FACT/GOG-Ntx. The modified 9-item scale FACT/GOG-Ntx measures the severity of neurotoxicity on a continuous scale. A change of 3 points has been proposed as the minimally significant (i.e., clinically important) difference for this subscale. *(23)* Standard deviations at ≥ 3 months after initiation of treatment are generally about 9 points; for design purposes, we assume a more conservative standard deviation of 10 points, corresponding to an effect of 0.3 points, a small to medium effect. *(24,25)* Greater dropout and non-response of 25% is assumed at 1 year, and 35% at 3 years. Based on these parameters and using a two-sided two-arm normal design with alpha=.0125, there will be 93% power to detect a difference of 3 points in the FACT/GOG-Ntx at 1 year after randomization and 89% at 3 years.

Consistent with the design, the analyses of the PROMIS-Fatigue and FACT/GOG-Ntx endpoints will be conducted using multiple linear regression analysis, adjusting for stratification factors and the baseline score as covariates. See Section 6.0 for stratification factors. We will also conduct longitudinal modeling of the outcome measures over time. Power for the longitudinal analysis will be greater since the addition of all available scores over time will provide more information. For longitudinal modeling, linear mixed models will be used. The potential for

differential dropout by arm will be mitigated by reminder notifications to site investigators to encourage proper assessment and submission of forms at every required time point for all patients. Dropout patterns will be monitored on an ongoing basis. Nonetheless the potential for non-random dropout exists. Cohort plots will be prepared to examine the extent to which missing data are informative (i.e., scores are higher (worse) for patients just before their data are missing for the subsequent assessment). If there is evidence of non-random dropout, pattern-mixture models will be utilized as a sensitivity analysis. Covariates for longitudinal modeling will include intervention assignment, assessment time, their interaction, the baseline score, and the stratification factors as covariates. We will also explore differences in trajectories by categorical age (12-17 years, 18-39 years, ≥ 40 years).

Secondary objectives include examinations by arm of fatigue and neuropathy at the other specified discrete timepoints (fatigue: beginning of Cycle 3, and 3 years after randomization; neuropathy: beginning of Cycle 3 and time of completion of treatment). Analyses by arm at these individual assessment times will be conducted using multiple linear regression, adjusting for stratification factors and the baseline score as covariates. For all secondary analyses, no adjustment for multiple comparisons will be made, as these are considered hypothesis-generating, requiring confirmation in independent analysis.

We will also examine patient-reported health-related quality of life by arm using the PROMIS Global for pediatric and adult patients. *(26,27,28)* Further, we will compare the quality-adjusted survival between the study arms, using the Q-TWiST method from diagnosis to the end of follow up. Utility weights for this analysis will be obtained from the PROMIS-Global, via established crosswalk algorithms. *(29)*

We will describe scores on all patient-reported measures at each time period using means, standard deviations, medians, 25th-75th percentiles, minimums and maximums, histograms, frequencies, and percentages. Missing data will be explored for all variables.

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18.3 Management Algorithms for Immuno-Oncology (I-O) Therapy for Endocrinopathy, Gastrointestinal, Hepatic, Neurological, Pulmonary, Renal and Skin Adverse Event Management for Nivolumab (Arm 1) Adverse Event Management

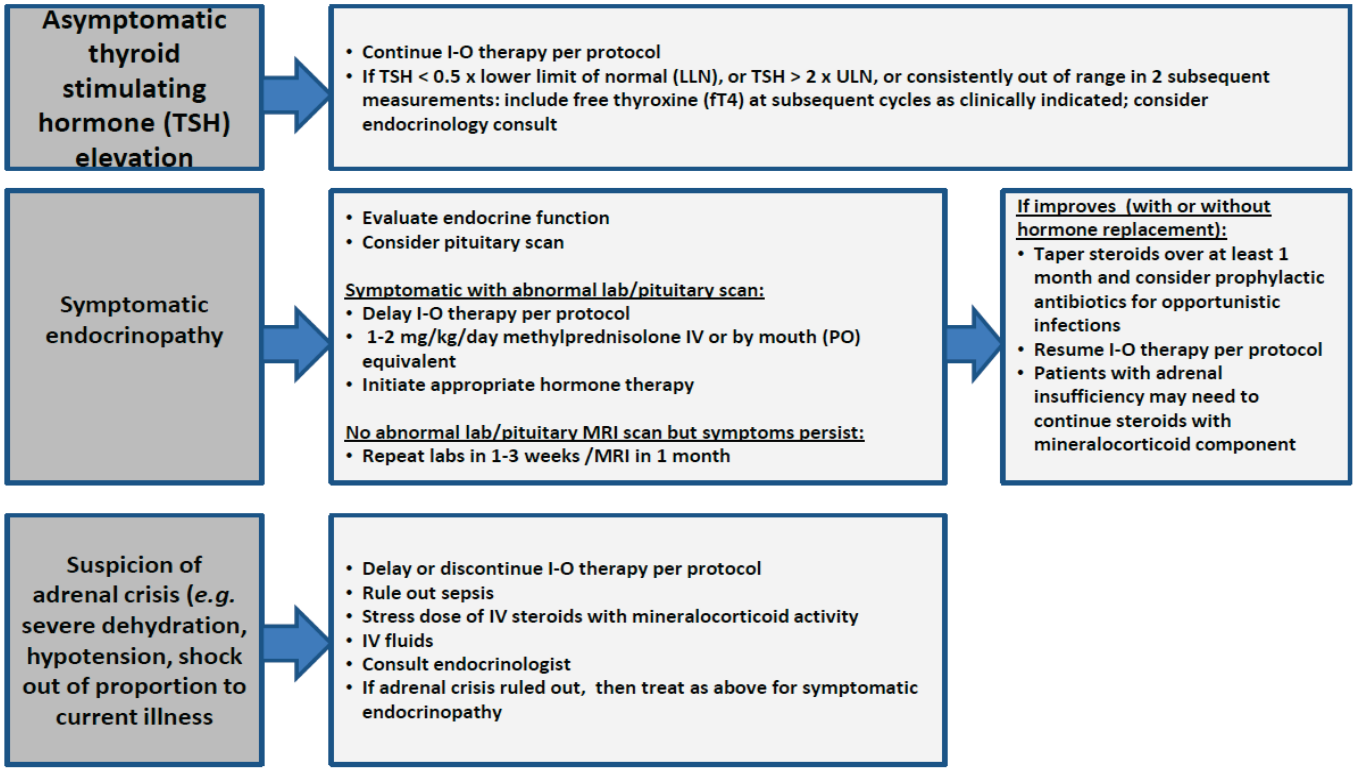
Note: For the following algorithms, prednisone PO may be utilized in place of methylprednisone IV.

Please see below.

a. Endocrinopathy Management Algorithm

Endocrinopathy Management Algorithm

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



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

b. GI Adverse Event Management Algorithm

GI Adverse Event Management Algorithm

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

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

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

c. Hepatic Adverse Event Management Algorithm

Hepatic Adverse Event Management Algorithm

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

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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

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

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

d. Neurological Adverse Event Management Algorithm

Neurological Adverse Event Management Algorithm

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

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

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

e. Pulmonary Adverse Event Management Algorithm

Pulmonary Adverse Event Management Algorithm

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

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

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

f. Renal Adverse Event Management Algorithm

Renal Adverse Event Management Algorithm

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

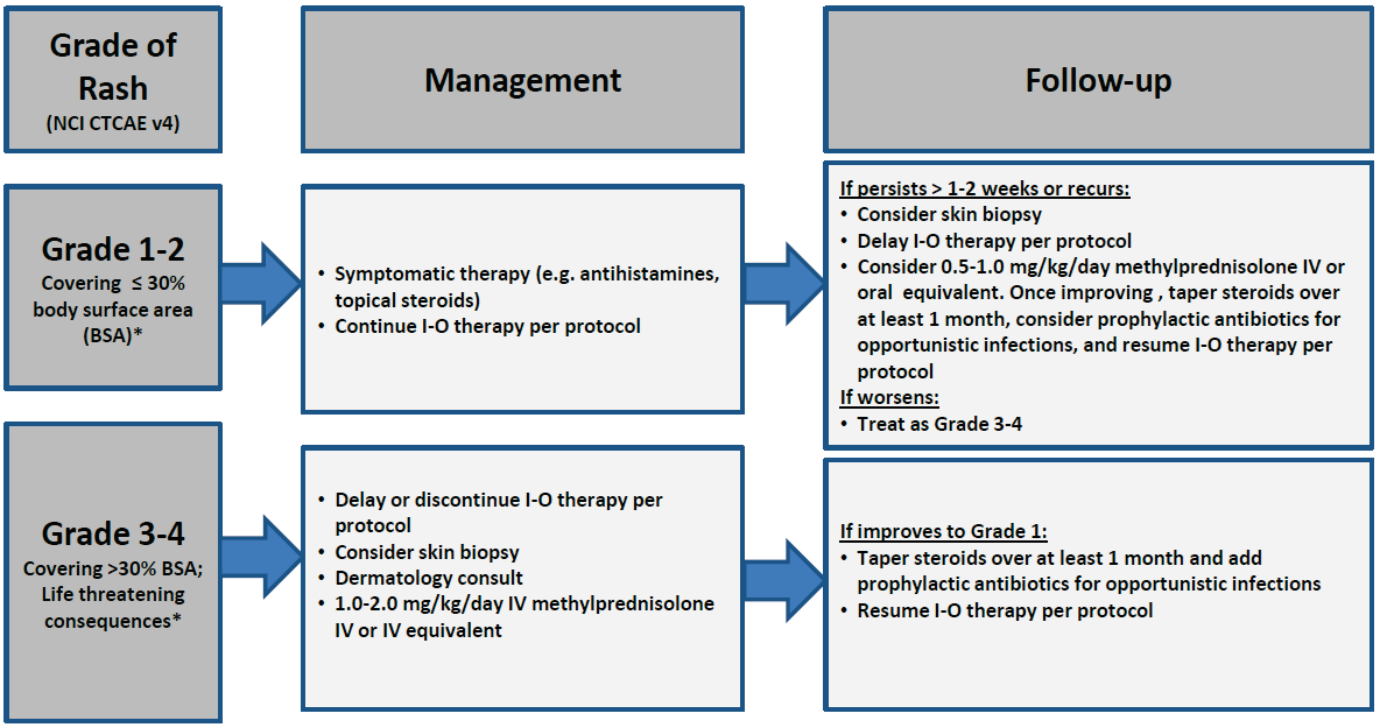
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol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

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

g. Skin Adverse Event Management Algorithm

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

18.4 Performance Status Scales

Performance Status Criteria Lansky performance scores are intended to be multiples of 10			
Zubrod		**Lansky***	
Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Fully active, normal.
		90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Active, but tires more quickly
		70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self- care, confined to bed or chair more than 50% of waking hours.	40	Mostly in bed; participates in quiet activities.
		30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Often sleeping; play entirely limited to very passive activities.
		10	No play; does not get out of bed.

*The conversion of Lansky to Zubrod scales is intended for NCI reporting purposes only.

18.5 FDG PET-CT Imaging Procedures and Image Acquisition

a. FDG-PET-CT Requirements for Participation

1. Access:

The participating center must have, or have access to, a facility with an integrated positron-emission tomography and computed tomography (PET-CT) scanner.

2. Electronic Submission

The participating center must have the ability to submit PET and CT studies electronically to the ACRIN Imaging Core Laboratory in digital DICOM format (other formats: BITMAP, JPG). Hardcopy or scanned files are not acceptable.

b. FDG-PET-CT Imaging Procedures

Patient Preparation
Patients must fast for at least four hours before the PET-CT scan. Oral hydration is strongly encouraged prior to and during injection of ^{18}F-FDG (250-500 mL water can be given PO during the uptake period). Intravenous fluids containing dextrose or parenteral feeding should be withheld for at least 6 hours prior to the injection of ^{18}F-FDG. No steroid administration is allowed for at least 7 days prior to FDG-PET imaging. Active exercise should be discouraged for at least 24 hours prior to the study. Muscle stress, tension, chewing, and movement during the uptake period should be minimized to decrease muscle uptake. Patients should not speak during the injection and uptake period. Interviews with the patient should be withheld until after completion of the imaging study.

The blood glucose level should be checked before ^{18}F-FDG injection. Blood sugar (measured by glucometer) must be less than 200 mg/dL at the time of the FDG-PET-CT study. If the blood glucose level is greater than 200 mg/dL, the FDG-PET-CT imaging should be rescheduled. If the blood glucose level still exceeds 200 mg/dL on the following scheduled day for PET scanning, the patient will not be included in the analysis. Insulin administration immediately before the PET-CT study to reduce the glucose levels is not allowed. Patients with diabetes should continue to adhere to their oral agents or insulin routines. These medications should not be administered near the ^{18}F-FDG injection time. In insulin-dependent patients, insulin should be administered at least 5 hours prior to the ^{18}F-FDG injection. Patients with diabetes who are on diabetic medication should take their medication 4-5 hours prior to the test.

Metallic objects should be removed from the patients whenever possible. Patients should be kept in a warm waiting room prior to ^{18}F-FDG injection to avoid brown adipose tissue uptake. In anxious and claustrophobic patients, administration of oral diazepam (0.06-0.10 mg/kg) is recommended 30-40 minutes prior to the initiation of the imaging study.

Weight (kg), height (cm), blood glucose (mg/dL), and the date and time of chemotherapy, glucose levels and colony stimulating factor administration (e.g., GCSF, GMCSF) should be recorded prior to the injection of ^{18}F-FDG.

The dose of ^{18}F-FDG should be based on the scanner manufacturer's recommendation (per institutional procedure). A 10-20 mL saline flush is recommended in reducing the venous retention of ^{18}F-FDG. The patient must wait at least 60 minutes (+/-10 minutes) prior to the initiation of the PET-CT acquisition for all PET-CT scans (both pre-and post-therapy scans). The imaging wait from injection period should be kept with a minimal variation of 10 minutes among patients. The wait period should not be shorter than 50 min and longer than 75 minutes at baseline. The time difference between baseline and other time points (i.e. interim and end of therapy) should **not** exceed 10 minutes.

The imaging will start after voiding the bladder. 150-200 mL of water should be given to the patient immediately prior to the study acquisition before they are positioned on the table to distend stomach and avoid physiologic stomach uptake.

c. FDG-PET-CT Image Acquisition

Patients should be positioned on the table in a headfirst, supine position with arms elevated above the abdomen to reduce beam-hardening artifacts at the level of the liver. The use of IV and oral contrast is at the discretion of each institution. However, IV-contrast CT acquisition is recommended to follow PET imaging acquired with non-contrast CT to avoid variations in FDG uptake in the blood pool and the tumor.

If IV contrast is not used, CT should be acquired using a current of not less than 120 mA/second to allow for sufficient resolution for definition of anatomic structures. Immediately after CT scanning, a PET emission scan will be obtained.

The PET-CT scan should cover at least from the mid skull to the 1/3 proximal femurs. The time/bed position should be in accordance with the manufacturer's recommendations for optimal imaging.

It is critical that follow-up PET-CT scans be performed in an identical way to the baseline scan, with the same scanner, same scan direction (skull to thighs or thighs to skull), and consistent arm positioning (arms up or arms down).

18.6 Radiation Therapy Guidelines

End of treatment Residual PET RT may be administered at the discretion of the treating physician, provided that the intent to deliver RT was declared at study enrollment and the criteria in Section 7.5 are met.

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

Radiotherapy (RT) for patients can only be delivered at approved RT facilities.

Pre-treatment Review of Radiation therapy plans will be conducted by IROC Rhode Island. Data detailed in Section 14.4 must be submitted one week prior to the start of Radiation Therapy for review and approval. This RT QA review will also confirm sites of partial response which will require radiation. Any radiation therapy delivered not consistent with the RT QA review response categorization will be considered a major protocol deviation.

a. Indications for Radiotherapy

The indication for RT will be based on imaging evaluation performed upon completion of 6 cycles of systemic therapy. In general terms, RT will be delivered when patients have 1-2 sites initially involved with HL that achieve only a partial response. Specifically, RT will be indicated when the patient has persistent sites upon completion of 6 cycles of systemic therapy that meet all of the following criteria:

1. Residual nodal mass ≥ 2.5cm in axial diameter, or residual extranodal lesion >1cm in axial diameter (e.g. lung nodule or splenic nodule), and
2. Has Deauville score = 4 or 5, and
3. Has ≥ 30% reduction in maximal transverse diameter compared to pre-treatment imaging.

RT may be given to one or two nodal sites.

The following circumstances are contraindications for RT:

1. Deauville score 5 due to development of new PET avid sites during systemic therapy.
2. Three or more persistent PET-avid (Deauville score 4-5) sites at completion of systemic therapy.
3. A PET-avid site contained within a CT abnormality that has not achieved at least 30% reduction in transverse diameter.

Patients with these features are unlikely to be cured with RT, and biopsy with alternative management should be considered.

b. Radiotherapy Dose and Schedule

PET Positive After 6 Cycles of Systemic Therapy (PET score 4-5)
Radiotherapy will consist of 3000-3600 cGy in fractions of 150-200 cGy per day. The treatment will be given 5 days per week. All fields should be treated once each day. The total elapsed treatment time will be approximately 4 weeks.

c. Timing of Radiotherapy and Starting Criteria

Treatment should begin 5-12 weeks from Cycle 6, Day 15 of chemotherapy or when blood counts have recovered.

Criteria include an ANC > 750/μL and platelets > 75,000/μL prior to treatment for each site.

d. Credentialing Requirements

Patients may receive RT with photons or proton therapy. Intensity Modulated Radiation Therapy (IMRT), VMAT (or its equivalents) or protons are allowed in circumstances where the treating oncologist believes these provide significant clinical benefits compared to conventional anterior-posterior parallel opposed pairs. Investigators may use proton therapy only if their institution has been appropriately credentialed by the IROC Houston QA Center. Credentialing requirements for proton therapy which include, but are not limited to, completion of a proton facility questionnaire, a successful IROC Houston site visit, which identifies the proton technique(s) which can be used, annual monitoring of the proton beam calibration, e.g. IROC Houston's monitoring program, and successful digital phantom data submission to IROC Houston (details for data submission are available at http://rpc.mdanderson.org). Centers not previously credentialed for use of proton therapy treatment of thoracic tumors must irradiate the Proton Lung Phantom available from IROC Houston.

The credentialing requirements by treatment modality are summarized in the following table.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org			
	Treatment Modality			
	3D-CRT	Photon	Proton	Key Information
Facility Questionnaire	**X**	**X**	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	**X**	**X**	**X**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation		**X**	**X**	Sites treating with IMRT and not previously credentialed for its use on COG trials must irradiate IROC Houston's thoracic phantom. Proton centers must complete all required phantom irradiations for IROC Houston credentialing, including the proton lung phantom. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site. (http://irochouston.mdanderson.org).
Motion Management (when used)		**X**	**X**	If treating with IMRT and gating or tracking methods are used to compensate for respiratory motion, IROC Houston's Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site. (http://irochouston.mdanderson.org)
Credentialing Notification Issued to:				
Institution				Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met.

e. Equipment

1. Modality

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

Proton therapy may be delivered using passively scattered proton or scanning beams provided that the specific beam line in use has been appropriately credentialed. Selected proton energies should be high enough to adequately provide target coverage. Range shifters may be used to make fine adjustment to the maximum proton range.

Use of IMRT in conjunction with gating or tracking techniques requires credentialing by the IROC Houston. The Motion Management Reporting Form shall be submitted with the Quality Assurance Documentation materials whenever motion management techniques are used.

2. Guidelines and Requirements for the Use of Proton Beam Therapy

Investigators using proton beam therapy will be required to comply with current guidelines for the use of protons in National Cancer Institute sponsored cooperative group trials. These guidelines are available on the IROC Houston website at http://irochouston.mdanderson.org. Questions regarding proton therapy on trial should be sent to Bradford Hoppe MD (hoppe.bradford@mayo.edu) and/or Stella Flampouri PhD (stella.flampouri@emory.edu). These guidelines specify the following for the participating institution: dose reporting will be in Cobalt Gy equivalent (1 CGE = 1 proton Gy * 1.1) which is the same as ICRU 78 DRBE; radiation doses shall be prescribed to protocol specified definitions for gross (GTV) and clinical (CTV). For CT number to proton stopping power calibration uncertainties, set-up uncertainties and target motion, additional margin, smearing, range of modulation will be added on a per beam basis for passive scattering and uniform scanning. The proton institution is required to participate in on-site and remote review according to COG requirements.

3. Treatment Planning

CT (volumetric) based planning is required to optimize dose to the targeted volume while documenting dose to normal tissues. Slices ≤ 5 mm thick should be taken throughout the extent of the irradiated volume.

In cases where the mediastinum or spleen is being treated, the entire thoracic volume should be scanned to create accurate estimates of lung and heart dose.

There are mandatory requirements for submission of the dose to selected normal tissues (see Section 18.6l). A Dose Volume Histogram (DVH) is necessary to determine target coverage and evaluate dose to normal tissues.

4. In-Room Verification of Spatial Positioning
Image guidance to verify patient position is an important standard feature of contemporary RT delivery. Institutional protocols should be in place common to verify patient position. Orthogonal pair (AP and lateral) portal images (MV or kV) or cone-beam imaging are acceptable. There is no central review of verification imaging.

f. Target Volumes

Recommendations of The International Commission on Radiation Units and Measurements (ICRU) for prescription methods and nomenclature will be utilized for this study (Reports 50, 62, and 78).

It is not necessary to treat initially involved sites that have achieved an anatomic and metabolic Complete Response. The indications for RT are outlined in Section 18.6a and should be the principal determinants in defining the gross tumor volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV).

Note: The following definitions apply only to sites of disease that meet the criteria for receiving RT.

1. Post-Chemotherapy GTVtotal

Following completion of 6 cycles of systemic therapy, the post-chemotherapy GTVtotal includes persisting imaging abnormalities seen on CT that encompass a PET-avid site (Deauville 4-5). Note that for RT planning purposes, this includes the parts of that mass that are PET-negative. The GTV (and CTV) are not just the PET-avid volume within the persistent CT abnormality. Residual nodal masses must be ≥2.5 cm in greatest axial diameter and residual extranodal lesions (lung nodules, splenic nodules) must be ≥1cm to be eligible for RT. The CTV and PTV encompassing the GTVtotal are to be prescribed 30Gy.

GTVPET+: This is defined as the volume of imaging abnormality that remains PET avid (Deauville score 4-5) following completion of 6 cycles of systemic therapy. This volume is contained within, and is typically smaller than, the post-chemotherapy GTVtotal defined above. This volume, and its surrounding PTV, should be boosted with an additional 6Gy (total 36Gy) provided the boost does not cause the normal tissue dose limits described below to be exceeded. The boost is not required if it causes the normal tissue constraints to be exceeded. When a boost is to be employed, a CTV expansion is not required around the GTVPET+ volume, although an ITV/PTV expansion is required.

2. Post-Chemotherapy Clinical Target Volume (CTV)

For this study, the CTV should encompass the GTVtotal volume described above, plus any additional volume that may be required to account for uncertainty in disease localization due to variation in imaging, patient positioning, etc. Since the at-risk CT abnormality encompasses the PET-avid volume, this volume will almost always be larger than the GTVPET+ volume.

Delineation of the CTV requires consideration of the expected routes of disease spread, and the quality of the imaging. For example, in some circumstances it can be difficult to clearly rule out disease (e.g. in the aorto-pulmonary window) or not possible to exactly locate the CT/PET abnormality within an exact location in an axial image of the involved nodal space. Consideration of other clinical and imaging factors should guide decisions regarding whether to include or exclude such areas from the CTV.

The CTV expansion cannot be rigidly determined a priori as there can be uncertainties inherent with GTV delineation due to inaccuracies in matching patient positioning and the variable internal anatomy shifts that change with patient position between diagnostic and treatment positions. As a guideline, a margin of 1.0 cm above and below the GTVtotal is recommended. When boosting the PET-avid volume, it is not necessary to add a CTV expansion around the GTVPET+ volume (i.e. the CTVPET+ and the GTVPET+ are the same).

Uncommonly, normal nodal tissue may be included in the CTV if located between two anatomically close (i.e. within 5 cm) sites requiring RT that are going to be joined and treated as a single volume.

3. Internal Target Volume (ITV)

The ITV encompasses the CTV with an added margin to account for variation in shape and motion within the patient. Respiratory motion, for example, will produce movement of the mediastinal structures and spleen, and an additional margin around the CTV is required to account for this. For proton treatments, target motion assessment should be performed 4DCT and dose distributions should be calculated and reviewed on the two extreme breathing phases. When motion reduction techniques are used such as breath-hold or abdominal compression, multiple scans should be acquired during simulation to evaluate the reproducibility of the method. ITV should encompass the CTV from all available scans.

4. Planning Target Volume (PTV)

The PTV should encompass the CTV and ITV, and accounts for geometric variation in daily setup. It should take into account the reproducibility of the immobilization, and the accuracy of the daily setup imaging.

Notably, for a CTV that includes inferior mediastinal structures, an isometric 5 mm expansion around will rarely provide adequate coverage. ITV+PTV margins in the mediastinum should range from 8-15 mm and should not be as small as 5 mm.

ITV+PTV margins around the spleen should be 10-15 mm, unless 4D simulation demonstrates the need for a larger margin.

Targets at non-contiguous sites need to be separately identified. Numerical or descriptive suffixes can be used such as GTV2, CTV2, PTV2; or GTV-pelvis, CTV-pelvis, PTV-pelvis, for instance. Generally, in cases for which two PTV targets are >5 cm apart, these should be treated separately unless there is a compelling reason to treat uninvolved tissue in between.

When proton therapy is used, the GTV and CTV are the same as for photons.

In patients with moving tumors within the lung, the iGTV is required for calculation of dose for proton therapy. The iGTV includes the GTV with a margin for GTV respiratory motion. The PTV is defined differently for the purpose of dose reporting vs. treatment planning. For dose reporting purposes the PTV will include a margin which is added to the CTV in 3-dimensions. The margin should be consistent with the motion control and setup accuracy for the particular type of treatment (scattered versus scanning) at the treating proton center. Robustness evaluation based on dose calculations of error scenarios as described in Section 18.6g.4a. is an alternative to PTV dose reporting.

For treatment planning, the goal will be CTV coverage at 100% directly with specific measures taken for each specific uncertainty. The PTV will vary with each individual field and will require additional adjustment including (1) the lateral margins, (2) smearing of compensator, (3) range of beam (depth of penetration) and, (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 2-7 mm) will be based on the range uncertainty, CT number uncertainty, internal motion, and set up error determined for the particular body site at the individual proton institution. The following parameters must be explicitly reported for each beam when using passive scattering or uniform scanning: range, modulation, smearing radius of the compensator, set-up margin (SM) and PTV margin. The specifics of dose reporting for the proton PTV and recommendations regarding the PTV margin are discussed in Section 18.6g.

5. Special Circumstances

Sites of initially involved nodal disease adjacent to PET-avid target site

It is not required to include within the CTV sites of initial involvement that are adjacent to a PET-avid mass and that have achieved anatomic and metabolic Complete Response. However, in some circumstances, inclusion of immediately adjacent sites in the CTV may be viewed as clinically appropriate and may be achieved without significantly increasing normal tissue dose (for example, adjacent extranodal involvement where recurrence could cause nerve root compression). In these circumstances, treating clinicians can include adjacent sites of involvement without incurring a protocol violation.

Circumstances in which PET-negative adjacent sites should be excluded from the CTV include: axillae in females, the high cervical nodes (salivary structures), and cardiophrenic/diaphragmatic nodes (heart).

Uninvolved adjacent sites should never be included, with the exception of the linking of two closely approximated sites that each meet criteria for requiring RT (see below).

Clinicians may contact IROC RI or one of the study radiation oncologists to discuss specific cases as necessary.

6. Joining separate sites of disease receiving RT

When two sites of disease meet criteria for receiving RT, these should typically be treated as separate targets if the PTV volumes are > 5 cm apart. Separate sites may be joined at the discretion of the treating oncologist in cases where the intervening nodal tissue was involved, or when issues of setup variability or concerns about the accuracy of dosimetry within small shielded areas between two treated sites may make linking two volumes preferable. When this is done, care should be taken to consider and treat the appropriate nodal anatomy in the intervening volume.

7. Specific Anatomic Sites

a. Spleen

The spleen will be treated if it is a site containing PET-avid lesion(s) meeting the criteria listed above. In such cases, the entire spleen should be targeted as the CTVtotal, not just the incompletely responding nodule.

NOTE: For patients with **involvement of the spleen**, vaccination against Pneumococcus, *Haemophilus influenza* and Meningococcus is strongly recommended **prior** to therapy. If not performed at this time, it should be administered prior to beginning radiation therapy. Waiting to immunize until after Cycle 6 may be affected by muted immune response at that time.

b. Lung, pericardium, liver, bone or other parenchymal nodules

These sites are treated only if they contain localized sites of incomplete response meeting the RT-eligibility criteria listed above. Irradiation of the whole lung, whole liver or entire bones is to be avoided.

c. Mediastinum (including hila)

In cases where the residual mediastinal disease is enmeshed within the major vessels, it is acceptable to contour the entire mediastinum as the CTVtotal at levels above the heart. However, at the level of the heart, effort should be made to localize GTV/CTV volumes as precisely as possible using the definitions above without including the heart in the CTV (unless there is direct pericardial/cardiac involvement).

In circumstances when the mediastinum is being treated for protocol-directed indications and when the adjacent nodal or extranodal sites (e.g. chest wall, internal mammary nodes, hilar nodes) were involved but achieved a complete anatomic response on CT and PET, it is not necessary to encompass the adjacent sites. However, the volume may be extended at the discretion of the treating oncologist to include these immediately adjacent sites if they are viewed to be at substantial risk and can be encompassed without significantly increasing normal tissue dose to the lung, female breast, or heart. This is not mandatory, however, and will not be counted as a protocol deviation.

d. Spleen only

In those patients scheduled to receive RT to the spleen because of incomplete response, the entire spleen should be treated as the CTVtotal. A 6Gy boost to the PET avid volume is allowable, but not necessary. Target delineation with 4D-CT imaging is preferred, but in the absence of 4D-CT, a 1.0 -1.5 cm field margin to account for respiratory movement is acceptable. The post-chemotherapy spleen volume should be used, as defined by CT scan. If the paraaortic lymph nodes were not initially involved, or achieved a metabolic complete response, they do not need to be included.

e. Paraaortic lymph nodes only

Intravenous contrast is recommended for RT planning CT scans. In cases where the involvement of lymph nodes meeting the criteria for RT is difficult to visualize following chemotherapy, the CTV should encompass a symmetric expansion around the para-aortic vessels of at least 12 mm. It is not necessary to include the spleen in the CTV unless it would otherwise meet criteria for requiring RT.

f. Pelvic lymph nodes

Intravenous contrast is recommended for RT planning CT scans. In cases where the lymph nodes are difficult to visualize following chemotherapy, the CTV should encompass a symmetric expansion around the major pelvic vessels of at least 10 mm.

For female patients, MRI simulation and/or fusion of pelvic MRI with planning CT should be performed to contour the ovaries and facilitate estimation of ovarian dosimetry. Females should have consideration for an oophoropexy moving the ovaries away from the PTV volume. The male gonads should also be shielded using a clam-shell type block, as appropriate. Positioning the legs apart may facilitate testicular shielding.

g. Pericardium

Whole pericardial irradiation is contra-indicated. If the pericardium was extensively involved by lymphoma and is part of the CTV definition, the mean dose to the heart should be limited to < 15 Gy. In circumstances where this cannot be achieved, the treating oncologist should review the case with a study investigator.

h. Sites of metastatic disease or isolated extranodal disease (lung, liver, bone)

Sites of metastatic or isolated extranodal disease are treated only if they meet the criteria listed above. Whole organ irradiation is contraindicated. For PET avid lung nodules, the involved portion of lung (or lungs) should be treated with at least a 1.5 cm margin. Patients presenting with a pleural effusion should not receive treatment to the whole hemithorax. Similarly, isolated liver or bone lesions meeting criteria for RT may be treated with GTV, CTV, and PTV definitions as described above. Whole liver or bone RT is not required.

i. Solitary Bone or Bone Marrow Lesion

A skeletal lesion seen on FDG-PET should only be considered true bone lesion if there is an associated bone abnormality seen on CT at the time of diagnosis. Abnormal sites involving the skeleton without an associated CT abnormality should be considered as bone marrow involvement.

RT is only indicated for true bone involvement that remains PET avid (Deauville 4-5) at completion of systemic therapy. Bone sites meeting the criteria for RT should be treated with at least a 1 cm margin around the radiological abnormality. No more than 2 sites should be considered for radiation. Some residual metabolic activity in bone may reflect bony healing, and thus interpretation within the context of the response of other involved areas may be appropriate. In these situations, WebEx conference between IROC, treating institutions and study committee chairs should be considered. The sites can be determined in evaluation and review with IROC.

g. Target Dose

The dose to the GTVtotal, CTVtotal, and PTVtotal, should be 3000-3600 cGy in 150-200 cGy fractions, with a sequential or concurrent boost of 600 cGy to the PET avid volume (GTVPET+/PTVPET+).

1. Dose Definitions

The absorbed dose is defined in centigray (cGy)-to-muscle. Proton dose will be reported in Gy (relative biological effectiveness, RBE), where 1 Gy (RBE) = proton dose Gy x RBE, and RBE = 1.1.

2. Plan Normalization

There are several ways in which plans cans be normalized, most commonly normalization to a point or to an isodose surface. In all cases the isodose coverage around GTV, CTV and PTV should be evaluated and the dose uniformity requirements indicated below should be satisfied. If normalization is to a point, the point should be in solid tissue, not in lung. If the central axis falls beneath a block in any field, an appropriate off-axis point may be used for calculations.

3. Heterogeneity corrections

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. When treatment beams traverse lung, planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. When protons are used, correlation between the institutional CT treatment planning system Hounsfield Units and “relative proton stopping power” must be established and documented. Proton therapy should be used with extreme caution when any of the treatment beams traverse normal lung parenchyma.

4. Dose Uniformity

For all treatments, 95% of the prescription dose must cover ≥ 99% of the CTV and ≥ 95% of the PTV.

For patients not receiving a 6Gy boost, no more than 10% of the CTV or PTV should receive more than 110% of the protocol dose (i.e. 3300cGy).

Concurrent boost will produce allowable dose inhomogeneity within the GTVtotal, CTVtotal and PTVtotal. For patients receiving a 600cGy boost, 95% of the total 3600cGy dose (i.e. 3420cGy) must cover >95% of the PTVPET+ volume, and no more than 10% of the PTVPET+ volume should receive more than 110% of the protocol dose (i.e. 3960cGy).

In addition, 95% of the prescription dose should cover ≥ 95% of the PTV and ≥ 99% of the CTV. The maximum dose in the patient should not exceed 110% of the prescription dose.

No more than 0.03 cc of the PTV should receive less than 85% of the prescription dose.

- If > 0.03 cc of the PTV receives 75-85% of the prescription dose, this will be a minor deviation.
- If > 0.03 cc of the PTV receives <75% of the prescription dose, this will be a major deviation.

a. Proton Specific Guidelines:

For protons, treatment planning does not specifically use a traditionally defined PTV for treatment planning. All uncertainties are taken into account explicitly to create a robust plan that provides full dose coverage of the CTV, generally from each beam – proton plans should be evaluated for adequate coverage provided by each individual beam and for PTV coverage from the summation of all beams. For passive scattering and uniform scanning, the aperture margin must include the appropriate beam penumbra for the selected beam energy, and PTV margin. These margins depend on the patient setup techniques used at the treating proton center. The aperture margin may be expanded further if a cold spot occurs near the edge of CTV due to insufficient lateral scatter. The smearing radius for the range compensator must be equal to the PTV margin. The beam range should be equal to the maximum water equivalent depth of the CTV plus a range margin. The main part of the range margin comes from uncertainty in CT accuracy and the conversion of the Hounsfield units to proton stopping power ratios. Additional range margin should be applied if internal motion could increase the water equivalent depth of the CTV. The modulation width should be increased consistently to ensure proximal coverage of the target volume. The beam range may be adjusted at the discretion of the treating radiation oncologist based on normal tissue dose concerns. For PBS, robust optimization should be used. If robust optimization is not available, treatment plan robustness should be evaluated. Dose distribution of each beam should be reviewed individually to ensure that CTV plus the lateral, distal and proximal margins are covered. In cases that CTV is affected by breathing

motion, coverage must also be reviewed in both inhale and exhale breathing phases. A PTV should be created by a uniform expansion from CTV for reporting purposes. A potential exception is when the range margin is smaller than the PTV expansion. As a result, the beam may not penetrate deep enough to sufficiently cover the distal portion of the PTV. This may occur for shallow target volumes where the maximum depth of the CTV is small and the range margin is small. This scenario is not expected for this protocol; however, such incomplete coverage of the PTV will not constitute a planning deviation because the plan should be sufficiently robust to cover the CTV with the protocol specified dose accounting for all uncertainties. In this case, robustness evaluation based on dose distribution calculations of error scenarios is recommended. CTV coverage must be maintained, and normal tissue constraints should not be violated in the presence of set-up errors, range calculation uncertainties and breathing motions. Target coverage should be maintained on inhale, exhale and under the worst-case scenarios that combine setup and range uncertainties. Questions related to proton therapy on trial can be made to Bradford Hoppe (hoppe.bradford@mayo.edu) and Stella Flampouri PhD (sstella.flampouri@emory.edu)

5. Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once RT has been initiated, treatment will not be interrupted except for any life-threatening infection or severe hematologic toxicity defined as ANC < 300/µL or platelets less than 40,000/µL during the course of treatment. Under these circumstances, RT shall be delayed until the counts have recovered. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size. If any area has been previously treated (emergently), care should be taken not to exceed normal tissue tolerance levels.

h. Treatment Technique

There is no limitation to the use of IMRT, Volumetric Arc Therapy (VMAT, or similar approaches) or protons, provided immobilization, motion management, target coverage and homogeneity requirements are met. In certain circumstances, the use of electron beam RT to treat superficial sites is permitted. Methods of patient immobilization and organ motion can be undertaken as per institutional protocols. Patients receiving RT to the neck should be immobilized in a thermoplastic mask. 4-D simulation and breath-hold techniques are permitted to estimate organ motion and minimize PTV expansions.

1. Selection of Proton Beam Arrangements

There are uncertainties (1-3 mm) in the distal range of the proton beam in which the RBE may be greater than 1.1; therefore, single proton beam plans which stop in the spinal cord will not be allowed.

2. Motion Management and Margins to Account for Target Volume and Organ Motion

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the internal motion (IM) component of the PTV and is meant to account for potential motion of the CTV. If adequate clinical data do not exist to define the IM component of the PTV margin, the following suggestions are provided:

- For a CTV susceptible to physiologic motion, a margin of at least 0.5 cm should be added to the CTV prior to PTV margin expansion or a PTV margin of 1 cm should be chosen, unless additional motion management (e.g. active breath hold and/or daily CT imaging) are employed.
- For tumors of the thorax or abdomen, an assessment should be made to determine the extent of motion present. PTV margins should include this motion as a component. In the mediastinum the PTV margin around the CTV should be ≥8 mm.
- It is strongly advised that when IMRT/VMAT or protons are used for targets within the thorax, the degree of tumor motion should be assessed and accounted for in an ITV. Motion of the target volume in three dimensions (cranial, caudal, anterior to posterior, and lateral) may be determined by 4-dimensional CT, respiratory gated CT, or other accepted techniques.
- In cases where 4D-CT is not used to assess target motion in the chest because a breath-hold technique is being employed, the superior and inferior PTV margin around the CTV should be ≥8mm. For protons is recommended that multiple CT scans on breath-hold are acquired during simulation to assess the reproducibility of the breath-hold and the robustness of the plan to variations.
- A description of the method used and evidence (i.e., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4-D CT) of the remaining tumor motion should be submitted on the Motion Management Reporting Form with the Quality Assurance Documentation materials as noted in Section 18.6l.

NOTE: For patients treated with IMRT, use of gating or tracking methods to compensate for respiratory motion requires irradiation of IROC Houston's Thorax-Lung Phantom with accompanying reciprocating platform to simulate motion. Contact IROC Houston (http://irochouston.mdanderson.org) for information about their phantoms.

i. Treatment Position

The patient should be treated entirely in the supine position. Some institutions may incline female patients to reduce breast dose, and this is acceptable. Reproducible setups are critical, and the use of immobilization devices are strongly encouraged.

j. Organs at Risk

1. Lungs

No more than 35% of the entire lung volume (i.e. bilateral lung) shall receive a *cumulative* dose greater than 2000 cGy (i.e. V20 should be ≤ 35%). The bilateral mean lung dose must be less than 1500 cGy.

2. Kidneys

If the GTV encroaches on one of the kidneys, the mean dose to the designated *ipsilateral* kidney should not be greater than 1500 cGy. In that instance, 50% of the contralateral kidney should receive no more than 800 cGy and no more than 25% should receive a cumulative dose greater than 1200 cGy. If both kidneys require treatment (beyond standard APPA fields to the para-aortic region) both kidneys may receive a mean dose of 1200 cGy and no more than 50% of either kidney should receive 1500 cGy.

3. Liver

No more than 50% of the liver shall receive a cumulative dose greater than *1500* cGy. No more than 25% of the liver may receive a dose greater than 2100 cGy.

4. Spinal Cord

Whenever the spinal cord is included in adjacent treatment areas, the field borders *will* be separated by an appropriate gap. The gap dose to the spinal cord at that gap should be calculated and submitted as part of the Quality Assurance Documentation. The maximum dose to the spinal cord for all combined RT treatments must be less than 4500 cGy.

5. Heart

The goal should be to limit the mean heart dose to less than 1500 cGy. If mean heart dose is anticipated to be greater than 1500 cGy, then IMRT deep inspiration breath hold, or proton therapy should be considered. A mean heart dose exceeding 2000 cGy will be considered a protocol deviation unless reviewed with IROC and a study radiation oncologist and deemed unavoidable prior to treatment.

6. Breast and Thyroid

Doses to the breast and thyroid should be kept as low as reasonably achievable.
Dosimetric data should be submitted for the following organs at risk: female breast (left, right and combined), lungs (left, right and combined), thyroid, liver, kidney (right, left), and heart when any of these tissues are in the entrance or exit path of any beam. (See below).

k. Dose Calculations and Reporting

1. Prescribed Dose

The prescribed dose for each target volume and/or phase of treatment shall be submitted using the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT or proton therapy is used, the monitor units generated by the IMRT/ proton therapy planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total dose delivered shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record.

2. Scanning Limits

The scanning limits must be adequate to produce whole organ estimates of normal tissue dosimetry as outlined below. Treatment of the mediastinum requires evaluation of the thyroid, female breasts, heart and lungs. Treatment of the spleen requires dose estimation to the heart (i.e. requiring scanning and contouring of the heart) in addition to the kidneys and liver.

3. Normal Tissue Dosimetry

Dose volume histograms (DVH) and tabular dose reports including mean and maximum dose shall be submitted for the following organs at risk: female breast (left, right and combined), lungs (left, right and combined), thyroid, liver, kidney (right, left), and heart.

These DVHs are required when the organ is in the entrance or exit path of any beam or beam segment. Where these organs are only exposed to "scatter dose" it is not necessary to scan the entire organ only for the purposes of creating a DVH.

A DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin and encompasses all tissues within a volume 2 cm above and below the PTV.

4. Standard Naming Convention for Structures

Please use the following standard naming convention for delineated structures.

Standard Name	**Description**
GTVtotal	Total GTV
CTVtotal	Total CTV
PTVtotal	Total PTV
Lung_L	Left lung
Lung_R	Right lung
Lungs	Combined left and right lungs
Kidney_L	Left kidney
Kidney_R	Right kidney
Liver	Liver
SpinalCord	Spinal cord
Heart	Heart
Breast_L	Left breast for female patients
Breast_R	Right breast for female patients
Breasts	Combined left and right breasts
Thyroid	Thyroid

I. Quality Assurance Documentation

1. Digital Submission

Submission of treatment plans as DICOM RT is required. Digital data must include treatment planning CT, structures, plan, and dose files.

Submission of required data below via TRIAD is strongly preferred. See Section 15.4 for TRIAD instructions. Due to the critical time constraints for submitting data for pre-treatment review, we encourage sites to submit data via TRIAD to ensure that the pre-treatment reviews are completed in a timely manner. In the event that a site has not completed all steps required for TRIAD data submission in time to meet the timeline for review, data submitted via SFTP will also be accepted. See the instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data (www.irocri.qarc.org). Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data.

2. At least 1 week prior to the start of radiotherapy, submit the following for **pre-treatment review**:

a. Treatment Planning System Output

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called “unspecified tissue.” This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field with outlines of target volumes only. Submission of DRR’s is not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

b. Supportive Data

- All diagnostic imaging used to plan the target volume.
- Copies of reports (radiology, operative, pathology, cytology) and any other information used in defining the target volumes. Note: Reports and imaging submitted for the central imaging review need not be resubmitted.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC and the radiation oncology reviewers.
- Documentation of any emergency RT administered prior to the protocol prescribed course of RT. Documentation should be provided in the form of the RT (treatment chart).

c. Forms

- RT-1 Dosimetry Summary Form
- Proton Reporting Form (if applicable)
- Motion Management Reporting Form (if motion management techniques are used)

3. Within 1 week following the completion of radiotherapy, submit the following:

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- RT-2 Radiotherapy Total Dose Record Form.

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
IROC Rhode Island
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865-4207
Tel: (401) 753-7600
Fax: (401) 753-7601
Email: physics@qarc.org

m. Definitions of Deviation in Protocol Performance

	Variation Acceptable	Deviation Unacceptable
Dose	10% PTV receives > 110% of protocol dose but ≤ 115% *or* < 95% but ≥ 90% of the protocol dose covers 95% of PTV or 99% of CTV	10% PTV receives > 115% of protocol dose *or* < 90% of the protocol dose covers 95% of PTV or 99% of CTV
Volume	Margins for CTV/PTV less than specified or excessively large	A portion of the GTV or potentially tumor bearing area (CTV) is not included in the treated volume
Organs at Risk	Dose to any required OAR exceeds the goal stated in Section 18.6j.	Will be assessed at the time of final review

18.7 Measurement-Based Response Assessment According to the Lugano Classification

Complete Response		**Complete radiologic response (all of the following)**	**Complete metabolic response (even with a persistent mass)**
	Lymph nodes and extralymphatic sites	• Target nodes/nodal masses must regress to ≤1.5 cm in longest diameter. • No extralymphatic sites of disease.	• Score ≤ 3* with or without a residual mass on 5-point scale†. • It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
	Nonmeasured lesion	Absent	Not applicable
	Organ enlargement	Regress to normal	Not applicable
	New lesions	None	None
	Bone marrow	Normal by morphology; if determinate, IHC negative	No evidence of FDG-avid disease in marrow
Partial Response		**Partial remission (all of the following)**	**Partial metabolic response**
	Lymph nodes and extralymphatic sites	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value • When no longer visible, 0 X 0 mm • For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation	• Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size • At interim, these findings suggest responding disease • At end of treatment, these findings indicate residual disease
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan

No response or stable disease		**Stable disease**	**No metabolic response**
	Target nodes/ nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable
	Organ enlargement	No increase consistent with progression	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	No change from baseline
Progressive disease		**Progressive disease requires at least 1 of the following**	**Progressive metabolic disease**
	Individual target nodes/ nodal masses	PPD progression:	Score 4 or 5 with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	An individual node/lesion must be abnormal with: • Longest diameter (LDi) > 1.5 cm and • Increase by ≥ 50% from PPD nadir and • An increase in LDi or smallest diameter (SDi) from nadir • 0.5 cm for lesions ≤ 2 cm • 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly	• New FDG-avid foci consistent with lymphoma at interim OR • end-of-treatment assessment
	Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site < 1.0 cm in any axis; if > 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma	• New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). • If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

18.8 Instructions for the SWOG Biospecimen Bank – Lab #201, Solid Tissue, Myeloma and Lymphoma Division

a. **Formalin-Fixed Paraffin-Embedded (FFPE) Tissue**: The SWOG Biospecimen Bank will receive FFPE specimens as either blocks or slides/sections at baseline.

1. If tissue block is received, then upon receipt, Bank will cut 1 H&E slide for Pathology Review. Any remaining tissue (in block) will be stored at room temperature. (Priority of slides for planned future TM objectives will be specified in a forthcoming revision.)

2. If slides are received, then 1 H&E slide will be scanned for Pathology Review and then all unstained slides will be stored refrigerated (2-8°C) and under desiccant, until distribution for planned future TM objectives.

a. Pathology review:

For each case, the Bank will scan 1 H&E slide to digital images at 40x magnification. The digital images and corresponding redacted pathology reports will be sent to study pathologists for QC pathology review. Case review will be split amongst the following pathologists and will be sent in batches throughout the duration of accrual.

b. The following pathologists will conduct Pathology review:

Joo Y. Song, M.D.
City of Hope Medical Center
1500 E Duarte Rd, # 2202A
Duarte, CA 91010
Phone: 626/256-4673 ext:62037
Fax: 626/218-8463
Email: josong@coh.org

William R. Macon, M.D.
Department of Laboratory Medicine and Pathology
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Phone: 507-284-1198
Fax: 507-284-5115
Email: Macon.William@mayo.edu

Anamarija Perry, M.D.
Department of Pathology
University of Michigan
2800 Plymouth Road, Bldg 35
Ann Arbor, MI 48109
Phone: 734-232-5376
Fax: 734-232-5360
Email: anaperry@med.umich.edu

Alexandra Kovach, M.D.
Department of Pathology and Laboratory Medicine
Children's Hospital Los Angeles
4650 Sunset Blvd, Mailstop #32
Los Angeles, CA 90027

Phone: 323-361-5405
Fax: 323-361-8039
Email: akovach@chla.usc.edu

b. **Peripheral Blood in cfDNA Streck Tubes:** The SWOG Biospecimen Bank will receive ambient peripheral blood in cfDNA Streck tubes at up to 4 timepoints. Upon receipt, the Bank will accession and process for plasma and buffy coat. Plasma is processed using the following double-centrifugation protocol: 1,500xg for 10 minutes at room temperature with brake (buffy coat is removed at this point); plasma is removed and centrifuged again at 3,000xg for 10 minutes at room temperature with brake. Plasma will be stored in 1-mL aliquots, and buffy coat will be stored as 1 aliquot; both plasma and buffy coat will be banked in a -80°C freezer until distribution. Planned future correlatives (ctDNA analysis) are planned for incorporation with a forthcoming revision.

18.9 CYP1A2 and CYP3A Inhibitors and Inducers

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[a], zafirlukast	methoxsalen, mexiletine, oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton
CYP3A	boceprevir, cobicistat[c], conivaptan[c], danoprevir and ritonavir[d], elvitegravir and ritonavir[d], grapefruit juice[e], indinavir and ritonavir[d], itraconazole[c], ketoconazole, lopinavir and ritonavir[c,j], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[d], posaconazole, ritonavir([c,d]), saquinavir and ritonavir[c,d], telaprevir[c], tipranavir and ritonavir[c,d], troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone[c], erythromycin, fluconazole[b], fluvoxamine[a], imatinib, tofisopam, verapamil[c]	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor[c], lomitapide, ranitidine, ranolazine[c], tacrolimus, ticagrelor[c]
	clarithromycin(c), diltiazem(c), idelalisib, nefazodone, nelfinavir[c]		

1. Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively. Strong inhibitors of CYP3A causing ≥10-fold increase in AUC of sensitive index substrate(s) are shown above the dashed line.
2. This table is prepared to provide examples of clinical inhibitors and is not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].
3. [a] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A.
   [b] Strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A.
   [c] Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).
   [d] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
   [e] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

4. Abbreviations: AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; OATP1B1: organic anion transporting polypeptide 1B1; OAT3: organic anion transporter 3; P-gp: P-glycoprotein.

	Strong inducers	**Moderate inducers**	**Weak inducers**
CYP1A2		phenytoin[(a)] rifampin[(b)], ritonavir[(c)], smoking, teriflunomide	-
CYP3A	carbamazepine[(d)], enzalutamide[(e)], mitotane, phenytoin[(b)], rifampin[(a)], St. John's wort[(f)]	bosentan, efavirenz, etravirine, modafinil	armodafinil, rufinamide

1. Note: Strong, moderate, and weak inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively.
2. This table is prepared to provide examples of clinical index inducers and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].
   [(a)] Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.
   [(b)] Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.
   [(c)] Strong inducer of CYP2C19 and moderate inducer of CYP1A2, CYP2B6, CYP2C9.
   [(d)] Strong inducer of CYP2B6, CYP3A, and moderate inducer of CYP2C9.
   [(e)] Strong inducer of CYP3A and moderate inducer of CYP2C9, CYP2C19, CYP3A.
   [(f)] The effect of St. John's wort varies widely and is preparation-dependent.
3. Abbreviations: AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction.

18.10 PRO-CTCAE Common Terminology Criteria for Adverse Events (PRO-CTCAE) Instrument

a. General Information:

The PRO-CTCAE instruments will be used to assess Patient-Reported toxicity outcomes.

Clinician graded CTCAE is the adverse event safety standard. PRO-CTCAE is intended to enhance the quality of adverse event data reporting in clinical trials, provide data that complements and extends the information provided by clinician reporting using CTCAE, represent the patient perspective of the experience of symptomatic adverse events, and improve detection of potentially serious adverse events.

The selection of PRO-CTCAE should be complementary to the clinician identified AEs for ongoing monitoring.

Adverse Event Characteristics: PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

Routine Adverse Event Reporting: Symptomatic Adverse Events reported by patients through PRO-CTCASE are not safety reporting and may be presented with other routine AE data.

PRO-CTCAE (adult and pediatric) assessment tools are available in the following languages. Estimated time of completion: 10 minutes.

- PRO-CTCAE: Available in English, Spanish, and French
- Ped PRO-CTCAE: Available in English

PRO-CTCAE is not currently available on the Medidata Patient Cloud ePRO.
Forms are accessible from the S1826 protocol abstract page on the CTSU website at www.ctsu.org. Administration instructions are included in Section 15.6.

Please refer to the PRO-CTCAE Terms of Use for more information.

b. Recall Period for the PRO-CTCAE measures is: 7 days

c. PRO-CTCAE Analyses

The examination of PRO-CTCAE is exploratory, given there are currently no standardized scoring rules for how to combine attributes into a single score or how best to analyze PRO-CTCAE data longitudinally. PRO-CTCAE responses are scored from 0 to 4. For each of the PRO-CTCAE adverse events examined, the scores for each attribute (frequency, severity and/or interference) will be presented descriptively using summary statistics at each assessment time. Additionally, the worst severity and/or interference over the entire course will be summarized.

d. Study-Specific PRO-CTCAE Questions for Adults (≥ 18 years of age):

Solicited Adverse Events: The following adverse events are considered expected and their presence/ absence should be solicited and severity graded at timepoints indicated in Section 9.0.

CTCAE Item - Adult	PRO-CTCAE Item (Attributes)
Mucositis oral	Mucositis oral (SI)
Nausea	Nausea (FS)
Vomiting	Vomiting (F)
Diarrhea	Diarrhea (F)
Abdominal pain	Abdominal pain (FSI)
Dyspnea	Shortness of breath (SI)
Cough	Cough (SI)
Rash	Rash (P)
Pruitis	Itchy Skin (S)
Peripheral Sensory Neuropathy	Numbness or tingling in hands or feet (SI)
Pain	Pain (FSI)
Myalgia	Aching muscles (FSI)
Arthralgia	Aching joints (FSI)
Decrease sexual interest	Decreased sexual interest (S)
Any other symptoms that you wish to report?	Other symptoms (PS)

Attribute Acronyms:

F: Frequency, S: Severity, I: Interference, P: Presence/Absence/Amount

Symptom AE	Attributes	PRO-CTCAE Items	Response options
Mucositis oral	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Nausea	Frequency	In the last 7 days, how OFTEN did you have NAUSEA?	Never, Rarely, Occasionally, Frequently, Almost constantly
	Severity	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?	None, Mild, Moderate, Severe, Very Severe

Symptom AE	Attributes	PRO-CTCAE Items	Response options
	Interference	--	--
Diarrhea	Frequency	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/ DIARRHOEA)?	Never, Rarely, Occasionally, Frequently, Almost constantly
	Severity	--	--
	Interference	--	--
Abdominal pain	Frequency	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?	Never, Rarely, Occasionally, Frequently, Almost constantly
	Severity	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Dyspnea	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Cough	Frequency	In the last 7 days, what was the SEVERITY of	Never, Rarely, Occasionally,

Symptom AE	Attributes	PRO-CTCAE Items	Response options
		your COUGH at its WORST?	Frequently, Almost constantly
	Severity	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?	None, Mild, Moderate, Severe, Very Severe
	Interference	--	--
Rash	Frequency	In the last 7 days, did you have any RASH?	Yes, No
	Severity	--	--
	Interference	--	--
Pruritis	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	--	--
Peripheral Sensory Neuropathy	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much

Symptom AE	Attributes	PRO-CTCAE Items	Response options
Pain	Frequency	In the last 7 days, how OFTEN did you have PAIN?	Never, Rarely, Occasionally, Frequently, Almost constantly
	Severity	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Myalgia	Frequency	In the last 7 days, how OFTEN did you have ACHING MUSCLES?	Never, Rarely, Occasionally, Frequently, Almost constantly
	Severity	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Arthralgia	Frequency	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?	Never, Rarely, Occasionally, Frequently, Almost constantly
	Severity	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?	None, Mild, Moderate, Severe, Very Severe

Symptom AE	Attributes	PRO-CTCAE Items	Response options
	Interference	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Decreased Sexual Interest	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your DECREASED SEXUAL INTEREST at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	--	--
Do you have any other symptoms that you wish to report?		Do you have any other symptoms that you wish to report?	Yes, No
Please list any other symptoms: (5 slots to list)	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of this symptom at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	--	--

e. Pediatric PRO-CTCAE Questions:

CTCAE Item - Pediatric	PRO-CTCAE Item (Attributes)
Mucositis oral	Mucositis oral (FSI)
Nausea	Nausea (FSI)
Vomiting	Vomiting (FI)
Diarrhea	Diarrhea (FI)
Abdominal pain	Abdominal pain (FSI)
Dyspnea	Shortness of breath (FSI)

Cough	Cough (FSI)
Rash acneiform	Pimples (bumps on face or chest) (S)
Pruitis	Itchy Skin (SI)
Peripheral Sensory Neuropathy	Numbness or tingling in hands or feet (SI)
Pain	Pain (FSI)
Myalgia	Aching muscles (FSI)
Arthralgia	Aching joints (FSI)

Attribute Acronyms:

f. Frequency, S: Severity, I: Interference, P: Presence/Absence/Amount

Symptom AE	Attributes	Pediatric PRO-CTCAE Items	Response options
Mucositis oral	Frequency	In the past 7 days, how often did you have pain in your mouth or throat?	Never, Sometimes, Most of the time, Almost all the time
	Severity	In the past 7 days, how bad was the pain in your mouth or throat?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did pain in your mouth or throat keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Nausea	Frequency	In the past 7 days, how often did you feel sick to your stomach (nausea)?	Never, Sometimes, Most of the time, Almost all the time
	Severity	In the past 7 days, how bad was your feeling sick to your stomach (nausea)?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did feeling sick to your stomach (nausea) keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Vomiting	Frequency	In the past 7 days, how often did you throw up?	Never, Sometimes, Most of the time, Almost all the time
	Interference	In the past 7 days, how much did throwing up keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot

Symptom AE	Attributes	Pediatric PRO-CTCAE Items	Response options
Diarrhea	Frequency	In the past 7 days, how often did you have runny or watery poop?	Never, Sometimes, Most of the time, Almost all the time
	Interference	In the past 7 days, how much did having runny or watery poop keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Abdominal Pain	Frequency	In the past 7 days, how often did you have stomach pain?	Never, Sometimes, Most of the time, Almost all the time
	Severity	In the past 7 days, how bad was your stomach pain?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did stomach pain keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Dyspnea	Frequency	In the past 7 days, how often did you have problems breathing (shortness of breath)?	Never, Sometimes, Most of the time, Almost all the time
	Severity	In the past 7 days, how bad were your problems breathing (shortness of breath)?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did your problems breathing (shortness of breath) keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Cough	Frequency	In the past 7 days, how often did you cough?	Never, Sometimes, Most of the time, Almost all the time
	Severity	In the past 7 days, how bad was your coughing?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did coughing keep	Not at all, Some, A lot, A whole lot

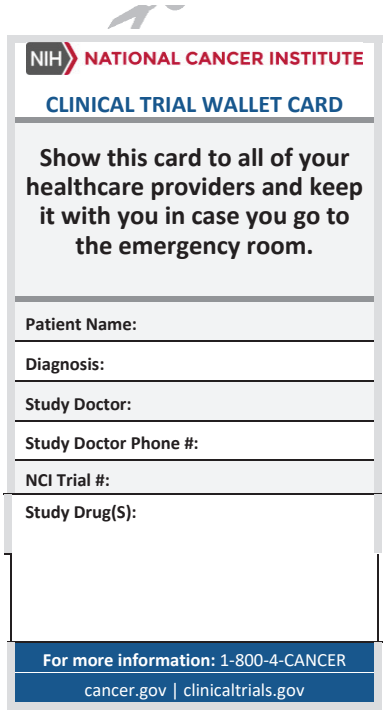
Symptom AE	Attributes	Pediatric PRO-CTCAE Items	Response options
		you from doing things you usually do?	
Rash		No Pediatric PRO-CTCAE item for Rash. Pediatric PRO-CTCAE does have Rash Acneiform or Hives	
Rash acneiform	Severity	In the past 7 days, how bad were your pimples (bumps on face or chest)?	Did not have any, A little bad, Bad, Very bad
Pruritus	Severity	In the past 7 days, how bad was your itchy skin?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did your itchy skin keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Peripheral Sensory Neuropathy	Severity	In the past 7 days, how bad was the numbness or tingly feeling in your hands or feet?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did the numbness or tingly feeling in your hands or feet keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Pain	Frequency	In the past 7 days, how often did you have pain?	Never, Sometimes, Most of the time, Almost all the time
	Severity	In the past 7 days, how bad was your pain?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did pain keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot

Symptom AE	Attributes	Pediatric PRO-CTCAE Items	Response options
Myalgia	Frequency	In the past 7 days, how often did your muscles hurt?	Never, Sometimes, Most of the time, Almost all the time
	Severity	In the past 7 days, how bad did your muscles hurt?	Did not have any, A little bad, Bad, Very bad
	Interference	In the past 7 days, how much did your muscles hurting keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Arthralgia	Frequency	How often did you have pain in any bendable part of your body (knees, ankles, shoulders, or fingers)?	Never, Sometimes, Most of the time, Almost all the time
	Severity	How bad was the pain in any bendable part of your body (knees, ankles, shoulder, or fingers)?	Did not have any, A little bad, Bad, Very bad
	Interference	How much did pain in any bendable part of your body (knees, ankles, shoulders, or fingers) keep you from doing things you usually do?	Not at all, Some, A lot, A whole lot
Decreased Sexual Interest		No Pediatric PRO-CTCAE item for decreased sexual interest	
Do you have any other symptoms that you wish to report?		Currently, our Pediatric PRO-CTCAE system does not provide options for children to report any additional symptoms they may be experiencing.	

g. References

- PRO-CTCAE Website: https://healthcaredelivery.cancer.gov/pro-ctcae/
- PRO-CTCAE Items Library
- PRO-CTCAE NCI Scientific Leadership Team
- PRO-CTCAE Development Team
- Publications

18.11 Patient Clinical Trial Wallet Card



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CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

18.12 AYA Educational Resource Information, COG Participating Site Frequently Asked Questions, NCTN Adult Group Participating Site Frequently Asked Questions

a. **AYA Educational Resource Information**

The "Enrolling Adolescent and Young Adults (AYAs) onto NCTN and NCORP Trials Frequently Asked Questions (FAQs)" document is accessible from the S1826 protocol abstract page on www.ctsu.org under the "Education and Promotion" tab. Additional pertinent AYA study conduct, regulatory, funding, CTSU navigational, RAVE access and other instructional information is accessible from the following NCTN training presentations for AYA studies. For access to the presentation links below, login to the CTSU website at www.ctsu.org prior to clicking on the links below.

How to Enroll onto Adolescent and Young Adult (AYA) Studies – A Step-by-Step Guide is accessible from: https://www.ctsu.org/readfile.aspx?sectionid=166924.The corresponding audio recording is accessible from: https://www.ctsu.org/readfile.aspx?sectionid=166925.

Webinar: Access to NCTN AYA Trials is accessible from: https://www.ctsu.org/readfile.aspx?sectionid=156366. The corresponding audio recording is accessible from: https://ctwestat.webex.com/ctwestat/lsr.php?RCID=23cf391fc69844928d537d8ec80167b5

Highlights of the "How to Enroll onto Adolescent and Young Adult (AYA) Studies – A Step-by-Step Guide," as relevant to **S1826** are excerpted below for ease of reference.

1. **Regulatory Considerations – Activating When Adult and Pediatric Groups at the same institution are BOTH Participating:**

- When Adults and Pediatric groups share the same IRB of Record (local or CIRB)
  - CTSU only accepts a single IRB approval for the institution
    - Identify who will do the regulatory submission
  - Only a single PI can be listed for the study
  - IRB paperwork needs to indicate both adults and pediatrics are listed in the accrual goals
  - Adult and Pediatric engaged research team members need to be listed on IRB paperwork
  - Adult and Pediatric consenters need to be listed in IRB paperwork
  - All locations (site codes) of research activity need to be listed

2. **Crediting Rules**

For NCTN AYA trials that are led by an Adult NCTN Group (e.g. SWOG), participating sites/investigators can credit any NCTN Group which they are a member of at the time of enrollment of each patient into OPEN.

3. **For COG-credited Patient Registration:**

For participating COG sites and sites crediting patient registration to COG:

- Prior to registration to **S1826**, a COG patient ID number must be assigned to all COG-credited patients. The COG patient ID is then used to complete the registration process.
  - The COG patient ID number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained.
  - The COG patient ID number is used to identify the patient in all future interactions with COG.
- If you have problems with the COG registration, please refer to the online help.
  - For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.
- Once the registration process is completed in OPEN, a SWOG Patient ID will be generated.
  - The SWOG Patient ID must be utilized for all data entry, specimen shipment, and TRIAD entry.

4. **Funding for AYA Trials:**

Whether COG or an adult NCTN Group is leading an AYA trial, funding for enrollments is determined as follows:

- AYA Enrollments credited to COG:
  - COG will provide funding to their member sites.
- AYA enrollments credited to an adult NCTN group:
  - Funding will be provided by the NCTN credited Group for Rostered sites (non-LAPS and non-
  - NCORP);
  - LAPS Grants provide funding for AYA trial enrollments;
  - NCORP Site Grants provide funding for AYA trial enrollments.
- Please review the funding information posted on the **S1826** protocol abstract page at www.ctsu.org.

b. **COG Participating Site Frequently Asked Questions:**

1. Does SWOG conduct a site initiation visit (SIV)?
   - No. As with all cooperative group trials, participating sites are responsible for conduct of the protocol, including ensuring site staff are trained on the procedures/assessments outlined in the protocol. To assist sites in managing initiation activities, there are three informational overview documents posted on the protocol abstract page at: www.ctsu.org under the Education and Promotion tab: 1) **S1826** Training Presentation; 2) **S1826** Investigator Training Reference for PET-CT, and 3) Financial Assistance Navigation Information.

2. How do I order nivolumab?
   - See protocol Section 3.1g for ordering instructions.
   - Note: A patient must be randomized to the N-AVD arm before the site can order drug.
   - Drug ordering, shipment, stability, and accountability questions should be directed to CTEP/PMB. Contact information is included in Section 3.1g.4.

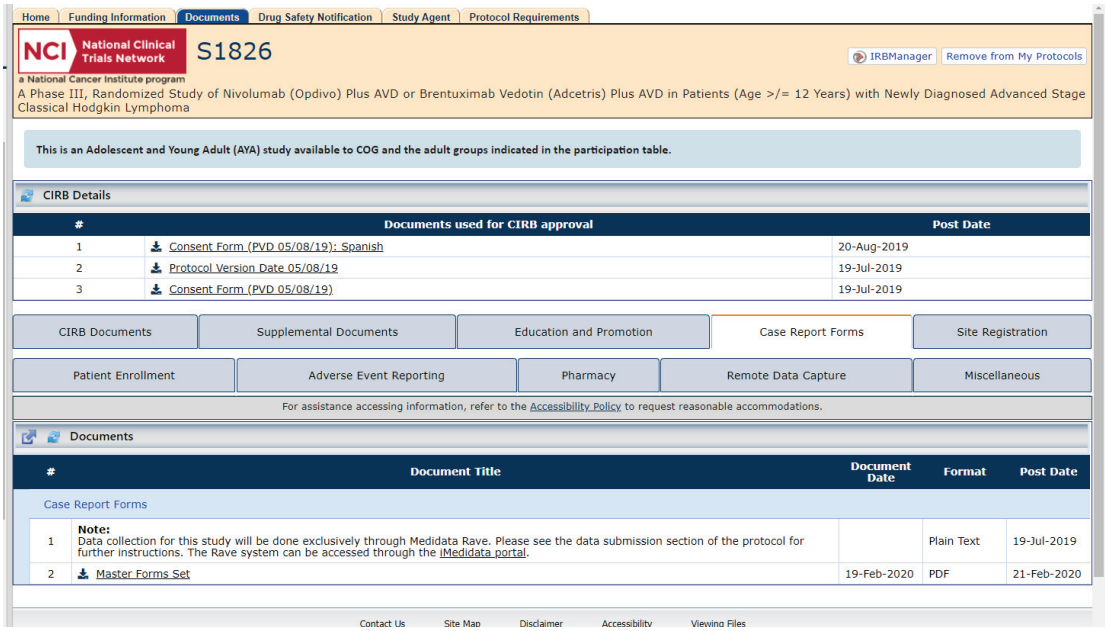
3. How do I order Streck tube kits?
   - See Section 15.2c for a link to the online ordering system.
   - Allow 5-7 days after placing the order for receipt of the shipment.

4. How do I get air bills or an account number to ship the specimens to the bank?
   - Neither air bills nor a courier account number are supplied.
   - Sites are to use their institutional account number (or similar institutional method of payment) for the shipment.
   - The shipping cost is offset via the NCTN site payment to the site for each sample submission timepoint.

5. For dosing based upon the patients' weight, should dose be re-calculated for each administration?
   - Dose should only be re-calculated if the patient has a change in weight that is >/= 10% from baseline.

6. If the patient turns 18 while on protocol, should the dose switch to the adult dose administration guidelines?
   - No. The patient should continue on the dose administered at previous administration unless there is a change in weight that is >/= 10% from the previous weight used to calculate BSA (applicable to nivolumab, brentuximab vedotin, and G-CSF).

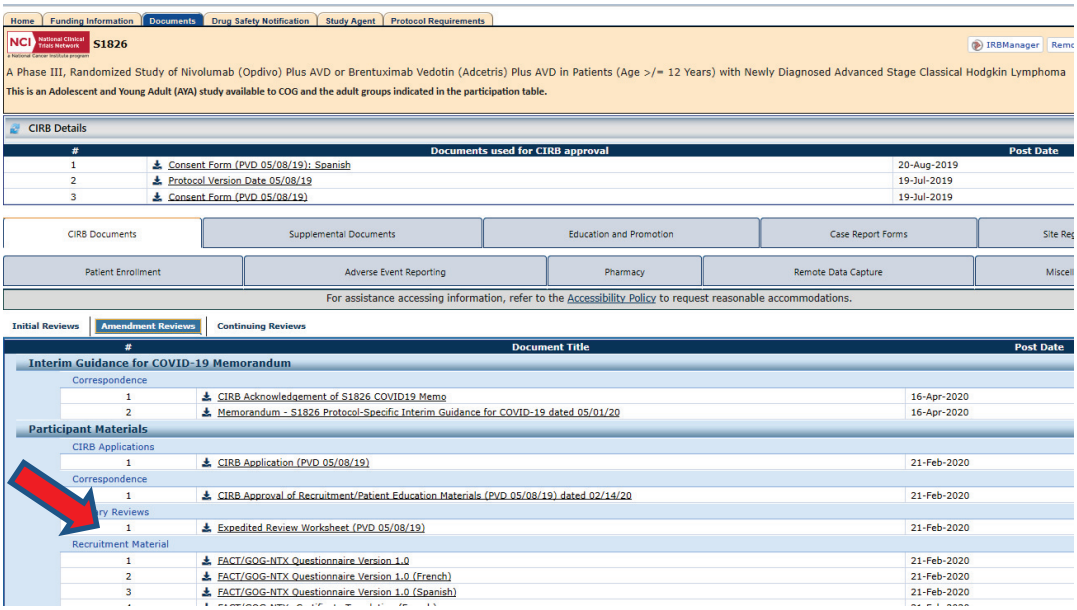
7. Is there an iMedidata RAVE guidance document?
   - No. The Master Forms Set, posted at: www.ctsu.org under the Case Report Forms tab (see snapshot below) includes paper versions of the case report forms (CRFs). The paper CRFs in the Master Forms Set contain the same entry fields as are included in RAVE, however, in some cases the paper versions include more detail/instruction than can be included in the RAVE system. Please direct questions regarding data entry (including cycle/scheduling questions as pertain to data entry), form instructions, query resolution to: LymphomaQuestion@crab.org.



8. Are Patient-Reported Outcomes (QOL and PRO-CTCAE) forms required?
   - **Yes.** If the patient is able to complete the forms in English, Spanish or French, then the forms are required at the timepoints indicated in Sections 15.5 and 15.6 of the protocol. Note: The Pediatric PROMIS Fatigue 10a is validated in English and Spanish only (not French). Baseline QOL forms must be completed by the patient **prior to registration**, or else the patient will be considered ineligible per Section 5.6.
   - **If the patient is not able to complete the forms in English, Spanish or French**, patient does not speak, read, or write in at least one of these languages), then the forms are not required to be completed. The participating site will document that the patient does not speak one of the languages in which the PRO forms are validated.

9. If a patient turns 18 while on protocol, does the patient complete the adult or the pediatric PRO forms?
   - Pediatric. (Patients are to complete the version of the forms that was appropriate for the patient at time of completion of the initial questionnaires.

10. Where do I access the Patient-Reported Outcomes (QOL and PRO-CTCAE) forms?
    - The current PRO (QOL and PRO-CTCAE) Forms are posted individually on the CTSU protocol abstract page at www.ctsu.org under “Documents” / “CIRB Documents” tab / “Amendment Reviews” subtab / “Participant Materials” section / “Recruitment Material” subsection.



11. Where do I find the address for the SWOG Biospecimen Bank?
    - Prior to shipment, all specimen must be entered into the SWOG online Specimen Tracking System.
    - Log on to the SWOG Specimen Tracking System using your CTEP IAM username and password.
    - If it is your first time logging in to the Specimen Tracking System (SpecTrack), please note that you can access start-up instructions (both written and demo) after signing into the online system.
    - You will be able to print labels via the online SpecTrack system.

12. What Grade AEs do I need to report?
    - ALL adverse events are reported for both arms (for the duration of the reporting requirement).

13. For adverse event reporting, when Medidata Rave requests an answer to "attribution to study intervention," how is that defined?
    - The attribution code indicates the likelihood that the condition/event observed is related to protocol treatment.

14. How do I clear the "sticky note" for the AE?
    - Sticky notes remain for AEs that may require reporting via CTEP-AERS. If you are certain that an AE does not require reporting, then you can override the request for submission of a CTEP-AERs report then you can override the request for submission of a CTEP-AERs report, but the sticky note will remain visible in RAVE as a record of the reporting recommendation.

15. My patient was deemed ineligible after registration. Can they continue with protocol treatment?
    - Yes. Once registered, all participants are to be treated per protocol as long as there is not a medical contra-indication for doing so.

c. **NCTN Adult Group Participating Site Frequently Asked Questions:**

1. Does our institution need an assent document?
    - For non-COG institutions enrolling pediatric patients, institutions are to document assent per the local policy. CIRB has approved the Youth Information Sheets for utilization in the Assent process.
    - If your institution/PI will not be enrolling patients under age 18, then an assent document is not needed.

2. Can we remove the Parent/Guardian and Physician/PNP signature lines from the consent document?
    - No, per CIRB guidelines, participating sites may not remove, replace, or revise any of the language in the CIRB-approved consent. Sites may request additions to boilerplate language, as indicated in the CIRB Quick guide titled, "Guidelines for Permitted Boilerplate Language Additions" which can be found on the NCI CIRB website under the "For Institutions" section: https://www.ncicirb.org/content/guidelines-permitted-boilerplate-language-additions.

18.13 Translational Medicine: Circulating Tumor DNA

a. Translational Medicine Objectives

1. Assess prognostic significance of genetic alterations in advanced stage cHL treated with N-AVD or BV-AVD.

2. Assess the prognostic significance of baseline and interim (i.e. 2-log reduction after 2 cycles), and end-of-treatment molecular tumor burden (MTB) in patients with advanced stage cHL treated with N-AVD or BV-AVD.

b. Background

The paucity of malignant Reed Sternberg cells (1-2%) in primary cHLs precludes conventional genetic analyses of bulk tumor specimens. As a consequence, emerging insights regarding disease-defining and potentially therapeutically actionable molecular alterations in cHL have not been translated into scalable robust genetic assays for use in clinical investigation or routine practice. Despite the paucity of RS cells in cHL tumors, next generation sequencing (NGS)-based detection of cell-free ctDNA is feasible in cHL. (*1*,*2*,*3*,*4*) Using a panel-directed NGS-based approach to ctDNA analysis, noninvasive genotyping of cHL is validated in cHL and enables monitoring of clonal evolution in patients with treatment failure. The presence and rate of ctDNA decline with standard treatment as well as with nivolumab treatment is highly associated with the presence of active lymphoma and with PFS. (*5*) Another study using a similar targeted ctDNA assay defined associations between dynamic ctDNA results and PFS. (*6*) The validation of ctDNA in cHL, as a sensitive and specific marker 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 the current gold-standard PET scans. There remain a high number of disease progression events in patients who have negative interim and EOT PET scans (e.g. 2/3 of the total PFS events in SWOG S0618 were in PET-negative patients).(*7*) Nevertheless, PET assessment of cHL remains the primary method of assessing response and guiding therapeutic interventions in cHL. Furthermore, interpreting PET scans is particularly challenging in the setting of PD-1 blockade, even requiring a modification to the standard lymphoma response assessment criteria (i.e. LYRIC criteria(*8*)).

In the current proposal, we will assess the prognostic impact of specific genetic alterations (i.e. 9p24.1) and MTB in patients with advanced stage cHL treated on S1826. To accomplish this, we will deploy our comprehensive targeted sequencing ctDNA assay to capture the cHL molecular signature, including genetic alterations associated with sensitivity to PD-1 blockade(*9*,*10*,*11*,*12*,*13*). CtDNA assessment provides real-time information about tumor burden and dynamic response to therapy, non-invasive genomic profiling, and monitoring of clonal dynamics – opening the door to numerous applications that could significantly impact the care of patients with cHL. We anticipate that the use of ctDNA as a non-real time integrated biomarker in S1826 will establish the clinical utility of ctDNA in cHL as: (1) “Liquid biopsy” – given the paucity of genetic data in primary cHL, our non-invasive genomic profiling via ctDNA of adult and pediatric patients with newly diagnosed advanced stage disease will be a major contribution to the field, enabling precision medicine approaches in cHL (e.g. prioritization of anti-PD1 therapy for patients with high burden 9p24.1 alteration); (2) Prognostic biomarker – current clinical prognostic indices (e.g. IPS score) inadequately risk-stratify advanced stage cHL patients for risk-adapted therapeutic approaches; however, MTB determined by ctDNA can provide a highly sensitive measurement of tumor burden prior to therapy as a tool for refining pre-treatment risk stratification and designing clinical trials studying intensification or de-escalation of therapy; (3) Dynamic measure of response – rather than relying on imperfect PET scans, ctDNA provides real-time, highly sensitive information about molecular depth of response (i.e. MTB) that will inform ctDNA-response driven clinical trials; (4) Disease monitoring – Imaging surveillance and the detection of clinically occult relapse is not associated with improved outcomes in cHL,(*14*) but detection of molecular relapse using ctDNA may provide the opportunity to study pre-emptive intervention with well-tolerated novel agents to prevent clinical relapse.

As a randomized evaluation of the incorporation of PD-1 blockade into frontline therapy, our proposed S1826 ctDNA analysis can identify the patients most likely to benefit from a particular frontline immuno-chemotherapy intervention (i.e. N-

AVD or BV-AVD) regardless of the result of the primary analysis and can inform the design of the next cHL clinical trial in the cooperative groups (e.g. response adapted therapy using ctDNA and/or PET).
We hypothesize that ctDNA will identify characteristic alterations of chromosome 9p24.1 (i.e. amplification) and genes (i.e. JAK/STAT pathway genes - SOCS1, STAT6) that result in overexpression of PD-1 ligands in cHL and that these genetic features will be selectively associated with favorable response and PFS in patients treated with N-AVD,(24, 29) but not after BV-AVD. Therefore, we are testing if treatment effect of N-AVD versus BV-AVD on PFS depends on 9p24.1 and specific gene alterations. Additionally, we hypothesize that MTB will be prognostic for PFS in patients treated with either N-AVD or BV-AVD (i.e. irrespective of regimen): (1) baseline MTB will be prognostic for PFS, (2) interim on-treatment kinetic changes in MTB (i.e. achievement of 2-log drop in MTB after 2 cycles) will be prognostic for PFS, and (3) MTB at EOT will have superior PPV and NPV to 5-point PET-CT at interim and EOT.

c. Experimental Approach and Assays

1. Sample Collection

Patients have 20mL of whole blood collected at baseline, on C3D1, at EOT, and at the time of relapse or progression (if applicable) in BCT cell-free DNA Streck tubes. Samples are shipped to the SWOG central biorepository where the whole blood is separated into plasma and buffy coat, yielding 10-12mL of plasma per time point, separated into 1mL aliquots. Samples are stored at -80C. Frozen samples will be shipped on dry ice from the SWOG biorepository to DFCI/Broad.

2. Collection Kits / Order of Sample Collection / Sample Collection and Submission Instructions

3. Description of Assay or Methods

We will utilize a custom targeted sequencing panel that includes 34 recurrently mutated genes (candidate cancer genes; CCGs), 6 somatic copy number alterations (SCNAs) and 3 structural variants (SVs) in cHL(*15*,*16*). The ~300kb panel also contains probes to identify microsatellite instability and determine EBV status, which are of particular importance in cHL(*17*). The coding portions of the CCGs from cHL are tiled in their entirety. Focal CNA regions identified in cHL by GISTIC2.0 are tiled with 120 bp SNP probes at a density of ~1 probe every 200 kb (but no less than 12 probes per CNA). To optimize assay performance, we prioritized SNPs residing in exonic regions with the alignment scores (ENCODE Mapability) of 1, meaning that the probe sequences align to the genome only once. Additionally, preference was given to SNPs with higher minor allele population frequency as reported in gnomAD database. All included SNPs were required to have a population frequency > 10% and an alignment score > 0.5. Finally, we prioritized high-quality SNPs that were included in the Affymetrix Human SNP Array 6.0. Structural variant regions were selected that contained recurrent breakpoints identified in cHL or PMBL and rearrangements of the immunoglobulin loci. Regions with a high density of breakpoints were tiled at 2x. Bait design was optimized using TWIST DNA chemistry which produces high-fidelity double-stranded DNA probes with increased specificity and uniform target enrichment. TWIST-designed probes are associated with increased sequencing depth due to the low frequency of dropout regions. CtDNA libraries also contain double-stranded unique molecular indices (UMI) with separate dual

barcoding which eliminates false positives, enables duplex consensus calling and results in dramatically improved error correction.

The computational pipeline combines evidence from two data types: Low pass (~0.2x) WGS (LP WGS) and targeted sequencing. LP WGS allows an estimate of the genome-wide CNA profile as well as an estimate of tumor fraction (TF). In patients with sufficient DNA input, we may perform deeper WGS as necessary to allow for optimal characterization of the tumor mutational profile and molecular tumor burden. From the targeted panel sequencing, at high coverage with duplex reads, the pipeline provides high precision detection of driver gene mutations, SCNAs, SVs, as well as other targeted sites that help estimate mutational signatures. The pipeline was built using both existing tools, many of which were developed by the Getz lab, along with new tools that were specifically designed for these data types. Some existing tools (such as Mutect1) were optimized for the deep coverage in the targeted panel and higher base qualities of duplex reads.

For the LP WGS data, we will use iChorCNA(30) to estimate the TF and generate genome-wide CNA profiles. More recently, the Getz lab has developed TuFEst (github.com/getzlab/TuFEst) which uses somatic differences in the ctDNA fragment length distribution as well as the tumor-specific CNA profile to estimate MTB. Using the deep coverage targeted panel data, we detect mutations, CNAs, and SVs. For each category of genetic alterations, we apply multiple algorithms in a consensus approach to optimize detection sensitivity. Of particular note, we developed a CNA algorithm (github.com/getzlab/Chute) which combines information from the LP WGS with Targeted Panel coverage and observed germline het-site allele fraction shifts to identify arm-level CNAs and focal CNAs. The pipeline is run in Terra, the Broad Institute's established workflow manager, allowing for secure, scalable, and reproducible analysis and collaboration.

Molecular tumor burden (MTB) estimate. For the estimate of Molecular Tumor Burden (MTB), we combine independent estimates of TF, weighted by their confidence. We derived TF estimates from mutation variant allele frequencies (VAFs), CNA profile (using Chute), and LP data (iChor and TuFEst) (Table 18.13).

Table 18.13 Protocol for sensitive and precise Molecular Tumor Burden (MTB) estimation.

Step	Methodological details
1	**For each cfDNA sample, obtain independent estimates of tumor purity:** **a) using LP WGS CNAs and fragment length,** **b) CNVs from the targeted panel data,** **c) mutation variant allele fractions (VAFs).** Since we have several independent estimates of tumor purity, each with its own confidence interval, we combine them with a weight that is inversely proportional to their variance.

2	**Convert the sample tumor purity to DNA tumor fraction:** **TF = (purity*ploidy) / (purity*ploidy + 2[1-purity])** This step requires an estimate of tumor ploidy, which can be challenging for samples with low tumor purity. In cases in which the ploidy is not known, we can use a representative ploidy value for ploidy value tumor cells (e.g., cHL median 3.1)(26).
3	**Convert DNA tumor fraction (TF) to units of Human Genome Equivalents (hGE):** **#hGE / ml ~ (TF*mDNA)/(mHG * vTube)** Where mDNA is the mass of DNA from sequencing library preparation, mHG is the mass of a human genome (~6.5e-3 ng), and vTube is the volume of blood collected (3ml for the preliminary data shown here).

4. Case Selection (if applicable)

As a first step, we will analyze the first half of patients enrolled to the study, who will have sufficient follow-up and a full set of specimens - baseline, C3D1, EOT, relapse (if applicable). We anticipate that about 80% of patients will have the full set of serial specimens. As of May 15, 2022, there were currently 400 patients with paired baseline, C3D1, EOT, and paired normal buffy coat samples banked at the SWOG biorepository. We will also analyze patients who progress on therapy but have baseline and at least one on-treatment sample (and paired baseline buffy coat specimen). We will reserve the samples from patients enrolled to the second half of the study for validation purposes and/or to further interrogate preliminary findings from the initial analysis.

5. Methods

d. Statistical Design and Underlying Assumptions

Endpoints and Definitions

The primary clinical endpoint is progression-free survival (PFS). Secondary clinical endpoints include complete response (CR), event-free survival (EFS), and overall survival (OS).

Progression-free survival (PFS) is defined as time from date of registration to date of first observation of progressive disease according to the 2014 Lugano classification, or death due to any cause. Patients last known to be alive and without report of progression are censored at date of last contact. Complete response (CR) at the end of therapy is defined according to the 2014 Lugano classification (e.g. Deauville score 1-3). Overall survival (OS) is time from date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact. Event-free survival (EFS) is defined as time from date of registration to date of first occurrence of EFS event. Patients last known to be alive and without EFS event are censored at date of last contact.
EFS Events are defined as:

- Disease progression/relapse

- Administration of non-protocol specified systemic anti-lymphoma therapy (i.e. salvage therapy) at any time after initiation of protocol therapy. o Administration of non-protocol specified systemic anti-lymphoma therapy for residual or relapsed Hodgkin lymphoma (whether or not confirmed by biopsy) in the absence of formal progression of disease according to the Lugano classification

- Administration of any non-protocol specified radiation therapy at any time after initiation of protocol therapy: o Administration of radiation therapy in a patient who was not declared eligible for radiation therapy at registration

- Administration of radiation in a patient who was declared eligible for radiation therapy but does not meet protocol-specified criteria for use of radiation

The biomarker analysis team at DFCI/Broad will be blinded to treatment arm and patient outcomes. Data standardization and coding will be completed by DFCI/Broad and prior to analysis of the outcome data. The SWOG biostatistical team (M. LeBlanc, H. Li) will assess the relationship between genetic alterations or MTB and patient outcomes.

The S1826 study will accrue 470 eligible patients per arm. Based on previous data, the 2-year PFS after BV-AVD is estimated to be approximately 82%. An exponential cure rate model is assumed for both arms. In addition, among the fraction of patients with disease progression, a hazard ratio of 1.67 is assumed between the arms. Under the above assumptions, for the proposed initial sampling size of 400 patients (accrued during the first half of study accrual) with samples and designed follow-up, we assume that there will be a total of 94 PFS events across both arms under the alternative hypothesis. Hence, we believe most power calculations are conservative.

Objective 1: To test if the treatment effect of N-AVD versus BV-AVD on PFS depends on specific genetic alterations, we will power this analysis using 9p24.1 amplification, which are characteristic in cHL. We assume 400 patients with evaluable samples and similar follow-up by study design. Based on our prior work, 9p24.1 amplification will be present in 50% of advanced stage cHL patients.(*18*) Based on its established prognostic impact in standard frontline chemotherapy-based treatment of cHL, it is assumed that 9p24.1 alteration will be positively associated with PFS after N-AVD but not after BV-AVD. A two-sample, two-sided level .05 of a Cox Regression score test of the interaction for patients with and without 9p24.1 amplification has power of approximately 80% to detect an interaction ratio of hazard ratios of 3.3. In addition, we will test the prognostic association in each of the treatment groups. Testing the prognostic association within the BV-AVD group, a two-sample log-rank test for patients as defined by 9p24.1 amplification among BV-AVD patients has power of approximately 90% to detect a hazard ratio of 2.5. In both analyses, the magnitude effect sizes are critical for interpretation and 95% confidence intervals will be presented. In addition, we will use descriptive statistics to characterize the frequency of each type of genetic alteration at baseline in the S1826 cohort, and evaluate associations with outcome.

We will use descriptive statistics to characterize the frequency of each type of genetic alteration at baseline in the S1826 cohort. We will investigate the impact of each identified recurrent genetic alteration on PFS in a univariable model. Specific alterations of interest that will be formally assessed are JAK/STAT pathway mutations (i.e. SOCS1, STAT6), EBV-associated alterations, and MSI-associated alterations. We will also evaluate the interaction between 9p24.1 alterations and JAK/STAT mutations and impact on PFS. Additionally, we will use Elastic Net(*19*) to select, out of all the genetic alterations, and clinical and demographic features, the ones important for the model, by using both linear and quadratic penalty components.

We will also assess differences in PFS for all of the above-mentioned prognostic factors (including 9p24.1 alteration and JAK/STAT mutations), now incorporating the randomized treatment assignment (N-AVD vs BV-AVD). Our prior studies(*20*, *21*) suggest that high-level 9p24 CNAs may be associated with a more favorable outcome in the N-AVD, but not the BV-AVD, treatment arm of S1826. We will first examine treatment by the individual alterations or dysregulated pathways, and then apply the Elastic Net model with the treatment arm as an additional available covariate. Next, we will allow the Elastic Net to also use clinical and demographic features. Thus, the final models will be able to combine features detected in the ctDNA, the randomized treatment arms, and the patient's clinical and demographic information. We will also assess whether specific molecular features are selectively predictive in one of the treatment arms.

We appreciate the sample size is limited to detect complex associations hence results will primarily hypothesis generating. However, to yield the most interpretable results we plan to pre specify potential alterations and clinical factors (age, IPS, Stage, extranodal involvement) and key tuning parameters for the elastic net algorithm. Model complexity will be selected by generalized cross-validation. By fully specifying the statistical algorithm we can then assess the statistical strength of the individual molecular components by utilizing the appropriate resampled permutation tests.

Objective 2: Assess the prognostic significance of MTB in patients treated with either N-AVD or BV-AVD. The primary MTB analysis will consider the change in MTB between baseline and C3D1, the cut-point will be the 2-log change. We anticipate 70% of patients will achieve the 2-log change (including those patients who transition to unmeasurable). Testing the prognostic association combining but stratified by treatment group, a two-sample log-rank test for patients landmarked at C3D1 has a power of approximately 93% to detect a hazard ratio of 2.1. The expected width of the 95% confidence interval for this effect is (1.4,3.2). Secondary analyses will consider MTB at baseline on the continuous log scale. In addition, if for the continuous scale there is a significant association with outcome, adaptive split point optimization will be considered. The algorithm to select cut point will be fully specified including the minimum fraction of patients above will be set at 20% of sample size prior to analysis of any outcome data. Permutation re-sampling will be used to assess significance in the context of this correlated multiple comparison problem (*22*eg. LeBlanc and Crowley, 1995)

We will characterize the MTB at baseline in units of HGE/ml and assess its prognostic value as a single variable and after adjusting for clinical prognostic features/stratification factors age (<18, 18-60, >60 yrs.) and International Prognostic Score (0-3 vs 4-7)(*23*33). We will also consider baseline MTB categorized by a median cut-point.

At subsequent time points, we will evaluate changes in MTB at both C3D1 and EOT compared to baseline. In cHL and other lymphoid malignancies, a 2-log (100-fold) decrease in MTB after 2 cycles of therapy (C3D1) predicts outcome(*24*34). We will use this parameter in S1826 trial patients as a binary covariate. Outcomes of interest will include both PFS (the primary endpoint of S1826) and achievement of CR at EOT as determined by PET/CT. We will characterize the magnitude of change descriptively for those who exhibit progressive disease within the 6 cycles of therapy and those who do not, and also by categories of response for those who do not progress. These measures look at per patient MTB changes, and do not rely on the baseline threshold(s) defined above.

We will initially investigate change in MTB in a univariable setting but will also use multivariable models incorporating other demographic and clinical features from diagnosis to understand how these additional features may modify the interpretation of changes in MTB. To more clearly consider the relationship between changes in MTB and PFS outcomes, we will also perform a landmark analysis of PFS including only those patients who remain alive without progression at EOT. All assessments of MTB and PFS will rely on log rank tests in the setting of a single threshold for all patients or stratified log rank tests in the setting of customized thresholds for the age and IPS risk score strata defined in the protocol, and Cox proportional hazards models for the multivariable setting, using either stepwise selection or a lasso approach. Again, to assess overall multivariable performance, variables and cut points will be specified prior to using the Lasso. In addition, it is recognized that cross-validated partial likelihood is unstable; therefore, model selection (complexity) will use generalized cross-validation.

We will specifically assess the PPV/NPV of detectable ctDNA at EOT and compare this to the gold standard EOT PET-CT scan response according to the 2014 Lugano Classification. We assume that approximately 20% of patients will be ctDNA positive at EOT, and 10% will be PET-CT positive (Deauville Score 4-5) at EOT. With approximately 200 patient samples per arm, then the PPV for either of those measures can be estimated to within +/- 11% (95% confidence interval) for the case with 20% ctDNA positive. Analogous results hold for PET-CT and NPV.

e. Materials Handling

Frozen samples will be shipped on dry ice from the SWOG biorepository at Nationwide Children's Hospital to DFCI/Broad for analysis.

f. Funding

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