Academic and Community Cancer Research United (ACCRU)

A Phase II Trial of PET-Directed Therapy using AVD (doxorubicin, vinblastine, and dacarbazine) plus Brentuximab Vedotin Induction Chemotherapy, with or without Brentuximab Vedotin plus Nivolumab, Followed by Nivolumab Consolidation for Patients with Previously Untreated Non-bulky Limited Stage Hodgkin Lymphoma

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site [redacted]

Study Chairs

ACCRU: [redacted]

Statistician: [redacted]

Drug Availability
Commercial Agents: AVD chemotherapy (Doxorubicin, Vinblastine, and Dacarbazine)
Drug Company Supplied: Brentuximab Vedotin (BV) and Nivolumab (NVB) –IND# 135112

√ Study contributor(s) not responsible for patient care.

Research Coordinating Center

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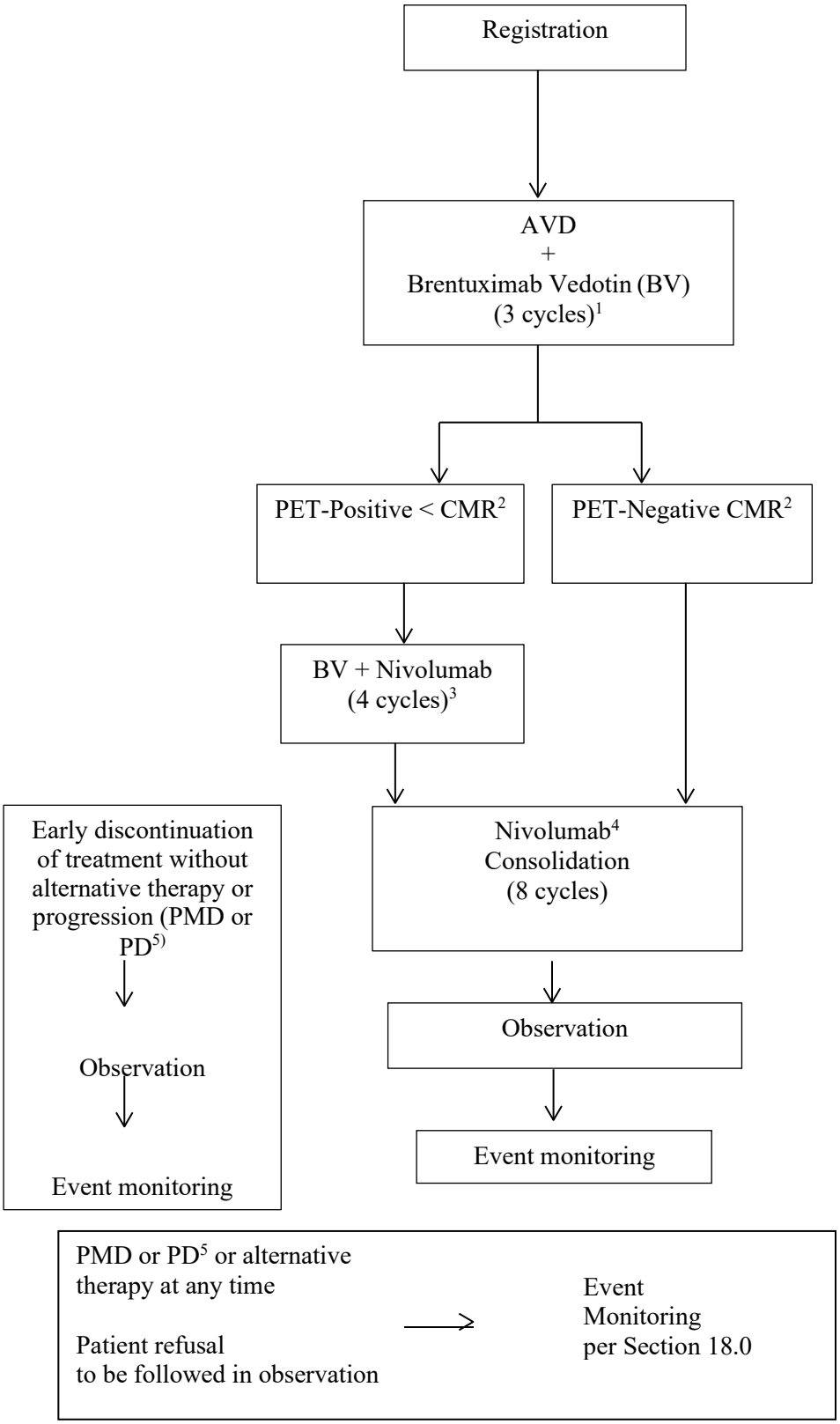
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Schema


Registration
AVD
+
Brentuximab Vedotin (BV)
(3 cycles)[1]
PET-Positive < CMR[2]
PET-Negative CMR[2]
BV + Nivolumab
(4 cycles)[3]
Early discontinuation of treatment without alternative therapy or progression (PMD or PD[5])
Observation
Event monitoring
Nivolumab[4]
Consolidation
(8 cycles)
Observation
Event monitoring
PMD or PD[5] or alternative therapy at any time
Patient refusal to be followed in observation
Event Monitoring per Section 18.0

[1] Cycle = 28 days. Interim-PET/CT after 3 cycles of AVD (no Bleomycin) plus BV (1.2 mg/kg Q2 weeks x 6 doses).
[2] See Section 11.0. Deauville score of ≤3 indicates CMR by PET-CT based response criteria. Patients with progressive disease (PD or PMD) post cycle 3 of AVD plus BV will be removed from protocol therapy.
[3] Cycle = 14 days. See Section 11.0. For Deauville score of >3 at interim PET/CT, 4 cycles of BV (1.2 mg/kg Q2 weeks) plus Nivolumab (3 mg/kg Q2 weeks) will be given. Repeat PET/CT will be obtained after 4 cycles of BV plus Nivolumab. Patients with PD or PMD post 4 cycles of BV plus Nivolumab will be removed from protocol therapy.
[4] Cycle = 14 days. Nivolumab consolidation (3 mg/kg Q2 weeks) x 8 cycles of nivolumab consolidation.
[5] Progressive disease by PET-CT or CT based response criteria (Deauville score >3, see Section 11.0).
PET confirmation of progressive disease (with or without biopsy) is per physician discretion.

Definitions

- **Observation:** Part of the Active Monitoring phase of a study. The time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule and may be required to return to the consenting site for protocol tests.

- **Event Monitoring:** Not part of the Active Monitoring phase of a study. The time period when the participant is no longer following the protocol test schedule. During Event Monitoring, the data collection schedule is dictated by the protocol but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death. Participants may not be required to return to the consenting site for study-related reasons or be required to have research-related tests performed. Samples from biospecimens collected in the course of clinical care may be requested but cannot be required of the participant.

Generic name: Doxorubicin Brand name(s): Availability: Commercial	Generic name: Vinblastine Brand name(s): Availability: Commercial
Generic name: Dacarbazine Brand name(s): Availability: Commercial	Generic name: Brentuximab Vedotin Brand name(s): Adcetris Availability: Seattle Genetics via Almac, Inc. (United States)
Generic name: Nivolumab Brand name(s): Opdivo Availability: Bristol-Myers Squibb	

1.0 Background and Rationale

1.1 Study Synopsis

Brentuximab vedotin (BV) and Nivolumab (NVB) are agents shown to be highly active in heavily-pretreated Hodgkin Lymphoma (HL) [1, 2]. Therefore, use of BV and NVB in addition to conventional chemotherapy may be effective and safe in treating Hodgkin Lymphoma (HL) as part of the induction or consolidation therapy in patients with previously untreated limited stage non-bulky HL. We plan to conduct a single arm Phase II trial evaluating AVD + BV induction therapy, with or without BV + NVB, followed by NVB consolidation in patients with previously untreated stage I or II non-bulky HL. Patients will receive 3 cycles of AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2; 28-day cycle) plus BV (1.2 mg/kg every 2 weeks X 6 doses). Subjects who are PET-negative after induction with 3 cycles of AVD + BV will proceed to consolidation therapy with NVB (3 mg/kg every 2 weeks X 8 cycles). Subjects who are PET positive after induction with 3 cycles of AVD + BV will receive 4 cycles of BV (1.2 mg/kg every 2 weeks) plus NVB (3 mg/kg every 2 weeks) followed by NVB consolidation (3mg/kg every 2 weeks for 8 cycles). The primary objective is to estimate 3-year progression-free survival (PFS) for AVD + BV induction therapy with or without BV + NVB followed by NVB consolidation in this patient population. The inclusion of interim positron-emission and computed tomography (PET-CT) is based on data showing that interim PET-CT in limited stage disease has a role in risk assessment and management of non-bulky disease [3, 4]. In this study, patients who progress during therapy will be removed from the treatment.

We plan to enroll 82 patients across participating centers over a 2 year period to ensure that at least 78 are evaluable for the primary endpoint and anticipate accrual to this study will be shared equally among sites.

1.2 Hodgkin Lymphoma

Hodgkin lymphoma (HL), a malignant neoplasm of lymphoreticular cell origin, is defined histopathologically by the presence of malignant Hodgkin Reed-Sternberg (HRS) cells [5]. HL occurs in both children and adults; The American Cancer Society projects that 8,500 new cases of HL will be diagnosed in the US in 2016 (3,710 in females and 4,790 in males). HL is a common malignancy in young adults [5] (ages 15 to 40), peaking in incidence in persons in their 20s

[redacted]

Various unfavorable prognostic factors have been identified for HL, including the presence of B symptoms (fever, night sweats, weight loss), erythrocyte sedimentation rate (ESR) >50, >3 sites of disease, and the presence of bulky disease. Bulky disease is defined as a mediastinal mass ratio greater than 0.33 maximum intrathoracic diameter on chest x-ray, and/or any single node or nodal mass ≥ 5 to 10 cm in its largest diameter [6]. Despite the identification of clinical prognostic factors, and the optimal use of primary and secondary treatments, HL remains fatal for more than 15% of patients, and even in patients who are cured, the morbidity of therapy is substantial and long lasting [7, 8]. Thus, treatment of HL requires a careful balance between providing effective therapy to

cure the disease while minimizing the toxic effect of therapy that could result in excessive long-term treatment-related complications [1].

1.3 Frontline Therapy for HL

At this time, the preferred treatment option for stage I or II non-bulky HL is the use of chemotherapy (e.g., doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVD) with or without involved-field radiation therapy (IFRT) [9, 10]. The NCIC and ECOG study randomized patients with limited stage non-bulky HL to either combined therapy with ABVD followed by radiation therapy or ABVD only [11]. While the 5-year freedom from progression (FFP; defined as time from random assignment until disease progression or death from disease progression) rate was significantly higher with the combined approach (93% in the combined modality vs. 87% in the ABVD only group), no significant difference was seen in event free survival (EFS); EFS of 88% (confidence interval 82 to 94) in the combined modality versus 86% (CI 80 to 91) in the ABVD only group at 5 years. The lack of difference in EFS suggests that deaths due to causes other than progression offset any benefit in FFP reported for the combined modality group. The lack of an overall survival (OS) benefit (94% in the combined modality versus 96% in the ABVD only group) may also be related to the effectiveness of salvage treatment for relapsed HL.

1.31 Role of interim-PET scan in Limited Stage HL

Data on use of interim PET-CT in HL suggests that PET scan may have an important role in risk assessment and the management of limited stage HL [4, 12, 13]. The United Kingdom National Cancer Research Institute (RAPID) study explored the role of PET scans in assessing response to treatment and guiding consolidation therapy [3]. The team sought to determine whether PET has high enough sensitivity and specificity to identify patients in whom radiotherapy could be avoided without unacceptably reducing disease control. Seventy five percent of patients achieved negative PET after 3 cycles of ABVD and were randomized to no further treatment or ISRT. The per protocol analysis of 3 year progression free survival (PFS) was 97% of PET negative patients who received ISRT and 90.7% of those who had no further treatment. Overall survival (OS) at 3 years was 97% in PET negative patients who received ISRT and 99.5% in those who received no further treatment. PFS and OS rates were 87.6% and 93.9%, respectively, in PET positive patients after treatment with 4 cycles of ABVD followed by IFRT at a median follow up of 62 months. The omission of RT in PET-negative was not inferior, the investigators concluded low-risk limited stage patients who are PET negative after 3 cycles of ABVD may achieve acceptable disease control while omitting ISRT[14]. However, almost 25% of the study population was PET positive and thus required consolidative radiation therapy post ABVD.

1.32 Concerns Related to Current Therapy for HL

Although approximately 90% of limited stage HL patients are projected to be cured with standard of care therapy (i.e., multi-agent chemotherapy ± radiation), many do not live their expected life span due to delayed treatment–related toxicities that include secondary malignancies and cardiovascular disease [15, 16]. In a recent retrospective study, survivors of HL treated with chemotherapy

alone had less incidence of secondary malignancies with a 30-year cumulative incidence of 5.8%, compared to 24.7% in HL patients who received consolidative radiation [17]. Given the unclear overall survival advantage, and the long-term toxicities associated with consolidative radiation, the use of this modality remains controversial in the treatment of HL. In addition, both an increased dose of radiation and anthracycline exposure were associated with significantly increased risk of cardiovascular complications [18]. Furthermore, salvage chemotherapy for patients who relapse includes high-dose chemotherapy followed by a stem cell transplant (SCT). While effective, the intensity of this approach also leads to long-term treatment-related comorbidities such as secondary acute myeloid leukemia and myelodysplastic syndrome [19, 20]. The two leading causes of death in HL survivors are second malignancies and cardiovascular disease. However, other key late complications may arise secondarily to therapy such as atherosclerotic disease, pulmonary disease, and endocrine dysfunction such as hypothyroidism and infertility [21].

1.4 Investigational Treatment of HL

Given the risks associated with current therapies for HL, novel treatment strategies for early stage disease are aiming to reduce the amount of conventional drugs given in comparison to standard therapy and obviate the need for radiation therapy while maintaining or improving upon current standard of care outcomes. A general opinion is that the success of traditional chemotherapy and radiation-based strategies for the treatment of HL has reached a plateau [22, 23]. The additive toxicities and limited efficacy of conventional regimens in achieving a cure has led to studies in pediatric cancers of immune-based or molecularly targeted therapy to prevent relapse or treat minimal disease. BV and NVB are examples of novel agents under investigation for HL that are showing promising activity [1, 2].

1.41 Brentuximab vedotin in HL

CD30 plays a role in regulating the function or proliferation of normal lymphoid cells [24]; it is expressed on virtually all HRS cells, and is therefore a potential target for both antibody-based immunotherapy and cellular therapies. BV is an antibody-drug conjugate targeting CD30 that is approved by the FDA for the treatment of patients at high risk of relapse post-stem cell transplant for consolidation, and in patients with relapsed/refractory HL or with anaplastic large cell lymphoma [2]. The drug conjugate is comprised of monomethyl auristatin E, a potent anti-microtubule cytotoxic compound. BV has emerged as one of the most promising agents for the treatment of HL. It has demonstrated overall and complete response rates of 75% and 34%, respectively, in patients with relapsed or refractory HL who failed multiple prior chemotherapies in a phase II study [2]. Long-term data from this study of BV in the relapsed/refractory setting (median follow up 33.3 months, range 1.8 to 57.3 months) recorded a median OS of 40.6 months and PFS of 9.3 months. The majority of treatment-related adverse events (TRAEs) in this trial have been Grade 1 or 2, with Grade 3 toxicities limited to the following: neutropenia (14%), peripheral sensory neuropathy (5%), thrombocytopenia and hyperglycemia (3% each), and fatigue (2%). Grade 4 TRAEs were neutropenia (4%), thrombocytopenia, abdominal pain, and pulmonary embolism (1% each).

In addition, the use of BV for consolidation after SCT was evaluated in the AETHERA study [23]. This was a phase III placebo-controlled randomized study of maintenance therapy in patients with high risk RRHL (defined as refractory to initial therapy, relapse occurring within 12 months, or relapse with extra-nodal involvement). A total of 329 patients were enrolled and superior PFS (43 months vs 24 months) was observed in the BV arm, with consistent benefit across all subgroups, although adverse events led to treatment discontinuation in 32% of patients. The 3-year overall survival rate of 80% in AETHERA is remarkable compared to historical survival data for high risk RRHL undergoing SCT and is consistent with clinical benefit of BV as both consolidation and rescue therapy.

1.42 Nivolumab in HL

The programmed cell death-1 (PD-1) pathway serves as a checkpoint to limit T-cell mediated immune responses and to prevent autoimmunity under normal circumstances [15, 25]. Programmed cell death ligands -1 and 2 (PD-L1 and PD-L2) engage the PD-1 receptor on the surface of T cells and inhibit T cell activation. Many tumor cells, including HRS cells and other cells within the immune microenvironment in lymphoma, aberrantly express PD-L1 and PD-L2, and thereby inhibit T cell activation. As a result, even though HRS cells are surrounded by large numbers of T cells, these T cells are rendered immunologically tolerant and incapable of eliminating cancer cells. Immune checkpoint inhibitors that block the PD-1 pathway have been shown to facilitate T-cell activation and enhance the antitumor response. NVB is a potent and highly selective humanized IgG4 monoclonal antibody (mAb) designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 [26]. Results from a Phase 1 trial (CA209-039) of NVB therapy (3 mg/kg IV at weeks 1 and 4 and then every 2 weeks for up to 2 years) in 23 HL patients were very encouraging [1, 27]. Twenty patients have responded to therapy (ORR = 86%; 14 PR, 6 CR) with 10 patients having durable responses per protocol assessment. NVB was active in all patients regardless of their treatment status [28]. With the median follow up of 86 weeks (range 32-107 weeks), responses were maintained for >40 weeks in 2 patients after discontinuation of NVB and 8 patients with durable response received NVB for greater than 1 year [27]. Twenty-two out of 23 patients enrolled in this study experienced adverse events, and Grade 3 adverse events occurred in 12 patients. The most common drug-related events were rash in 5/18 subjects (22%) and decreased platelet count in 4/22 (17%) subjects. Grade 3 drug-related events occurred in 5 patients (22%) including myelodysplastic syndrome (MDS), pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, an increased lipase level, a decreased lymphocyte count and leukopenia; no Grade 4 or 5 drug-related events were reported. The patient with MDS had received 6 prior lines of therapy that included chemotherapy, radiation and autologous SCT. Overall, NVB demonstrated substantial therapeutic activity and acceptable safety in relapsed/refractory HL, and it is currently approved by the US FDA for HL relapsed or progressed after ASCT and post-transplant BV.

1.43 Rationale for AVD + BV Combination Therapy

As noted, a goal for improving current treatment is to reduce the amount of chemotherapy given to patients with HL without compromising efficacy.

Bleomycin in the ABVD regimen is the agent most associated with unpredictable, life-threatening toxicity with the lowest amount of single agent activity in HL [29]. Pulmonary toxicity associated with bleomycin occurs in approximately 10-25% of patients [30-32] either during or the months following completion of ABVD therapy. The mortality of patients who develop bleomycin-related pulmonary toxicity (BPT) is 24% and BPT lowers the 5-year OS rate of HL patients who develop this complication compared to patients who do not develop BPT (63% vs 90%, respectively) [31]. Retrospective analyses of two Alliance studies (CALGB 8251 and 8952) indicated that bleomycin may play a limited role in the efficacy of the ABVD regimen, as response or relapse rates for patients who had bleomycin discontinued during frontline therapy were no different from those who did not discontinue bleomycin [33]. As a result, multiple ongoing randomized studies are currently investigating AVD as a frontline regimen to understand the feasibility of eliminating bleomycin from this standard of care regimen.

Given the promising single agent activity and tolerability of BV in HL as summarized above, evaluation of BV in front-line therapy as a replacement for bleomycin in the AVD combination regimen is ongoing [34]. A Phase I trial of BV (1.2 mg/kg given every 2 weeks) with AVD showed that this combination was generally well-tolerated as induction therapy while ABVD + BV was not [35]. Additional trials of AVD + BV have recently completed. Abramson, et al. [36] conducted a Phase II trial in patients with non-bulky limited stage HL of 2 doses of BV (1.2 mg/kg) given every 2 weeks followed by PET-CT to assess single agent activity. Patients with progressive disease (PD) were withdrawn at this point, and patients without PD received 2 cycles of AVD + BV administered on days 1 and 15 of a 28-day cycle followed by PET-CT. Patients with a complete response (CR) or partial response (PR) received an additional 2 or 4 cycles of AVD + BV. A total of 34 patients were enrolled and 94% of patients completed treatment. Patients had stage IA (18%), IIA (71%) or IIB (12%) disease and risk was classified as early favorable (62%) and early unfavorable (38%). Achievement of a CR was the primary endpoint. After 2 cycles of BV, the CR rate was 53% and the PR rate was 47%. After 2 subsequent cycles of AVD + BV, the CR rate was 97%. After a median follow up of 14 months, 1-year PFS is 94% ((5% CI, 77%-99%) and 1-year OS was 97% (95% CI, 81%-100%).

The preliminary efficacy and safety of AVD + BV in early stage unfavorable risk HL has shown promise as well [37] in an ongoing Phase II trial. Patients in this study undergo PET-CT after treatment cycles 2 and 4 of AVD + BV and are evaluated based on Deauville scoring [38]. Patients with a Deauville score of 1 to 3, and those with a Deauville score of 4 or 5 and a negative biopsy, receive ISRT(30 Gy) while patients with active disease are removed from the study [37]. Of the 20 patients who have completed study treatment, none have relapsed after a median follow up of 11 months and approximately 90% of patients showed negative imaging scans after 2 and 4 treatment cycles. Activity was observed in patients with bulky disease; and the plan is to add additional subjects (n=29) to evaluate AVD + BV for 4 cycles, plus 20 Gy ISRT.

Additionally, our group has conducted a phase II study of ABVD followed by BV consolidation to replace radiation therapy in patients with previously untreated limited stage non-bulky HL (LCCC1115). The primary objective of

this trial is to establish the feasibility of achieving PET-negative disease status and avoid consolidative radiation therapy in ≥ 85% of patients with limited stage non-bulky HL. Our preliminary data suggest that 6 doses of BV may be safe and effective in eradicating residual tumors after initial chemotherapy and may potentially replace radiation for consolidative therapy in patients with previously untreated limited stage non-bulky HL [39].

1.44 Rationale for BV + NVB in previously untreated HL

The promising single agent activity of BV and NVB in the relapse/refractory setting has generated interest in evaluating these agents in combination for HL. Notably, a phase I/II study of combined therapy with BV and NVB is being conducted in relapsed or refractory HL (NCT02572167). The hope is that these two novel agents used in combination will alter the treatment landscape of HL in the relapse/refractory and frontline settings. If these novel agents can replace IFRT consolidation in early stage disease and/or replace the need for chemotherapy in the relapse/refractory setting, this would be a significant step forward in reducing the risks associated with current therapies as alternative novel approaches may improve survival outcomes while minimizing treatment-related toxicity for patients with HL.

1.5 Rationale for the Proposed Study ACCRU-LY-1601

Our proposed single arm Phase II trial will evaluate AVD (ABVD without bleomycin) combined with BV and NVB as frontline therapy for limited stage non-bulky HL, and it will be the first study to investigate combination therapy with BV and an immune checkpoint inhibitor in this patient population. The primary objective is to determine 3-year PFS for AVD + BV induction therapy, with or without BV + NVB, followed by NVB consolidation in non-bulky HL. The trial design for ACCRU-LY-1601 is similar to but also in contrast to the UK-Based Rapid trial [3] shown in Figure 1. In ACCRU-LY-1601, concurrent therapy with AVD and BV will be administered for 3 cycles. If subjects are PET-negative after AVD + BV induction; they will receive 8 cycles of NVB consolidation therapy; this is in contrast to the UK-RAPID trial where patients who were PET-negative after 3 cycles of ABVD received no further treatment. If subjects are PET-positive after AVD + BV induction in ACCRU-LY-1601, 4 cycles of additional therapy with BV + NVB will be given followed by 8 cycles of NVB consolidation. Conversely, in the UK-RAPID trial, patients who were PET-positive after 3 cycles of ABVD received 1 additional cycle of ABVD followed by IFRT (30 Gy) for consolidation.

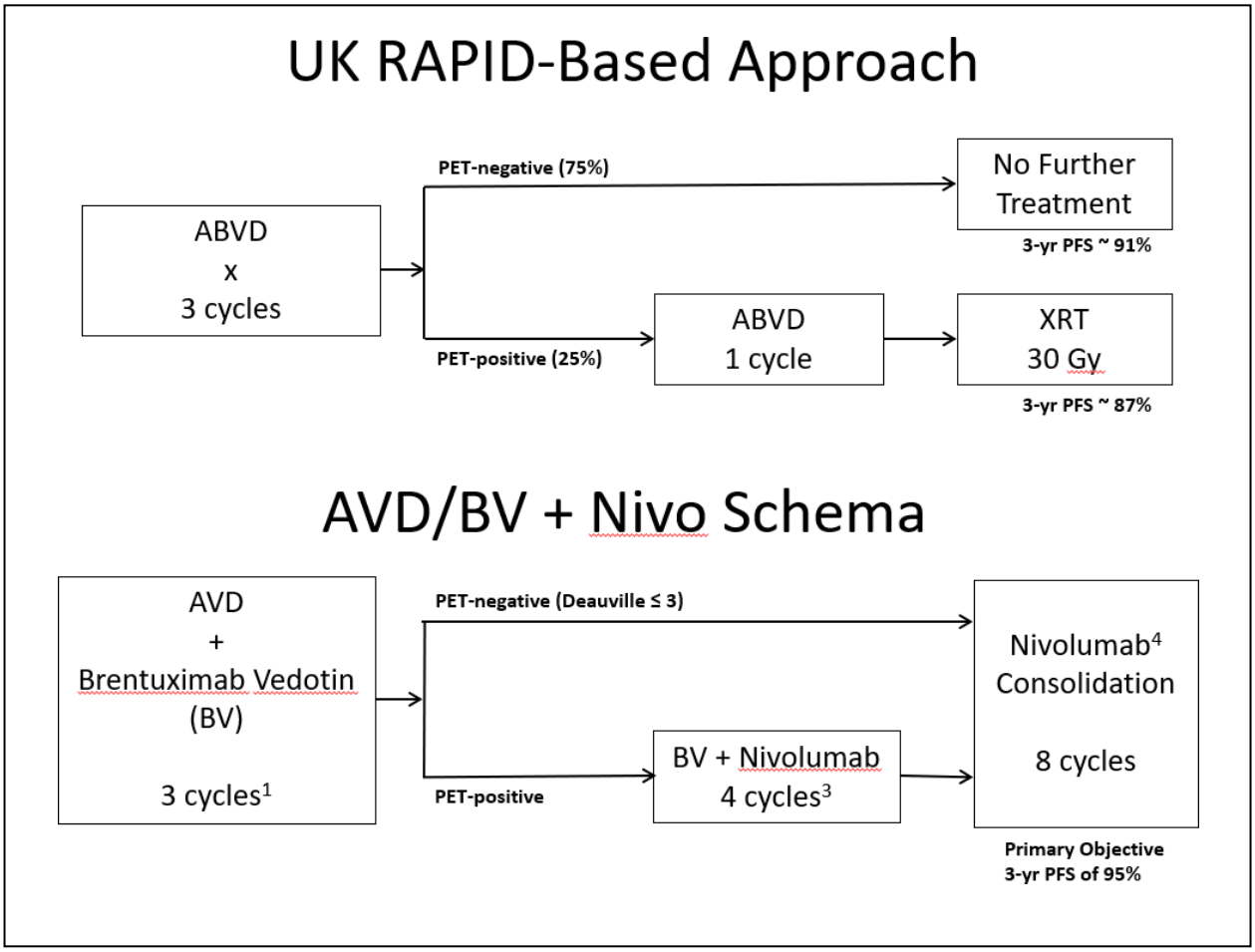


Figure 1. Study Design of ACCRU-LY-1601 compared to UK RAPID-BASED Study

[1]Interim-PET/CT after 3 cycles of AVD (no bleomycin) plus BV (1.2 mg/kg Q2wks x 6 doses)
[2]Deauville score of ≤ 3 indicates CR; Patients with PD post cycle 3 of AVD + BV will be removed from protocol therapy (Refer to Section 4.2).
[3]For Deauville score of > 3 at interim PET/CT, 4 cycles of BV (1.2 mg/kg Q2wks) + NVB (3mg/kg Q2wks) will be given; Repeat PET/CT will be obtained after 4 cycles of BV plus NVB; Patients with PD post 4 cycles of BV plus NVB will be removed from protocol therapy
[4]Nivolumab consolidation (3 mg/kg Q2wks) x 8 cycles. Restaging PET/CT after 8 cycles of NVB consolidation

The treatment approach in ACCRU-LY-1601 is supported by previous studies showing that AVD + BV is safe for induction [35] and data emerging from our ongoing LCCC1115 trial of ABVD (2-6 cycles) followed by BV consolidation, in which BV is showing promise for potentially replacing consolidative IFRT in limited stage HL. Given that BV and NVB are considered to be the two most active agents in HL, the combination of BV and NVB in addition to conventional chemotherapy may be effective and safe in eradicating chemoresistant tumors in HL. Furthermore, this approach may 1) achieve similar or superior survival outcomes to the current standard chemotherapy with or without radiation therapy, 2) reduce the total amount of conventional chemotherapy drugs

given in comparison to standard therapy and, 3) obviate the need for radiation therapy in patients with limited stage HL. Ultimately, a successful outcome in this trial could lead to improved survival of patients with HL and change the current standard of care for previously untreated HL.

2.0 Goals

2.1 Primary Objective

To estimate progression-free survival (PFS) at 3 years in patients with previously untreated stage I or II non-bulky HL who received AVD plus BV induction therapy followed by NVB consolidation therapy.

2.2 Secondary Objectives

2.21 To estimate the overall survival (OS) rate at 3 years in patients with previously untreated stage I or II non-bulky HL who received AVD plus BV induction therapy followed by NVB consolidation therapy.

2.22 To estimate the percentage of patients with untreated stage I or II non-bulky HL who are PET positive versus PET negative after 3 cycles of AVD plus BV induction therapy.

2.23 To estimate PFS and OS at 3 and 5 years separately for patients who are PET negative versus PET positive after 3 cycles of AVD plus BV induction followed by NVB consolidation therapy.

2.24 To estimate time to progression (TTP) in patients with previously untreated stage I or II non-bulky HL who received AVD plus BV induction therapy followed by NVB consolidation therapy.

2.25 To estimate the overall response rate and the number of patients who convert to complete response (CMR) after NVB in patients with partial response (PMR) at the end of AVD plus BV induction therapy.

2.26 To estimate the duration of response in patients with previously untreated stage I or II non-bulky Hodgkin's Lymphoma who received AVD plus BV induction therapy followed by NVB consolidation therapy.

2.27 To evaluate the toxicity and tolerability of AVD plus BV induction followed by NVB consolidation therapy as assessed via the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4).

2.3 Exploratory Objectives

2.31 Optional biopsy tissue samples will be collected for future analysis.

2.32 Optional blood sample will be collected for future analysis.

2.33 Cost-benefit analysis of AVD plus BV followed by NVB consolidation, compared to the current standard therapy with ABVD with or without radiation therapy.

3.0 Patient Eligibility

3.1 Registration – Inclusion Criteria

3.11 Age ≥18 years and ≤60 years of age.

3.12 Measurable disease (≥ 1.5 cm) as assessed by 2 dimensional measurement by CT.

3.13 Previously untreated stage I or II non-bulky (defined as a mass measuring < 10 cm in the longest dimension by CT) Classical Hodgkin lymphoma.

3.14 ECOG Performance Status (PS) 0-2. (Form is available on the ACCRU web site [redacted]

3.15 Life expectancy ≥3 months.

3.16 Documented negative serologic testing for human immunodeficiency virus (HIV), hepatitis B (unless serologically positive due to prior vaccination), and hepatitis C ≤1 year prior to registration.

3.17 Adequate bone marrow function (without transfusion support >7 days prior to registration) function as demonstrated by:

- White blood cell ≥ 2,000 /mm^3
- Hemoglobin ≥ 8.5 g/dL
- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3
- Platelet count ≥ 75,000/mm^3

3.18a Adequate hepatic and renal function obtained ≤14 days prior to registration as demonstrated by:

- Alanine and Aspartate aminotransferase (ALT/AST) ≤ 2.5 × upper limit of normal (ULN)
- Total serum bilirubin ≤ 1.5 × ULN (if documented Gilberts syndrome ≤ 3 x ULN)
- Serum creatinine ≤ 1.5 × ULN or measured calculated creatinine clearance ≥ 40 ml/min for subject with creatinine levels > 1.5 x institutional ULN (per Cockcroft-Gault formula below; see Appendix III - Renal Impairment Guidelines).

Cockcroft-Gault Equation:

Creatinine clearance for males = $\dfrac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\dfrac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.18b Negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to registration in women of child-bearing potential (WOCBP).

3.18c Sexually active female of reproductive capability ie, WOCBP, has agreed to use a medically accepted form of contraception from time of registration to completion of study therapy through 24 weeks (6 months) after last dose of NVB or BV. Note: Females of non-child-bearing potential are those who are postmenopausal for > 1 year or who have had a bilateral tubal ligation or hysterectomy.

3.18d Male subjects agree to use an adequate method of contraception starting with the first dose of study therapy through 31 weeks after the last dose of study therapy.

3.18e Provide informed written consent.

3.18f Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.22 Prior therapies including involved field radiation therapy.

3.23 Bulky disease (defined as a nodal mass measuring ≥ 10 cm by CT).

3.24 Known CNS involvement.

3.25 Moderate or severe hepatic insufficiency Child-Pugh score >6 (see Appendix IV - Child- Pugh Hepatic Impairment Score).

3.26 Severe renal impairment (i.e. creatinine clearance < 40 mL/min; see Appendix III - Renal Impairment Guidelines).

3.27 Symptomatic cardiac disease including ventricular dysfunction, left ventricular ejection fraction < 45%, symptomatic coronary artery disease or symptomatic arrhythmias.

3.28 Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy ≤ 7 days prior to registration.

3.29a Known history of active TB (Bacillus Tuberculosis).

3.29b Requires therapy with agents that have a predisposition for hepatoxicity.

3.29c Hypersensitivity to NVB or any of its excipients or to any component of AVD+ BV therapy.

3.29d Requires immunosuppressive doses of corticosteroid therapy (>10 mg/day prednisone equivalents) for ≥2 weeks prior to registration.

3.29e Active, known, or suspected autoimmune disease that requires systemic treatment (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

3.29f Active infection requiring systemic IV antibiotic therapy.

3.29g History of Steven's Johnson's syndrome, toxic epidermal necrolysis syndrome (TENs) or motor neuropathy.

3.29h History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.29i Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.29j Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

3.29k Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.29l Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.29m Received a live vaccine ≤30 days prior to registration. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed. Routine vaccinations, including seasonal influenza, must be given ≥2 weeks prior to registration.

3.29n History of allergies and adverse drug reaction to study drug components.

3.29o History of another primary malignancy that has not been in remission for at least 3 years. (Note: The following are exempt for the 3-year limit: nonmelanoma skin cancer, fully excised melanoma in situ [Stage 0], curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear).

3.29o Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.29p Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.29q Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.29r History of progressive PML, known history of pancreatitis, active grade 3 or higher viral, bacterial or fungal infection ≤ 2 weeks prior to registration and documented history of cerebrovascular event (stroke or TIA) ≤6 months prior to registration.

4.0 Test Schedule

Interim PET+ (positive) patients only. To start 2-4 weeks after Cycle 3 Day 28 of AVD + BV (Section 7.0).

Interim PET – and + (negative and positive) patients. To start 4-8 weeks after Cycle 3 Day 28 of AVD + BV (Section 7.0).

AVD + BV given D1, D15: 28-day cycle x 3
BV + NVB given D1: 14-day cycle x 4
NVB given D1: 14-day cycle x 8

Study Assessment	Active Monitoring							Observation/Follow up		
	Pre-study[1]	D1/D15 of each cycle [2] (+/- 3 days)	End of 3 Cycles of AVD + BV (+/- 3 days)	D1 of each BV + NVB Cycle[2] (+/- 3 days)	End of 4 Cycles of BV + NVB (+/- 3 days)	D1 of each NVB cycle[2] (+/- 3 days)	Unexpected/Unplanned End of Treatment due to PD/ Withdrawal/ Removal[12]	4 Weeks after End of Treatment (+/-7 days)	8 Weeks after End of Treatment [*, 5] (+/-7 days)	Subsequent Follow-up[5] (+/-7 days for every 3 month visit and +/- 15 days for every 6 monthscans)
Informed Consent	X									
History and PE[3]	X	X (D1)		X (Cycles 1 and 3)		X (Cycles 1,3, 5 and 7)	X	X	X	X
Performance Status	X						X[14]		X	X[14]
Pregnancy Test[6]	X	X (D1)		X (D1)		X (D1)	X	X	X	
PET/CT chest, abdomen, pelvis	X		X[7]		X[7]		X[4]		X[5]	X[5, 12]
CT chest, abdomen, pelvis							X[5,12]			X[5, 12]
CBC/diff, platelets	X	X[2]		X		X	X	X	X	X
Complete Metabolic Panel[8]+ other tests[8]	X	X (D1)		X(D1)		X (D1)	X	X	X	
TSH (free T3/T4)[9]	X	X (D1)		X		X	X[15]	X	X	
PT or INR	X	Repeat as clinically indicated								
ESR	X									
HBVsAg, HCVAb	X									
MUGA/ECHO	X	Repeat as clinically indicated								

Infusion Reaction Assessment[10]		X		X			X			
Optional tumor biopsy slides (Banking)[11, R]	X									
Optional blood sample (Banking)[16,R]	X									
Toxicity Evaluation[13]	X	X		X		X	X	X	X	X
Concomitant Meds[13]	X	X		X		X	X	X		

[1]Laboratory evaluations must be obtained ≤14 days of prior to registration unless otherwise noted. Obtain baseline tumor evaluations ≤28 days prior to registration. ECHO may be obtained ≤28 days prior to registration.

[2]Laboratory evaluations are not required at D1C1 if screening evaluations completed within 7 days of D1C1 with exception of CBC/differential/platelets, which should be repeated ≤48 hours of D1C1. For all other treatment-related study visits (D1 and 15 of each AVD + BV cycle, D1 of BV+ NVB, or D1 of NVB), also at end of AVD + BV treatment and end of BV + NVB laboratory evaluations should be performed ≤2 days prior to study visit. NOTE: The specific treatment day of each cycle may be delayed for toxicities (see Section 8.3). When this happens, laboratory evaluations should be scheduled for the day of treatment.

[3]Complete history at baseline only (including history of HBV, HCV or HIV), thereafter focused history on symptoms/toxicity; Physical to include height (baseline only), weight, vital signs (BP, temperature, respiratory rate, pulse, and oxygen saturation) calculation of body surface area (BSA), and record if unfavorable risk factors for HL are present (see Appendix V – Unfavorable risk factors for Stage I/II HL). H & P only required on D1 of odd cycles of BV + NVB and NVB consolidation.

[4]To be done at progression (early withdrawal), or if taken off treatment early for any reason-to include tumor evaluation at the discretion of the investigator. Subjects who progress prior to initiation of nivolumab (NVB) consolidation will complete the early withdraw visit, which will complete their participation in the study. Subjects who start NVB consolidation will be followed per protocol until disease progression.

[5]At 8 weeks and subsequent disease evaluations in Follow-up /Observation:

- If patient is PET/CT-positive and has evidence of relapse (PD or PMD), they will go to event monitoring.
- If patient is PET/CT-positive but no evidence of relapse, they should receive a biopsy or PET/CT every 3 months until PET/CT becomes negative or there's clear evidence of relapse.
- If the patient is PET/CT-negative or becomes PET/CT-negative, patient should receive CT of chest/abdomen/pelvis (with contrast) every 6 months.
- See Section 4.3 for additional details. Refer to Appendix VI – Deauville Score.

[6]Baseline serum β-HCG in WOCBP ≤ 7 days prior to registration, cycle 1-3 of AVD + BV treatment (serum or urine). Repeat pregnancy tests on D1, cycle 1 at start of a subsequent induction or consolidation regimen (serum or urine) and *repeated every 4 weeks during induction or consolidation therapy and at the end of treatment. For induction with BV+NVB and consolidation with NVB (each test must be conducted within 24 hr of D1 of the relevant treatment cycle).

[7]Positron Emission Tomography (PET)/Computed Tomography (CT) scan at the end of AVD + BV should occur within 1 week after Cycle 3, Day 28 (+/-3 days). If a patient completes treatment with BV + NVB, a PET/CT scan should occur within 4 weeks after the 4th cycle, Day 14 (+/-3 days) of BV + NVB. Please note that patients without progressive disease, including SD and PR will remain on the study. Refer to Appendix VI – Deauville Score.

[8]To include CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus Mg, LDH, amylase, and lipase. Please Note: Amylase and lipase labs are not required during Nivolumab treatment alone or during Observation and Follow-up.

[9]Thyroid function test to include TSH (free T3/T4). Should be performed on Day 1 prior to initiating treatment with AVB + BV, BV + NVB or NVB and performed every 4 weeks during BV + NVB and NVB treatment (i.e. 1 x prior to the 3rd cycle of BV + NVB and prior to the 3rd, 5th and 7th cycles of NVB) and at the end of BV + NVB treatment (each test must be within 72 hours of day 1).

[10]To include infusion reaction assessment. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

[11]Slides should be submitted as described in Section 17.0.

[12]When patient goes off treatment:
- If patient has evidence of relapse (PD or PMD), they will go to event monitoring.
- If patient does not have evidence of relapse (PET/CT can be positive or negative), they will go to 4 weeks, 8 weeks and subsequent Observation for a maximum of 5 years from registration. Observation is 4 weeks after the End of Treatment.
- *Please Note: The End of Treatment is the last day of the cycle.

[13] Including at the end of each cycle of AVD + BV treatment and BV + NVB treatment.

[14] ECOG performance status at progression (withdrawal).

[15]Conducted if discontinued while on BV + NVB.

[16]Optional blood draws for research should not be collected and submitted until after the patient is registered onto the study, but prior to the study treatment initiation. See Section 14.0 for details.

R Research funded (see Section 19.0)

*Note:

- **Observation Phase**: Part of the Active Monitoring Phase of a study. The time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule and may be required to return to the consenting site. Participants will be required to return to the consenting site for follow-up.
- **Event Monitoring:** Not part of the Active Monitoring Phase of a study and should not be included in the Test Schedule. The time period when the participant is no longer following the protocol test schedule. During Event Monitoring the data collection schedule is dictated by the protocol but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study the participant is being monitored for key study events such as progression, new primaries, and death. Samples from biospecimens collected in the course of clinical care may be requested but cannot be required of the participant.
- **End of Treatment: End of treatment is considered the last day of the cycle.**

4.1 Pre-Study Assessments

Clinical evaluation: complete history (including history of hepatitis B, C or HIV), physical examination (including height and weight), ECOG performance status, and presence/absence of unfavorable risk factors for Stage I/IIHL
Cardiac evaluation: MUGA or ECHO

Laboratory studies:
- complete blood count (CBC) with differential; platelets;
- PT or INR
- CMP + other test; CMP [BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus Mg, LDH, amylase, and lipase ,
- erythrocyte sedimentation rate (ESR)
- Pregnancy test: serum β-HCG (if applicable for WOCBP).
- TSH (free T3/T4)
- HBVsAg,HCV Ab

Disease Measurements: PET-CT scan of chest, abdomen and pelvis
Correlative studies: Optional biopsy slides and blood sample
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.0
Concomitant medications

4.2 Treatment Assessments

The following evaluations will be repeated on D1 of each AVD + BV; BV + NVB or NVB cycle:

Clinical evaluation: symptom directed history, physical examination (including weight and vital signs). H&P on D1 of odd cycles only during BV+NVB or NVB.
Laboratory studies:
- complete blood count (CBC) with differential; platelets;
- CMP + other tests: CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus Mg, LDH, amylase, and lipase. Please Note: For NVB cycle alone, amylase and lipase are not required.
- Thyroid tests (free T3/T4) for regimens including NVB: Day 1 cycle 1, and then every other cycle (ie, monthly) for induction with BV+NVB and consolidation with NVB (each test must be conducted within 72 hr of D1 of the relevant treatment cycle)
- serum or urine β-HCG in WOCBP D1 of each cycle for AVD+ BV (within 7 days of D1 for each treatment cycle). D1 cycle 1, and repeated every 4 weeks for induction with BV+NVB or consolidation with NVB (each test must be conducted within 24 hr of D1 of the relevant treatment cycle)
- PT or INR if clinically indicated
- Cardiac evaluation: ECHO/MUGA if clinically indicated

(**NOTE**: for cycle 1 of AVD + BV, laboratory evaluations (other than CBC with differential and platelets) done for screening do not need to be repeated if they were performed within 7 days of D1 of AVD + BV)
Infusion reaction assessment:
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.0
Concomitant medications:

The following evaluations will be repeated on Day 15 of each AVD + BV cycle:

Clinical evaluation: symptom directed history

Laboratory studies:
- complete blood count (CBC) with differential; platelets;
- PT or INR if clinically indicated

Infusion reaction assessment:
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.0
Concomitant medications:

At End of Treatment/PD/withdrawal/removal

If patient goes off treatment:
- If patient has evidence of relapse (PD or PMD), they will go to event monitoring.
- If patient does not have evidence of relapse (PET/CT can be positive or negative), they will go to 4 weeks, 8 weeks and subsequent Observation for a maximum of 5 years from registration.

Clinical evaluation: symptom directed history, physical examination (including weight and vital signs) and ECOG performance status (at progression).
Disease Measurements: PET-CT scan of chest, abdomen and pelvis.
Laboratory studies:
- complete blood count (CBC) with differential; platelets
- CMP + other tests: CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus Mg, LDH
- Thyroid tests (free T3/T4): conducted if discontinue while on BV+ NVB
- PT or INR if clinically indicated
- Serum or urine B-HCG in WOCP

Cardiac evaluation: MUGA or ECHO (if clinically indicated)
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.0
Concomitant medications:

4.3 Observation/Follow-up Assessments

Subjects who receive protocol treatment will be followed until disease progression in observation for a maximum of 5 years from registration.

4.31 4 Weeks after End of Treatment

Clinical evaluation: symptom directed history, physical examination (including weight and vital signs)
Cardiac evaluation: MUGA or ECHO (if clinically indicated)
Laboratory studies:
- complete blood count (CBC) with differential; platelets
- CMP + other tests: CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus Mg, LDH
- Thyroid tests (free T3/T4)
- PT or INR if clinically indicated
- serum or urine β-HCG in WOCBP

Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.0
Concomitant medications:

4.32 8 Weeks after End of Treatment

Clinical evaluation: symptom directed history, physical examination (including weight and vital signs) and ECOG performance status
Cardiac evaluation: MUGA or ECHO (if clinically indicated)
Disease Measurements: PET-CT scan of chest, abdomen and pelvis. If PET-CT scan is borderline (i.e., Deauville score of 4 or standardized uptake value (SUV) < 3.5), then biopsy may be considered for histological confirmation prior to taking the patient off the study therapy. If the biopsy is positive, the patient will come off study therapy and be treated with radiation as per standard of care. If the biopsy is negative, the PET-CT will be repeated in 3 months. If the PET-CT continues to be positive with high clinical suspicion of persistent disease, the patient will come off study therapy and be treated with radiation as per standard of care.

Alternatively, if no biopsy is performed, the PET-CT will be repeated in 3 months. At the 3 month visit, if the PET-CT is still positive but stable or improved, biopsy may be considered for histological confirmation prior to taking the patient off the study therapy. If the biopsy is positive, the patient will come off study therapy and be treated with radiation as per standard of care. If the biopsy is negative, the PET-CT will be repeated in 3 months

At the next 3 month follow-up visit, if the PET-CT is still positive with evidence of disease progression, the patient will come off study therapy and be treated with radiation as per standard of care. If the PET-CT scan becomes negative, PET-CT scans will be repeated every 6 months until negative CT of chest/abdomen/pelvis (with contrast) should replace PET/CT once negative PET/CT is documented.
Laboratory studies:

- complete blood count (CBC) with differential; platelets
- CMP + other tests: CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus Mg, LDH
- PT or INR if clinically indicated
- Thyroid tests (free T3/T4)
- serum or urine β-HCG in WOCBP

Toxicity: Toxicity will be assessed according to the NCI-CTCAE, version 4.0

4.33 Subsequent Follow up Assessments: Every 3 months

At subsequent disease evaluations in Follow-up /Observation:

- If patient is PET/CT-positive and has evidence of relapse (PD or PMD), they will go to event monitoring.
- If patient is PET/CT-positive but no evidence of relapse, they should receive a biopsy or PET/CT every 3 months until PET/CT becomes negative or there's clear evidence of relapse.
- If the patient is PET/CT-negative or becomes PET/CT-negative, patient should receive CT of chest/abdomen/pelvis (with contrast) every 6 months.

The following evaluations will take place:

Clinical evaluation: Symptom directed history, physical examination to include weight and vital signs (BP, temperature, respiratory rate, and pulse) and performance status.
Laboratory studies:

- complete blood count (CBC) with differential; platelets
- PT or INR if clinically indicated

Toxicity: Toxicity assessed according to NCI CTCAEv4.0. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, and then will be followed up per protocol.
Disease Measurement:
CT of neck/chest/abdomen/pelvis with contrast or PET-CT to be used for disease measurement in follow up. Scans should be performed at a minimum of every 6 months for years 1 and 2, and once a year for years 3 through 5.

5.0 Stratification Factors OR Grouping Factor: None

6.0 Registration Procedures

6.1 To register a patient, access the ACCRU web page at [redacted] go to the Remote Application section, click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Remote Application section, "Remote Application Training."
Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Remote Registration, Installation & Entry Instructions" under "Training Material Manuals."

6.2 Documentation of IRB approval must be on file with ACCRU before an investigator may register any patients. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ACCRU no less than annually. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is required until the study is closed through your IRB.

6.3 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 At the time of registration, the following will be recorded:

- Patient has/has not given permission to collect and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her tissue sample(s) to outside researchers.
- Patient has/has not given permission to collect and use his/her blood sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her blood sample(s) to outside researchers.

6.5 Treatment cannot begin prior to registration and must begin ≤7 days after registration.

6.6 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.8 Treatment on this protocol must commence at an ACCRU institution under the supervision of a health care professional.

6.9 a Study drug is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

This study is a single arm Phase II trial evaluating AVD + BV induction therapy, with or without BV + NVB, followed by NVB consolidation for patients with previously untreated stage I or II non-bulky HL. We plan to enroll 82 patients across participating centers (12 sites) over a 2year period to ensure that 78 are evaluable for the primary objective. The primary objective is to estimate 3 year PFS for AVD + BV induction

therapy, with or without BV + NVB, followed by NVB consolidation in this patient population. Patients will receive 3 cycles of AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2; 28-day cycle) plus BV (1.2 mg/kg every 2 weeks X 6 doses). Subjects who are PET-negative after induction with 3 cycles of AVD + BV will proceed to consolidation therapy with NVB (3 mg/kg every 2 weeks X 8 cycles). Subjects who are PET positive after induction with 3 cycles of AVD + BV will receive 4 cycles of BV (1.2 mg/kg every 2 weeks) plus NVB (3 mg/kg every 2 weeks) followed by NVB consolidation (3mg/kg every 2 weeks for 8 cycles). Data on use of interim PET-CT in limited stage disease suggest that PET may have a role in risk assessment and management of limited stage disease [3, 4]. In this study, patients who progress during therapy will be removed from protocol therapy.

7.11 Premedication/Hydration

Premedication (including prophylactic antiemetics) and hydration should be provided as per institutional guidelines and per standard of care for AVD administration.

Infusion-related reactions (including anaphylaxis) may occur during the infusion of BV or NVB. Therefore, the infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. Monitor patients during infusion. If anaphylaxis occurs immediately and permanently discontinue administration of BV or NVB and administer appropriate medical therapy per institutional standards. If a mild or moderate infusion-related reaction occurs, the infusion should be interrupted or the rate of infusion slowed and appropriate medical management instituted. Patients who experienced prior infusion-related reaction to either BV or NVB should be pre-medicated for subsequent infusions per institutional standards. Premedication may include acetaminophen, an antihistamine and a corticosteroid.

7.12 Treatment Dosage and Administration

Concurrent therapy of AVD (doxorubicin 25 mg/m2, vinblastine 6 mg/m2, dacarbazine 375 mg/m2; in a 28-day cycle for 3 cycles) and Brentuximab Vedotin (BV; 1.2 mg/kg every 2 weeks for 6 doses)

If subjects are PET-negative after AVD + BV induction: Nivolumab consolidation (NVB; 3mg/kg, once every 2 weeks for 8 cycles).

If subjects are PET-positive after AVD + BV induction: Additional therapy with BV (1.2 mg/kg every 2 weeks x 4 cycles) plus NVB (3 mg/kg every 2 weeks x 4 cycles) will be given followed by NVB consolidation (3mg/kg, once every 2 weeks for 8 cycles).

All dosing for AVD will be determined by the patient's body surface area (BSA) calculated from actual weight on D1 of each cycle or the patient's baseline weight on day of cycle 1, as measured according to institutional standards.

NVB or BV dosing should be based on the patient's baseline weight on day 1 of cycle 1, as measured according to institutional standards; doses will be adjusted for patients who experience a ≥10% change in weight during the study. Actual weight will be used except for patients weighing greater than 100 kg; BV dose will be calculated based on 100 kg for these individuals (max 120 mg). The dose should be rounded to the nearest whole number of milligrams.

NVB consolidation (interim PET-negative patients only) should begin within 4 to 8 weeks after the Cycle 3, Day 28 of AVD + BV. BV + NVB (interim PET-positive patients only) should begin 2 to 4 weeks (+/- 3 days) after the Cycle 3, Day 28 of AVD + BV

NVB consolidation for interim PET-positive patients should begin 4 to 8 weeks after the 4^{th} cycle of BV + NVB.

AVD + BV Dosing Schedule			
Drug	**Dose & Route**	**Schedule**	**Cycles[1]**
Doxorubicin (A)	25 mg/m^2 IV over 3-5 minutes or per institutional standards	Day 1 and D15 (+/-) 3 days	Every 28 days
Vinblastine (V)	6 mg/m^2 IV over 3-5 minutes or per institutional standards	Day 1 and D15 (+/-) 3 days	Every 28 days
Dacarbazine (D)	375 mg/m^2 IV over ≥30 minutes or per institutional standards	Day 1 and D15 (+/-) 3 days	Every 28 days
Brentuximab Vedotin[2,3,4] (BV)	1.2 mg/kg IV over 30 minutes	Day 1 and D15 (+/-) 3 days	Every 28 days
Filgrastim[5]	5 µg/kg/day SC	Start ≥ 24 hrs after chemo	NA

[1] AVD + BV will be administered for 3 cycles of therapy. See schema for details.
[2] BV should not be mixed with, or administered as an infusion with, other medications, **AND MUST NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS. MAXIMUM DOSE 120 MG.**
[3] Patients must have an ANC ≥500 and platelets ≥50,000 cells/mm^3 to be eligible for treatment on day 1 of each cycle.
[4]BV should be administered within approximately 1 hr of AVD infusion on days 1 and 15
[5]Filgrastim (5 µg/kg/day) must be administered ≥ 24 hrs after chemo for ≥ 3 days as supportive care per institutional standard.
See Section 9.0.

BV + NVB Dosing Schedule (only for PET+ patients)			
Drug	**Dose & Route**	**Schedule**	**Cycles[1]**
Brentuximab Vedotin[2,3] (BV)	1.2mg/kg IV over 30 minutes	Day 1 (+/-) 3 days	Every 2 weeks
Nivolumab (NVB)[4]	3mg/kg IV over 30 minutes	Day 1 (+/-) 3 days	Every 2 weeks

[1] BV + NVB will be administered for 4 cycles of therapy. See schema for details.
[2] BV should not be mixed with, or administered as an infusion with, other medications, **AND MUST NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS. MAXIMUM DOSE 120 MG.**
[3] Patients must have an ANC ≥500 and platelets ≥50,000 cells/mm^3 to be eligible for treatment on day 1 of each cycle.
[4]NVB should be given within 2 hours of BV infusion

NVB Consolidation Dosing Schedule			
Drug	**Dose & Route**	**Schedule**	**Cycles[1]**
Nivolumab (NVB)	3mg/kg IV over 30 minutes	Day 1 (+/-) 3 days	Every 2 weeks
[1] NVB will be administered for 8 cycles of therapy. See schema for details.			

7.2 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at on Day 1 and Day 15 of each cycle during AVD + BV treatment, Day 1 of BV + NVB treatment, and Day 1 of NVB consolidation treatment (Active Monitoring Phase).

7.3 Treatment by a local medical doctor (LMD) is not allowed.

8.0 Dosage Modification Based on Adverse Events

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Level Reduction of BV

Dose Level	Brentuximab vedotin
0	1.2 mg/kg
-1	0.9 mg/kg

8.2 Dose Level Reduction of NVB

Dose reductions or dose escalations of NVB are not allowed. NVB dose should either be withheld or permanently discontinued depending on the severity of the adverse event (See Section 8.33 for further details).

Dose Level	Nivolumab
0	3 mg/kg

8.3 Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed regularly for the development of any toxicity according to the Time and Events table (Section 4.0). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. See Section 10.0.

During AVD + BV induction therapy, if a patient experiences ≥2 or more SARs simultaneously that require different dose reductions, the lowest (dose or greatest dose reduction) should be used. A maximum of 2 dose-level reductions for SARs are allowed for AVD on this protocol, and 1 dose-level reduction for SARs is allowed for BV. If >1 dose reductions are required for BV, BV is to be discontinued. Patients who received at

least 2 does of BV (i.e. 1 cycle of AVD + BV) are allowed to continue without BV for the remaining therapy at the discretion of the study PI if the toxicity related to BV is considered significant and does not resolve within one week. Significant toxicity is Grade 3 or higher pancreatitis, Grade 3 or higher hepatitis, diagnosis of PML or any serious adverse event directly related to BV. If the interim PET is negative, patient is to be treated AVD only and proceed with NVB consolidation at the end of induction therapy per protocol. If the interim PET is positive or patient is unable to tolerate AVD, patient is to come off the study treatment and be treated per institutional standard and followed per protocol. For BV dose reduction, please refer to the table in Section 8.1.

During BV + NVB induction therapy, if >1 dose reduction is required for BV, protocol therapy is to be discontinued and patient is to be treated with NVB only and followed per protocol. For BV dose reduction, please refer to the table in Section 8.1.

NVB should be withheld for AEs moderate in severity until resolution to ≤ Grade 1 or first occurrence Grade 3 events until resolution to ≤ Grade 1. NVB should be permanently discontinued for Grade 2 or 3 AEs lasting 12 weeks or longer, following the second occurrence of the same Grade 3 event, or following the occurrence of a severe or life-threatening AE (See section 8.33). If NVB is permanently discontinued, patient is to come off the study treatment and be treated per institutional standard and followed per protocol.

During NVB consolidation therapy, NVB should be withheld for AEs moderate in severity until resolution to ≤ Grade 1 or first occurrence Grade 3 events until resolution to ≤ Grade 1. NVB should be permanently discontinued for Grade 2 or 3 AEs lasting 12 weeks or longer, following the second occurrence of the same Grade 3 event, or following the occurrence of a severe or life-threatening AE (See Section 8.33). If NVB is permanently discontinued, patient is to come off the study treatment and be treated per institutional standard and followed per protocol.

8.31 Dose Modifications/Delays for AVD + BV
Note: AVD treatment should be modified or discontinued per applicable label/Summary of Product Characteristics (SmPc) instructions or institutional chemotherapy standard.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**Adverse Event**	**Severity**	**Action****
Blood and lymphatic system disorders	Anemia	**≤Grade 2**	Continue at same dose level
		≥Grade 3	Manage per institutional guidelines.
Investigations	Neutrophil count decreased	**≤Grade 2**	Continue at same dose level

		≥Grade 3	Manage by extending the duration of granulocyte colony stimulating factor (G-CSF) per institutional guidelines (≥ 3 days after chemo).
	Platelet count decreased	**≤Grade 2**	Continue at same dose level
		≥Grade 3	Consider platelet transfusion and/or proceed according to institutional guidelines.
Nervous system disorders	Peripheral motor neuropathy	**Grade 1**	Continue at same dose level.
		Grade 2	Continue at same dose level. For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level
		Grade 3	Omit BV until toxicity is ≤Grade 2, then restart at 1.2 mg/kg and resume treatment. For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level (AVD may be continued or hold all drugs concurrently at physician's discretion.)
		Grade 4	Discontinue BV.
	Peripheral sensory neuropathy	**Grade 1**	Continue at same dose level.
		Grade 2	Continue at same dose level. For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level

		Grade 3	Omit BV until toxicity is ≤Grade 2, then restart at 1.2 mg/kg and resume treatment. For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level (AVD may be continued or hold all drugs concurrently at physician's discretion.)
		Grade 4	Discontinue BV.
All other nonhematologic	All other nonhematologic events (excluding neuropathy	**≤Grade 2**	Continue at same dose level.
		≥Grade 3	Hold AVD + BV until toxicity has resolved to ≤Grade 2 or has returned to baselinea Or omit one dose of brentuximab vedotin (BV), then resume treatment at the next scheduled AVD administration if toxicity is ≤ Grade 2 or has returned to baseline.

a. Subjects who develop clinically insignificant Grade 3 or 4 electrolyte abnormalities may continue study treatment without interruption.

8.32 Dose Modifications/Delays for BV (BV + NVB)

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←			
CTCAE System/Organ/Class (SOC)	**Adverse Event**	**Severity**	**Action****
Investigations	Neutrophil count decreased	**≤Grade 2**	Continue at same dose level
		≥Grade 3	Add growth factor support (G-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. For unresolved Grade 4 neutropenia, BV may be withheld after discussion with the study chair.

Nervous system disorders	Peripheral motor neuropathy	**Grade 1**	Continue at same dose level.
		Grade 2	Continue at same dose level.For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level
		Grade 3	Omit BV until toxicity is ≤Grade 2, then restart at 1.2 mg/kg and resume treatment. For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level (AVD may be continued or hold all drugs concurrently at physician's discretion.)
		Grade 4	Discontinue treatment with BV. Continue NVB only.
Nervous system disorders	Peripheral sensory neuropathy	**Grade 1**	Continue at same dose level.
		Grade 2	For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level
		Grade 3	Omit BV until toxicity is ≤Grade 2, then restart at 1.2 mg/kg and resume treatment. For recurrent/persistent symptoms, consult with sponsor to consider reducing by 1 dose level (AVD may be continued or hold all drugs concurrently at physician's discretion.)
		Grade 4	Discontinue treatment with BV. Continue NVB only.
All other nonhematologic	All other nonhematologic events (excluding neuropathy	**≤Grade 2**	Continue at same dose level.
		≥Grade 3	Omit one Brentuximab vedotin (BV) dose, then resume treatment at the

			next scheduled BV + NVB administration if toxicity is ≤ Grade 2 or has returned to baseline.[a] If ≥ Grade 3 toxicity persists for > 2 weeks, discontinue BV and continue NVB only

a. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

8.33 Dose Modifications/Delays for NVB

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←			
CTCAE System/Organ/Class (SOC)	**Adverse Event**	**Severity**	**Action****
Endocrine Disorders	Adrenal insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
		Grade 3 or 4 adrenal insufficiency	Permanently discontinue
	Endocrine disorders – other, specify	Grade 2 or 3 hypophysitis	Withhold dose[a]
		Grade 4 hypophysitis	Permanently discontinue
Gastrointestinal Disorders	Colitis	Grade 2 colitis	Withhold dose[a]
		Grade 3 colitis	Withhold dose[a] when administered as a single agent or with BV
		Grade 4 colitis	Permanently discontinue
	Diarrhea	Grade 2 diarrhea	Withhold dose[a]
		Grade 3 diarrhea	Withhold dose[a] when administered as a single agent or with BV
		Grade 4 diarrhea	Permanently discontinue
Infections and Infestations	Encephalitis infection	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
		Immune-mediated encephalitis	Permanently discontinue

	Hepatitis	Aspartate aminotransferase (AST)/ or alanine aminotransferase (ALT) more than 3 and up to 5 X the ULN or total bilirubin > 1.5 and up to 3X ULN	Withhold dose[a]
		AST or ALT more than 5X ULN or total bilirubin > 3X ULN	Permanently discontinue
Investigations	Creatinine increased	Serum creatinine more than 1.5 and up to 6X ULN	Withhold dose[a]
		Serum creatinine more than 6X ULN	Permanently discontinue
Metabolism and Nutrition Disorders	Hyperglycemia	Grade 3 hyperglycemia	Withhold dose[a]
		Grade 4 hyperglycemia	Permanently discontinue
Respiratory, Thoracic and Mediastinal Disorders	Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
		Grade 3 or 4 pneumonitis	Permanently discontinue
Skin and Subcutaneous Tissue Disorders	Rash maculo-papular	Grade 3 rash	Withhold dose[a]
		Grade 4 rash	Permanently discontinue
Other Adverse Events	Other Adverse Events	Other Grade 3 adverse reaction First occurrence	Withhold dose[a]
		Recurrence of same Grade 3 adverse reaction	Permanently discontinue
		Life-threatening or Grade 4 adverse reaction	Permanently discontinue
		Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
		Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

a) Resume treatment when adverse reaction returns to Grade 0 or 1. If toxicity persists > 6 weeks, permanently discontinue NVB.

* Located at [redacted]

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restartdrugs.
- Discontinue = The specified drug(s) are totally stopped.

Dose Delay Criteria for NVB
Because of the potential for clinically meaningful NVB-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories [see current Investigator Brochure and Appendix VII].

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

NVB administration should be delayed for the following:

Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:
- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE

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

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

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

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

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

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

Management Algorithms

Guidelines for the management of immune-related events can be found in the current NVB Investigator Brochure AND in the approved USPI in the US.

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

Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological. (See Appendix VII)

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

Discontinuation Criteria for NVB

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
- AST or ALT > 8 x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
- Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical

sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 lymphopenia or leucopenia
- Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator
- Any dosing interruption lasting > 6 weeks with the following exceptions:
- Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
- Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

8.34 Treatment of Nivolumab-Related Infusion Reactions

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

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAEv4.0 guidelines.

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

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

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

Stop the NVB infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when

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

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

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

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

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetic's may be used at the discretion of the attending physician.

9.2 Blood products should be utilized as clinically warranted and following institutional policies and recommendations. Filgrastim must be administered ≥ 24 hrs after chemo for ≥ 3 days as supportive care per institutional standard. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006; 24:3187-3205. Please Note: G-CSF support includes neupogen, nuelasta, udenyca, and equivalent growth factor products per the institutional standard.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Concomitant Medications/Treatments

Patients should be up-to-date on any recommended vaccinations prior to study entry. Vaccination(s) during study treatment must be approved by the treating physician.

The use of transfusions, platelet and/or colony-stimulating factors per institutional practice is permitted during therapy at the Investigator's discretion. Patients may not receive other investigational drugs, immunosuppressive medications (other than dexamethasone or prednisone for use as anti-emetics, or if steroids are needed to treat an infusion reaction), or antineoplastic therapy during the study. The routine use of steroids as premedication prior to BV is discouraged.

In-vitro data indicate that monomethyl auristatin E (ie, drug conjugate of BV) is a substrate and inhibitor of the P450 isoenzyme CYP3A4. Patients who are receiving strong CYP3A4 inhibitors such as ketoconazole with BV should be closely monitored for adverse reactions. Co-administration with potent CYP3A4 inducers, such as rifampin, should be avoided. BV is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes. A frequently updated list of CYP3A4 inhibitors and inducers can be found at [redacted]

Suggested Management of Adverse Events Related to Study Treatments

Renal and Hepatic Impairment
Brentuximab Vedotin (BV):

- For mild-moderate renal impairment (creatinine clearance between 30-80mL/min; see Appendix III – Renal Impairment Guidelines (Appendix III – Renal Impairment Guidelines), dose of 1.2mg/kg or lower may be maintained.
- For severe renal impairment (creatinine clearance <30mL/min), BV should be discontinued.
- For moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment, BV should be discontinued (see Appendix IV – Child-Pugh Hepatic Impairment Score (Appendix IV – Child-Pugh Hepatic Impairment Score).

Nivolumab (NVB):

- No dose adjustment is needed for NVB in patients with renal insufficiency.
- No dose adjustment is recommended in patients with mild hepatic impairment.
- NVB has not been evaluated in patients with moderate or severe hepatic impairment.

Special warnings and precautions for use

- NVB is associated with immune-related AEs. Subjects should be monitored continuously (at least up to 5 months after the last dose) as an AE with NVB may occur at any time during or after discontinuation of NVB therapy.

- For suspected immune-related reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, NVB should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an AE, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening of the AE. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms
Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 4.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

Unanticipated Adverse Device Event (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination)Arm

When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.5). *

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Blood and lymphatic system disorders	Anemia	≤Grade 4
Investigations	Neutrophil count decreased	≤Grade 4

	Platelet count decreased	≤Grade 4
	White blood count	≤Grade 4
	Lymphocyte count decreased	≤Grade 4

These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol or to administer protocol directed treatment (i.e. 131I therapy)
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event

*An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.331 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.332 Secondary Malignancy

- 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.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic 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.

10.333 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.

10.335 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", 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. Include any available medical documentation.

10.3351 BMS Reporting: If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives (100 days) after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify [redacted] of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS].

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS and Seattle Genetics. Information on this pregnancy will be collected on the Pregnancy Surveillance Form [provided upon request from BMS].

10.3352 Seattle Genetics Reporting: Pregnancies from time of first drug until 6 months after last dose, including any that occur in male patient's partner must be reported within 48 hours of awareness.

Email or fax the Seattle Genetics Pregnancy Report Form to [redacted] All pregnancies that occur during this time period will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks. Abortion, whether accidental, therapeutic or spontaneous, should be reported as an SAE.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 **Phase 1 and Early Phase 2 Studies:** Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **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 sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	24-Hour; 3 Calendar Days	24-Hour; 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.

[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 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 16, 2017

Follow site-specific reporting guidelines.

Submit the ACCRU Adverse Event Expedited Report Form to ACCRU Safety via email at: [redacted]
The ACCRU SAE Coordinator will forward by fax or e-mail to Seattle Genetics at: Facsimile [redacted] or Email: [redacted] and Bristol-Myers Squibb at: Facsimile: [redacted]

The ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v4.0 grading. If CTCAE v4.0 grading is not used, note the grading scale used in the table below

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
Nervous System Disorders	Peripheral motor neuropathy	X	X
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	X	X
	Pneumonitis	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)
Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable)

10.531 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.533 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.55 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.56 ACCRU will provide a study-specific cumulative SAE line listing of all SAEs including an assessment of causality to the Product. This will be e-mailed monthly to Seattle Genetics at: [redacted]

10.57 ACCRU agrees to conduct reconciliation of all SAE's submitted to BMS on a

quarterly basis. ACCRU will request a quarterly reconciliation report from BMS for the preceding 3 months by emailing [redacted]

11.0 Treatment Evaluation Using Lugano Guideline

11.1 Response Considerations

Schedule of Evaluations: PET/CT scans are required at baseline for all patients. In addition to a baseline PET/CT scan, confirmatory scans should also be obtained per the test schedule in Section 4.0. During observation, CT scan should be obtained every 6 months during the first two years and once a year during years 3 to 5 of follow up to evaluate for disease progression.

Definitions for clinical response for patients with lymphoma are from the recently revised Cheson's et al criteria published in 2014, derived from the original criteria published in 2007. (Cheson et al, 2014)(Cheson et al, 2007). Lymph node measurements should be taken from the CT portion of the PET/CT, or other dedicated CT scans where applicable. Measurement of lymphadenopathy for purposes of assessing for PR will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). The PPD of a single node is sufficient to evaluate for PD (see Table 11.2). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically and pathologically negative.

Response is based on PET/CT based on the revised 2014 Lugano Classification. (Cheson et al, 2014). Of note, PET-based response criteria take precedence of CT-based response criteria if both are done at the same time. CT-based response criteria is used ONLY when PET is not available. PET-based responses and CT-based responses therefore may differ within the same assessment, but the patient's overall response will be determined by PET status.

Progressive disease is based on either PET-CT based (PMD) or CT based (PD) response criteria. PET confirmation of progressive disease is per physician discretion. Of note, if the PET is negative (CR) at the end of treatment, subsequent follow-up CT scans are considered negative (CR) even if they show residual nodal mass as long as there is no interval progression (i.e. significant interval enlargement of the existing lymph nodes and/or new sites of disease).

If the PET/CT result is equivocal (e.g. Deauville score of X) at the end of nivolumab consolidation therapy, subsequent PET/CT scans with a definite result will be used to document the treatment response. Biopsy is recommended, but not required, to confirm disease progression.

11.2 Lugano Classification Response criteria (Cheson et al, 2014)

	PET-CT Based Response	**CT-Based Response**
Complete Response	**Complete metabolic response (CMR)**	**Complete radiologic response (CR) (all of the following)**
Lymph nodes and	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi

extralymphatic sites	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	**Partial metabolic response (PMR)**	**Partial remission (PR) (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not Applicable
No Response or Stable Disease	**No metabolic response (NMR)**	**Stable disease (SD)**
Target nodes/nodal masses, extranodal	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met

lesions		
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not Applicable
Progressive disease	**Progressive metabolic disease (PMD)**	**Progressive disease (PD) requires at least 1 of the following**
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement
Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.		

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET Deauville 5PS: 1, no uptake above background; 2, uptake≤mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

12.0 Descriptive Factors: None.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Duration of Therapy
Patients who achieve a CMR post 3 cycles of AVD + BV treatment per protocol may continue study therapy until they complete 8 cycles of NVB consolidation. Patients with PD or PMD post cycle 3 of AVD + BV will be removed from protocol therapy. Patients who do not achieve a CMR post 3 cycles of AVD + BV may receive 4 cycles of BV + NVB therapy; a repeat PET/CT will be obtained after 4 cycles of BV + NVB. Patients with PD or PMD post 4 cycles of BV + NVB will be removed from protocol therapy. Patients who have not progressed (including SD and PR) may continue per protocol and receive 8 cycles of NVB consolidation. A restaging PET/CT will be performed per protocol after 8 cycles of NVB consolidation.

13.2 Patients should continue protocol therapy as described above until:
- Disease progression (PD or PMD)
- Inter-current illness prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

13.3 Patients who develop progressive disease at any time (PD or PMD) or choose an alternative therapy or refuse to be followed in observation will go to the event-monitoring phase per Section 18.0 for a maximum of 5 years from registration.

13.4 Patients who go off protocol treatment for reasons other than PD or PMD will go to observation per Section 4.0 for a maximum of 5 years from registration. Patients removed from study treatment for unacceptable AEs will be followed in observation until resolution or stabilization of the event(s). Observation visits should be every 3 months (+/-7 days) until PMD/PD, death, or withdrawal from Observation.

13.5 Event Monitoring: Patients will be followed for up to 5 years from registration after removal from treatment.

13.6 Study Withdrawal
If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

13.7 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.8 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.9 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens:

14.1 Body Fluid Biospecimen NOTE: Patients must have consented to submission of the optional body fluid biospecimen(s) listed in the following table.

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

Type of biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for specimen submission**

Type of biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for specimen submission**
Blood/blood products (EDTA whole blood)	Optional	Pre Treatment[1]	Banking (Section 14.311)	Section 14.4

[1] Optional blood draw for research should not be collected and submitted until after the patient is registered onto the study, but prior to the study treatment initiation.

14.2 Blood/Blood Products Handling

14.21 There are no kits for this study. However, the collection tube must be plastic. Either a plastic 10 mL EDTA tube or smaller plastic EDTA tubes to make 10 mLs of blood may be used. All samples should be collected **Monday-Friday.**

14.22 Label specimen tube(s) with protocol number, ACCRU patient ID number, and time and date blood is drawn. Gently invert the sample 8-10 times to gently mix the sample and place into the -80° freezer until ready to ship on dry ice.

14.221 Summary Table of Research Blood/Blood Products to be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product submitted by participating site	Pre-Treatment [2]	Additional processing required at site after blood draw?	Storage/ shipping conditions[1]
Optional[1]	EDTA (purple)	10 mL (1)	Whole Blood	X	No	Frozen (Dry Ice)

[1] Frozen samples may be batch shipped quarterly.
[2] Optional blood draw for research should not be collected and submitted until after the patient is registered onto the study, but prior to the study treatment initiation.

14.23 Shipping

14.231 Verify ALL sections of the Specimen Submission: Blood (Baseline) form (see CRF Packet), BAP Requisition Form, and specimen collection labels are completed and filled in correctly. Pair Requisition Form with samples.

Frozen samples may be batch shipped quarterly via Priority Overnight service on dry ice.

Ship samples to:



14.3 Study Methodology and Storage Information

14.31 Blood/blood product samples will be collected for the following research.

14.311 DNA extraction and storage of DNA will be stored frozen at -80°C by BAP until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND number - 135112

15.1 Doxorubicin (Adriamycin®, ADR)

15.11 **Background**: Doxorubicin inhibits DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II and be steric obstruction. Doxorubicin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA. Doxorubicin is also a powerful iron chelator; the iron-doxorubicin complex can bind DNA and cell membranes and produce free radicals that immediately cleave the DNA and cell membranes.

15.12 **Formulation**: Commercially available for injection as:
Injection, powder for reconstitution: 10 mg, 50 mg
Injection, solution: 2 mg/mL (5 mL, 10 mL, 25 mL, 100 mL)

15.13 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials of solution under refrigeration and protect from light; store intact vials of lyophilized

powder at room temperature. Reconstitute lyophilized powder with NS to a final concentration of 2 mg/mL. Reconstituted vials are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Infusions are stable for 48 hours at room temperature when protected from light. Solutions diluted in 50-1000 mL D5W or NS are stable for 48 hours at room temperature when protected from light. Stable with vincristine in NS for five days at room temperature protected from light.

15.14 **Administration:** Refer to the treatment section for specific administration instructions. Doxorubicin is administered I.V. push over at least 3-5 minutes, IVPB over 15-60 minutes, or continuous infusion. Avoid extravasation. Flush with 5-10 mL of I.V. solution before and after drug administration. Incompatible with heparin.

15.15 **Pharmacokinetic information**:
Distribution: V_d: 809-1214 L/m^2; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta
Protein binding, plasma: 70% to 76%
Metabolism: Primarily hepatic to doxorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides
Half-life elimination:
Distribution: 5-10 minutes
Elimination: Doxorubicin: 1-3 hours; Metabolites: 3- 3.5 hours
Terminal: 17-48 hours
Male: 54 hours; Female: 35 hours
Excretion: Feces (~40% to 50% as unchanged drug); urine (~5% to 12% as unchanged drug and metabolites)
Clearance: Male: 113 L/hour; Female: 44 L/hour

15.16 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP2D6 (major), 3A4 (major); **Inhibits** CYP2B6 (moderate), 2D6 (weak), 3A4 (weak)
Increased Effect/Toxicity: Bevacizumab, trastuzumab, and cyclophosphamide may enhance the cardiotoxic effect of doxorubicin. Docetaxel and paclitaxel may enhance the adverse/toxic effect of doxorubicin; may increase the serum concentration of doxorubicin and may also increase the formation of toxic doxorubicin metabolites in heart tissue. Cyclosporine and sorafenib may increase the levels/effects of doxorubicin. CYP2D6 inhibitors may increase the levels/effects of doxorubicin. CYP3A4 inhibitors may increase the levels/effects of doxorubicin. Doxorubicin may increase the levels/effects of CYP2B6 substrates.
Decreased Effect: Digoxin may diminish the cardiotoxic effect of doxorubicin. Doxorubicin may decrease the absorption and serum concentration of cardiac glycosides. CYP3A4 inducers may decrease the levels/effects of doxorubicin.
Herb/Nutraceutical Interactions: Avoid St. John's wort (may decrease doxorubicin levels). Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.17 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Dermatologic: Alopecia
Gastrointestinal: Mucositis, nausea, vomiting
Genitourinary: Discoloration of urine
Hematologic: Leukopenia/neutropenia (75%; nadir: 10-14 days; recovery: by Day 21); thrombocytopenia and anemia

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Congestive heart failure
Central nervous system: Malaise
Dermatologic: Itching, rash, discoloration of saliva, sweat, or tears, radiation recall
Endocrine & metabolic: Amenorrhea, dehydration, infertility (may be temporary), hyperuricemia
Gastrointestinal: Abdominal pain, anorexia, diarrhea, GI ulceration, colon necrosis
Local: Skin "flare" at injection site, urticaria
Neuromuscular & skeletal: Weakness

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Dermatologic: Photosensitivity, ulceration or severe reaction at the injection site if extravasation occurs.

15.18 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.19 Nursing Guidelines:

15.191 Check CBC and platelet counts. Instruct patient to watch for signs of infection, bleeding, and anemia.

15.192 Advise patient of red discoloration of urine for approximately 24 hours after administration of the drug.

15.193 Adriamycin is a vesicant. Check IV patency before and frequently during administration. If extravasation occurs, refer to institutional extravasation policy.

15.194 Hair loss occurs 2-4 weeks after initial injection and can be complete. Regrowth begins 2-3 months after discontinuation.

15.196 Beware of Adria "flare" that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also demonstrate red streaks. Urticaria and pruritus can be associated with the reaction. The use of corticosteroids and/or antihistamines has been helpful.

15.197 Administer antiemetics to minimize nausea and vomiting.

15.198 Assess for alterations in mucous membranes. Stomatitis occurs within 7-10 days after injection. It begins with burning sensation and can progress to ulceration, which can last 3 days. Carafate slurry may be useful. Adequate nutritional counseling is important. Topical anesthetics such as viscous Xylocaine can be used symptomatically.

15.199a Advise patient that there is often significant malaise and fatigue 1-2 weeks after injection.

15.199b Adriamycin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated Cyclophosphamide (Cytoxan, CTX) induced hemorrhagic cystitis.

15.199c Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alerts to early signs of cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales. Instruct patients to report any of these signs or symptoms to their health care provider.

15.199d Document cumulative dose, which should not exceed maximum cumulative dose.

15199e Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.

15199f Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection.

15199g Monitor for signs and symptoms of cardiomyopathy. Calculate total cumulative dose with each administration.

15.2 Vinblastine (VLB)

15.21 **Background:** Vinblastine binds to tubulin and inhibits microtubule formation, therefore, arresting the cell at metaphase by disrupting the formation of the mitotic spindle; it is specific for the M and S phases. Vinblastine may also interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization.

15.22 **Formulation:** Commercially available for injection as a 1 mg/mL solution (10 mL vial).

15.23 **Preparation, storage, and stability**: Refer to the package insert for complete preparation and dispensing instructions. Store intact vials of solution in the refrigerator. Reconstituted vinblastine, 1 mg/mL, is stable for 28 days in the refrigerator. Further diluted to a concentration of 0.01 mg/mL in normal saline or 5% dextrose, vinblastine is stable for 24 and 72 hours, respectively, at room temperature. The 10 mg vial is reconstituted with 10 mL of 0.9% sodium

chloride or bacteriostatic normal saline, yielding a concentration of 1 mg/mL. Vinblastine is physically stable in normal saline solutions for at least five days.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. Vinblastine may be administered IV push over at least 3 to 5 minutes, IV piggyback via gravity a minimum of 2 minutes, or continuous infusion. Avoid extravasation.

15.25 Pharmacokinetic information:
Metabolism: Hepatic (via CYP3A) to active metabolite
Half-life elimination: Terminal is approximately 25 hours
Excretion: Feces (10%), urine (14%)

15.26 Potential Drug Interactions:
Cytochrome P450 Effect: Substrate of CYP2D6 (minor), CYP3A4 (major), P-glycoprotein
Increased Effect/Toxicity: CYP3A4 inhibitors (strong and moderate) may decrease the metabolism of vinblastine. Macrolide Antibiotics may increase the serum concentration and distribution of vinca alkaloids into certain cells and/or tissues. Acute pulmonary reactions may occur with mitomycin-C. Previous or simultaneous use with mitomycin-C has resulted in acute shortness of breath and severe bronchospasm within minutes or several hours after vinca alkaloid injection and may occur up to 2 weeks after the dose of mitomcyin. P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.).
Decreased Effect: CYP3A4 inducers may decrease the levels/effects of vinblastine.
Ethanol/Nutrition/Herb Interactions: St John's wort may decrease vinblastine levels.

15.27 **Known potential toxicities:** Consult the package insert for the most current and complete information.
Cardiovascular: Angina pectoris, cerebrovascular accident, ECG abnormality, hypertension (common), ischemic heart disease, limb ischemia, myocardial infarction, Raynaud's phenomenon
Central nervous system: Decreased deep tendon reflex, depression, dizziness, headache, malaise (common), metallic taste, neurotoxicity (duration: >24 hours), paresthesia, peripheral neuritis, seizure, tumor pain (common), vertigo
Dermatologic: Alopecia (common), dermatitis, skin blister, skin photosensitivity (rare), skin rash
Endocrine & metabolic: Hyperuricemia, SIADH (syndrome of inappropriate antidiuretic hormone secretion)
Gastrointestinal: Abdominal pain, anorexia, constipation (common), diarrhea, enterocolitis (hemorrhagic), gastrointestinal hemorrhage, intestinal obstruction, nausea (mild), paralytic ileus, stomatitis, toxic megacolon, vomiting (mild)
Genitourinary: Azoospermia, urinary retention

Hematologic & oncologic: Anemia, bone marrow depression (common), granulocytopenia (common; nadir: 5 to 10 days; recovery: 7 to 14 days; dose-limiting toxicity), hemolytic uremic syndrome, leukopenia (common; nadir: 5 to 10 days; recovery: 7 to 14 days; dose-limiting toxicity), rectal hemorrhage, thrombocytopenia (recovery within a few days), thrombotic thrombocytopenic purpura
Local: Local irritation
Neuromuscular & skeletal: Jaw pain (common), myalgia, ostealgia (common), weakness
Ophthalmic: Nystagmus
Otic: Auditory disturbance, deafness, vestibular disturbance
Respiratory: Bronchospasm, dyspnea, pharyngitis
Miscellaneous: Radiation recall phenomenon

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 Nursing guidelines:

15.291 Velban is a vesicant. Assess patency of IV site before and throughout infusion. Drug should be given slow IVP over 1 2 minutes through sidearm of running IV. Refer to your agency policy if extravasation occurs.

15.292 Monitor for neurotoxicity--numbness, tingling, ataxia, loss of deep tendon reflexes, etc. Instruct patient to report any of these symptoms to the health care team.

15.293 Instruct patient in possible constipation and prevention measures--may require prophylactic laxatives.

15.294 Premedicate with antiemetics prn. Nausea and vomiting are rare.

15.295 Instruct patient about possible alopecia.

15.296 Monitor CBC. May cause severe bone marrow depression. Neutropenia is common. Thrombocytopenia may be severe in patients who have had prior XRT or chemotherapy. Instruct patient to report any signs/symptoms of infection, any usual bruising or bleeding to the health care team immediately.

15.297 Observe for bronchospasm (rare).

15.3 Dacarbazine (DTIC®)

15.31 **Background**: Dacarbazine is an alkylating agent. It is converted to the active alkylating metabolite MTIC. The cytotoxic effects of MTIC are manifested through alkylation of DNA at guanine positions which appears to attack cross-

links strands of DNA resulting in the inhibition of DNA, RNA, and protein synthesis.

15.32 **Formulation**: Commercially available for injection as:
Injection, powder for reconstitution: 100 mg, 200 mg

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials under refrigeration and protect from light; intact vials are stable for 4 weeks at room temperature. Reconstituted solution is stable for 24 hours at room temperature and 96 hours under refrigeration when protected from light, although the manufacturer recommends use within 72 hours if refrigerated and 8 hours at room temperature. Solutions for infusion are stable for 24 hours at room temperature if protected from light. Decomposed drug turns pink. The manufacturer recommends reconstituting 100 mg and 200 mg vials with 9.9 mL and 19.7 mL Sterile Water For Injection, respectively, to a concentration of 10 mg/mL; some institutions use different standard dilutions (e.g., 20 mg/mL). Use appropriate precautions for handling and disposal.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. Dacarbazine is diluted in 250-1000 mL of D5W or NS. Infuse over 30-60 minutes; rapid infusion may cause severe venous irritation. Dacarbazine may also be administered as a continuous infusion depending on the protocol. Local pain, burning sensation, and irritation at the injection site may be relieved by local application of hot packs. If extravasation occurs, apply cold packs. Protect exposed tissue from light following extravasation.

15.35 **Pharmacokinetic information**:
Distribution: V_d: 0.6 L/kg; exceeding total body water; suggesting binding to some tissue (probably liver)
Protein binding: ~5%
Metabolism: Extensively hepatic to the active metabolite
Half-life elimination: Biphasic: Initial: 20-40 minutes, Terminal: 5 hours; Patients with renal and hepatic dysfunction: Initial: 55 minutes, Terminal: 7.2 hours
Excretion: Urine (~40% as unchanged drug)

15.36 **Potential Drug Interactions**:
Metabolism/Transport Effects: Substrate of CYP1A2 (major)
Increased Effect/Toxicity: The levels/effects of Dacarbazine may be increased by CYP1A2 inhibitors, CYP2E1 inhibitors,
Decreased Effect: The levels/effects of Dacarbazine may be decreased by CYP1A2 inducers.
Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (due to GI irritation). Avoid dong quai, St. John's wort (may also cause photosensitization).

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information. US Boxed Warnings include: Bone marrow suppression, hepatotoxicity, carcinogenic and teratogenic.

Common known potential toxicities, > 10%:
Gastrointestinal: Nausea, vomiting, anorexia

Less common known potential toxicities, 1% - 10%:
Dermatologic: Alopecia, hyperpigmentation, photosensitivity
Hematologic: Anemia, leukopenia, thrombocytopenia
Respiratory: flu-like symptoms

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Cardiovascular: Facial flushing
Central nervous system: Headache, impaired vision, confusion, lethargy, convulsions, facial paresthesias
Dermatologic: Erythema, maculopapular exanthema, urticaria, administration site irritation
Gastrointestinal: Diarrhea
Hematologic: Pancytopenia, Agranulocytosis
Hepatic: Hepatic necrosis due to veno-occlusive disease of the liver, elevation of liver enzymes
Renal: Impaired renal function
Immunologic: Anaphylactic reactions

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 Nursing Guidelines:

15.391 Monitor CBC. Instruct patient on signs and symptoms of infection, unusual bruising or bleeding. Instruct patient to report these to the health care team.

15.392 Anemia is common with long term treatment. Instruct patient about fatigue and ways to conserve energy.

15.393 Monitor liver and renal function tests.

15.394 Instruct patient about alopecia

15.395 Anaphylaxis is possible. Monitor for signs and symptoms of hypersensitivity reaction, such as flushing, bronchospasms, rash, difficulty breathing. Stop infusion immediately and initiate proper emergency treatment.

15.396 Flulike syndrome may occur approximately 7 days after treatment and may last up to 3 weeks. Symptoms may include malaise, headache, and myalgia. Instruct patient on symptom management with use of acetaminophen, increased fluid intake, and proper rest.

15.397 DTIC is an irritant. Pain may be caused at injection site that is not usually relieved with slowing of the infusion. If pain is experienced and

IV is patent may use ice at the injection site. This may provide some relief. May need to consider central line placement. Discuss with treating MD.

15.398 Administer antiemetics as ordered. Evaluate their effectiveness. Instruct patient that severity of nausea and vomiting should decrease with subsequent doses.

15.399 Photosensitization may occur with higher doses. Instruct patient to wear a hat and sunscreen when outside.

15.4 Brentuximab vedotin (SGN-35, Adcetris®)

- Investigator brochure
  Available on the ACCRU website.

15.41 **Background**: Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The anticancer activity of brentuximab vedotin is due the binding of the ADC to CD30- expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell.

15.42 **Formulation**: Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-use vials. Each vial of brentuximab vedotin contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80.

Brentuximab vedotin is an ADC composed of a CD30 targeted chimeric monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the anti-tubulin agent MMAE. cAC10 has a typical structure of the human IgG1 subclass. Brentuximab vedotin is produced by the chemical conjugation of MMAE to cAC10. Each antibody molecule has, on average, two of its interchain disulfides reduced and the resulting cysteine residues alkylated with SGD-1006 Intermediate (enzyme-cleavable inker + MMAE), leading to a molar ratio of four drugs per antibody.

15.43 **Preparation and storage**:

Vials containing brentuximab vedotin must be stored under refrigeration at 2-8°C.

Reconstitution

1. Reconstitute lyophilized brentuximab vedotin by adding 10.5 mL Sterile Water for Injection, USP to the 50 mg vial, directing

the stream to the side of the vial. The concentration of reconstituted brentuximab vedotin is 5 mg/mL with a total volume of 11mL.

2. Gently swirl the vial until contents are completely dissolved. The vial must not be shaken. Slight "bubbling" of the solution upon reconstitution may be observed.

3. Allow the reconstituted vial to settle for a minute to allow bubbles to dissipate. The reconstituted product should be a colorless, clear to slightly opalescent solution with no visible particulates.

4. Reconstituted vials must be stored under refrigeration (2-8°C) and must be administered within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

Dose Calculation

Actual weight will be used except for patients weighing greater than 100 kg; the dose for patients with weight greater than 100 kg will be calculated based on 100 kg. Brentuximab vedotin dose should be rounded to the nearest whole number of milligrams.

Dose Preparation

1. Transfer the required volume of reconstituted product to a bag. The following bag types are compatible with brentuximab vedotin: polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, or polyethylene. Closed System Transfer Devices (CSTDs) can be used in the preparation of brentuximab vedotin.

2. Dilute reconstituted product in either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's solution, USP, or dextrose 5% in water (D5W), USP. The final concentration of brentuximab vedotin in infusion bag should be in the range of 0.4–1.8 mg/mL.

3. Gently invert the infusion bag. DO NOT SHAKE.

4. Prior to administration, inspect the prepared dosing solution (in infusion bag) for any particulate matter or discoloration.

5. Do not prepare a single dose of brentuximab vedotin using vials from different lots. Use vials from the same lot number for a given dose.

6. The prepared dosing solution must be stored in an infusion bag under refrigeration (2-8°C) and must be used within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

15.44 **Administration:** BRENTUXIMAB VEDOTIN MUST NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS. Brentuximab vedotin should be administered over approximately 30 minutes and cannot be mixed with other medications. In-line filters should not be used during the IV administration.

15.45 **Pharmacokinetic information**:
a) Blood levels – The maximum concentrations for serum PK of

brentuximab vedotin ADC following an IV dose of 1.8 mg/kg were typically observed at the end of infusion. The half-life is 4 to 6 days. Minimal to no accumulation was observed with multiple doses with the q3wk regimen. The PK of brentuximab vedotin when dosed by body-weight (mg/kg) is associated with body-size. The exposure (AUC) of ADC increases with increasing body size, although the magnitude of this increase is small in relation to the overall variability in ADC exposure. Additionally, this population PK meta-analysis indicated that gender, age and race do not have a meaningful effect on the PK of brentuximab vedotin and that no dosing adjustment based on these intrinsic factors is recommended in adult patients.
b) Distribution – Following an IV dose of brentuximab vedotin (1.2 to 2.7 mg/kg), the steady-state volume of distribution was approximately 6 – 10 L, indicating that brentuximab vedotin was primarily limited to the vascular space.
c) Metabolism and Excretion – The primary route of excretion of MMAE was via feces, whereas urinary excretion was moderate. Intact MMAE was the primary species excreted and MMAE was excreted in both feces (72%) and urine (27%), suggesting a low propensity for metabolism-based biotransformations. The terminal half-life ($t_{1/2}$) is approximately 4 to 6 days.

Brentuximab vedotin ADC PK in pediatric patients was similar to the PK of adults. The median cycle 1 AUC0-∞ in patients <12 years of age and adolescents (≥12 years of age) was slightly lower than that in adult patients (14% and 3% lower, respectively) patients with moderate interindividual variability (32.2%CV).

Hepatic/Renal Impairment: Patients with hepatic impairment (Child-Pugh class A to C) and patients with severe renal impairment (CrCl<30 mL/min) exhibited a trend toward moderate decreases in ADC exposure and increases in MMAE exposure. Therefore, the recommended dose in subjects with hepatic impairment or severe renal impairment will be specified in the protocol and consistent with approved product labeling. Clinical studies evaluating the effect of renal or hepatic impairment on the PK of brentuximab vedotin have not yet been done in patients with diseases other than cancer; therefore, it is unknown if these findings are applicable to treating non-cancer patients (e.g., patients with autoimmune liver disease or lupus nephritis) with brentuximab vedotin who have hepatic or renal impairment.

15.46 **Potential Drug Interactions**: In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5. Co-administration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Co-administration of brentuximab vedotin with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

Brentuximab vedotin is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity that occurred in some patients receiving this combination of treatments.

15.47 **Known potential toxicities**:
Very common known potential toxicities, ≥ 10%:
Cardiovascular: Peripheral edema
Central nervous system: Neuropathy, peripheral sensory neuropathy, fatigue, peripheral motor neuropathy, headache
Dermatologic: Pruritus, alopecia, maculopapular rash
Endocrine & metabolic: Weight loss
Gastrointestinal: Nausea, diarrhea, vomiting, decreased appetite, a bdominal pain, constipation
Hematologic & oncologic: Neutropenia, anemia, t hrombocytopenia
Immunologic: Antibody development
Neuromuscular & skeletal: Arthralgia, myalgia, asthenia, muscle spasm
Respiratory: Upper respiratory tract infection, cough, dyspnea
Miscellaneous: Fever

Common known potential toxicities, 1% - <10%:
Central nervous system: Chills
Dermatologic: Cellulitis
Hepatic: Hepatotoxicity
Respiratory: Pulmonary toxicity, pneumonia

Uncommon and rare known potential toxicities, <1%, post marketing and/or case reports:
Acute pancreatitis, acute respiratory distress syndrome, anaphylaxis, bacteremia, enterocolitis, febrile neutropenia, gastrointestinal erosion, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal ulcer, hyperglycemia, increased serum bilirubin, increased serum transaminases, interstitial pulmonary disease, intestinal obstruction, JC virus infection, neutropenic enterocolitis, opportunistic infection, pancreatitis, pneumonitis, progressive multifocal leukoencephalopathy, sepsis, septic shock, serious infection, severe hepatotoxicity, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Serious events of hyperglycemia, such as new-onset hyperglycemia, exacerbation of pre-existing diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported in ADCETRIS-treated patients. Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Any patient, with or without diabetes, who experiences an event of hyperglycemia should have their serum glucose closely monitored. Antidiabetic treatment should be administered, as appropriate.

Hyperglycemia has been reported with BV, notably in patients with high Body Mass Index or preexisting hyperglycemia. Any patient, with or without diabetes, who experiences an event of

hyperglycemia should have their serum glucose closely monitored. Antidiabetic treatment should be administered, as appropriate.

Drug procurement: Brentuximab vedotin will be provided free of charge from Seattle Genetics for investigational use to Almac, Inc. Each participating ACCRU treating location will order the drug from Almac, Inc. Email or fax the Investigational Drug Request Form (found on the ACCRU web site) to:

Seattle Genetics:

[redacted]

Outdated vials or drug remaining after the last patient has received their last dose may be destroyed on-site as per procedures in place at each institution.

15.48 Nursing Guidelines

Dosing should be based on actual weight for patients weighing ≤100kg. Patients weighing greater than 100 kg, will be dosed based on 100 kg. Round doses to the nearest whole milligram.

DO NOT administer by IV push or bolus. Brentuximab must be given over approximately 30 minutes. Do not mix with other medications. In-line filters should not be used during infusion.

Cytopenias are common. Monitor CBC w/differential closely. Instruct patient to report any signs or symptoms of infection, and/or bleeding.

Rash is common. Rarely patients can develop Steven's Johnson Syndrome or TENS. Instruct patient to report any rash.

Instruct patient that sensory neuropathy is common. Assess for symptoms of neuropathy prior to each infusion and discuss with treating MD any ≥grade 2 neuropathic symptoms.

Fatigue is common. Discuss with patient energy conserving lifestyle and interventions.

GI side effects can be seen, including diarrhea, nausea, vomiting and abdominal pain. Treat symptomatically and monitor for effectiveness.

Anaphylaxis and septic shock can be seen but are rare. Monitor for signs and symptoms of these during infusion. Administer emergency medications as ordered.

Monitor for respiratory symptoms (cough, URI). Treat symptomatically and monitor for effectiveness.

Assess patients medications. Patients who are taking medications that are CYP3A4 inhibitors (i.e ketoconazole) should be closely monitored for adverse reactions.

15.5 Nivolumab (Opdivo®, BMS-936558)

Investigator brochure
Available on the ACCRU website.

15.51 **Background**: Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted. This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

15.52 **Formulation**: Available for injection only 100 mg, 10mg/ml Nivolumab vials will be provided for this study. There are 5 vials per carton. [contains in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80]

15.53 **Preparation and storage**: When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to concentrations as low as 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. Mix diluted solution by gentle inversion. Do no shake. Discard partially used vials or empty vials. Store at room temperature for no more than 8 hours (includes time of administration) or under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation. Protect from light and freezing.

15.54 **Administration:** Administer over 30 minutes through a line with a sterile, nonpyrogenic, low protein binding 0.2 to 1.2 micrometer in-line filter. It cannot be administered as an IV push or bolus injection. Do not administer other medications through the same IV line. Flush IV line at the end of the infusion.

15.55 **Pharmacokinetic information**:
Distribution: Vd: 6.6L
Half-life elimination: ~25days
Renal Impairment: No clinically important differences in the clearance of nivolumab were found between subjects with mild or moderate renal impairment and subjects with normal renal function. Data from subjects with severe renal impairment are too limited to draw conclusions on this population.
Hepatic Impairment: No clinically important differences in the clearance of nivolumab were found between subjects with mild hepatic impairment and normal hepatic function. Nivolumab

has not been studied in subjects with moderate (total bilirubin > 1.5 to 3 times ULN and any AST) or severe hepatic impairment (total bilirubin > 3 times ULN and any AST).

15.56 **Potential Drug Interactions**: Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

15.57 **Known potential toxicities**: Consult the package insert for the most current and complete information.

Common known potential toxicities, 1% - < 10%:
Respiratory: Pneumonitis

Uncommon known potential toxicities, 0.1% - < 1%:
Ear: Vertigo
Endocrine and metabolic: Adrenal insufficiency, hyperglycemia, hypothyroidism, hypophysitis,
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, colitis, pancreatitis
General: Pyrexia, fatigue, asthenia
Hepatic: Autoimmune hepatitis
Immune system: Infusion related reaction
Infections: Upper respiratory tract infection, bronchitis
Investigations: Increased AST/ALT, increased bilirubin
Metabolism and Nutrition disorders: Decreased appetite, hyponatremia, dehydration
Musculoskeletal: back pain
Nervous system: Peripheral neuropathy, headache, peripheral sensory neuropathy, peripheral motor neuropathy, dizziness, myasthenia gravis, Guillain-Barre syndrome, demyelination, polyneuropathy, encephalitis, myasthenic syndrome Renal and urinary: Acute kidney injury, tubulointerstitial nephritis
Respiratory: Interstitial lung disease, dyspnea, respiratory failure
Skin and subcutaneous tissue disorders: Rash

Rare known potential toxicities, < 0.1% (Limited to life-threatening):
Cardiac: Arrhythmia, ventricular arrhythmia, atrial fibrillation, tachycardia
Endocrine: Diabetic ketoacidosis, autoimmune hypothyroidism, diabetes mellitus, hypopituitarism, autoimmune thyroiditis, hyperthyroidism, thyroiditis
Eye disorders: Iridocyclitis, uveitis, diplopia

Gastrointestinal: Autoimmune colitis, gastritis, stomatitis, enterocolitis, autoimmune pancreatitis, constipation, acute pancreatitis, intestinal perforation
Hepatic: Acute hepatitis, hepatitis, drug-induced liver injury, hyperbilirubinemia.
Immune system: Anaphylactic reaction, sarcoidosis, hypersensitivity
Musculoskeletal: Myositis, myalgia, myocarditis, arthritis, polymyalgia rheumatic, polymyositis, rhabdomyolysis
Nervous system: Polyneuropathy, encephalitis, Myasthenia gravis, Guillain-Barre syndrome, demyelinating polyneuropathy, demyelination, myasthenic syndrome
Renal: Nephritis, autoimmune nephritis, renal failure
Respiratory: Organizing pneumonia, acute respiratory distress syndrome, cough, lung infiltration
Skin and subcutaneous tissue disorders: Erythema multiforme, maculo-papular rash, pemphigoid, pruritus, psoriasis, drug eruption, drug eruption, Stevens Johnson syndrome, generalized pruritis, generalized rash, macular rash, pruritic rash, dermatitis acneiform, pustular rash, toxic epidermal necrolysis
Other: Solid organ and tissue transplant rejection, graft versus host disease, increased risk of transplant-related complications

15.58 **Drug procurement:** Investigational nivolumab is provided free of charge by Bristol-Myers Squibb Research and Development. Each participating ACCRU treating location will order the drug from Bristol-Myers Squibb Research and Development using the drug order form (found on the ACCRU web site).

BMS will not be responsible for any destruction or accept any return drugs. It is solely the sponsor's responsibility.

15.59 Nursing Guidelines:

Nivolumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids. Additionally combination therapy (with ipilimumab) tends to have a higher rate of immune mediated side effects.

Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

Rash/pruirits/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.

Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, new onset diabetes and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well" . Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

Pancreatitis is possible with nivolumab. Instruct patients to report abdominal pain, nausea and vomiting to the study team.

Patients who are started on steroid therapy for any side effects of nivolumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

Monitor renal function as patients may experience acute interstitial nephritis. Report any increase of levels to the study team.

Patients who have previously undergone a solid organ or tissue transplant and subsequently undergo therapy with nivolumab are at increased risk of organ/tissue rejection. Instruct patients that they stay in touch with their transplant team during treatment.

Patients who have undergone allogenic BMT are at higher risk of GVHD and death when receiving nivolumab. Monitor patients closely for GVHD symptoms and instruct patients to report these symptoms to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Overview

This single arm Phase II trial will evaluate AVD + BV induction therapy with or without BV + NVB followed by NVB consolidation in patients with previously untreated stage I or II non-bulky HL. Patients will receive 3 cycles of AVD +BV. Subjects who are PET-negative after induction with AVD + BV will proceed to consolidation therapy with

NVB. Subjects who are PET positive after induction with AVD + BV will receive 4 cycles of BV +NVB followed by NVB consolidation.

16.11 Primary Endpoint: The primary endpoint of the trial is the progression-free survival rate where progression is defined in Section 11.0. A success will be defined as a patient being alive and progression-free at 3 years from registration, where progression is by CT-based or PET-CT based criteria (PD or PMD). The primary analysis will be completed at 3 years after the last patient is registered on trial, or after 5 events, whichever comes first (See Section 16.12).

16.12 Decision Rule: A one-sided, one-sample log-rank test calculated from a sample of 78 subjects achieves 90.2% power at a 0.1 significance level to detect a 3-year progression-free survival proportion of 95% in this population when the survival proportion is 88% in historic control. The probability that a subject will experience an event during the study is 6.6%. The expected number of events during the study is 5.

16.13 Sample Size, Accrual Rate and Study Duration: The anticipated accrual rate is approximately 40 evaluable patients per year. Accounting for a 5% increase in sample size to account for ineligibles and cancels, it will take approximately 24 months to enroll 82 (78 with an extra 4 (5%) patients to account for cancels and ineligibles) patients. The maximum total study duration is expected to be approximately 5 years, or until the last patient accrued has been observed for at least 3 years.

16.2 Statistical Design Considerations:

16.21 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section16.313.

16.22 Other: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint in this trial is the progression-free survival rate at 3 years. A success will be defined as a patient being alive and progression-free at 3 years from registration, where progression is by CT-based or PET-CT based criteria (PD or PMD). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for progression-free survival, with the exception of patients who are determined to be a major violation.

16.312 Analysis: The primary analysis will be completed at 3 years after the last patient is registered on trial, or after 5 events, whichever comes first (See

Section 16.12). The distribution of progression-free survival time will be estimated using the method of Kaplan-Meier and the efficacy will be determined by the log rank statistic. Overall progression-free survival at 3 years will be reported.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in decision-making process; however, they will be included in final point estimates and confidence intervals.

16.32 Secondary Outcome Analyses

16.321 Overall survival time is defined as the time from registration to death due to any cause. The distribution of overall survival time will be estimated using the method of Kaplan-Meier. The rate of overall survival at 3 years and 5 years will be estimated in each group.

16.322 The proportion of patients who are PET negative after 3 cycles of treatment will be estimated by the number of patients who are PET negative divided by the total number of evaluable patients. Similarly, the proportion of patients who are PET positive will be estimated. PET will be considered negative if the patient is given a Deauville score of ≤ 3.

16.323 Progression-free survival will be evaluated by PET status after 3 cycles of treatment (PET positive vs. PET negative) in patients who complete the cycle 3 response assessment. PFS will be defined as the time from registration to relapse or death due to any cause. Differences between the groups will be assessed by log-rank statistics. The rates of progression-free survival at 3 and 5 years will be estimated in each group.

16.324 The overall response rate (ORR) will be estimated by the number of patients with an CR/CMR/PR/ PMR or better divided by the total number of evaluable patients. The ORR may be analyzed when all patients are off treatment. Exact binomial 95% confidence intervals for the true overall response rate will be calculated.

16.325 Time to progression is defined as the time from registration to the earliest date of documentation of disease progression (PD or PMD). Patients who are progression-free will be censored on the date of their last disease assessment. The distribution of time to progression will be estimated using the method of Kaplan-Meier.

16.326 The proportion of patients who convert from partial response (PMR) at the end of AVD plus BV induction therapy to complete response (CMR) after NVB will be estimated by the number of patients who convert divided by the total number of evaluable patients who receive at least one dose of NVB induction therapy. Exact binomial 95% confidence intervals for the true conversion rate will be calculated.

16.327 Duration of response is defined for all evaluable patients who have achieved a PR or CR as the date at which the patient's objective status is first noted to be a response to the earliest date progression is documented. The distribution of duration of response will be estimated using the method of Kaplan-Meier.

16.328 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.4 Data & Safety Monitoring:

16.41 The principal investigator(s) and the study statistician will review the study at least monthly to identify accrual, adverse event, and any endpoint problems that might be developing. Further, the Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) will review accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Futility Stopping Rule: The PET-positive arm (BV + NVB) will close if > 2 out of the first 5 treated patients failed to maintain remission at 1 year.

16.43 Adverse Event Temporary Hold Rules: The hold rules specified below are based on the knowledge available at study development. We note that the Adverse Event Temporary Hold Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 3 or more patients in the first 15 treated patients experience a Grade 4 or higher non-hematologic adverse event (including but not limited to peripheral neuropathy, hepatotoxicity, pancreatitis, colitis, pneumonitis and infection) at least possibly related to treatment with the following exceptions: nausea, vomiting, or diarrhea will not count against the AE stopping rule.
- if after the first 15 patients have been treated, 20% of all patients experience a Grade 4 or higher non-hematologic adverse event (including but not limited to peripheral neuropathy, hepatotoxicity, pancreatitis, colitis, pneumonitis and infection) at least possibly related to treatment with the following exceptions: nausea, vomiting, or diarrhea will not count against the AE stopping rule.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on ClinicalTrials.gov:
At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 6 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 3 years.

16.6 Inclusion of Women and Minorities

16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

NOTE: Patients must have consented to submission of the optional tissue(s) listed in the following table.

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for biospecimen submission**
6 unstained slides with corresponding H&E	Optional	≤60 days after registration	Banking (Section 17.4)	Section 17.3

17.2 Original Biopsy Slides

17.21 Submit 1 H&E slide and 6 unstained slides from the original biopsy. Slides should be mounted on charged glass. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** The remaining unstained slides will be processed as described in 17.4. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

17.22 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- 6 unstained slides with corresponding H&E.
- Specimen Submission: Tissue (Baseline) form
- Surgical Pathology Report
- Operative Report *(optional)*

Note: Please include the ACCRU patient ID number on all materials listed above. Please do not use sticky labels.

17.23 The slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.

17.24 Tissue specimens must be shipped ≤60 days after registration.

17.25 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue (Baseline) form into the remote data entry system on the same day the specimen is submitted (see CRF Packet).

17.26 Ship all slide tissue specimens and accompanying materials to the ACCRU Research Base:



17.27 When an appropriate request is submitted, the ACCRU Operations Office will forward the slides to the [redacted] for processing as outlined in Section 17.4.

17.3 Frozen Tumor tissue: (None)

17.4 Study Methodology and Storage Information

17.41 Submitted tissue samples will be analyzed as follows:

17.42 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office (Attn.: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.15). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.43 Banking of tumor tissue, according to the patient consent permission (see Section 6.4), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU studies).

17.44 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.

17.45 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.46 Return of Genetic Testing Research Results: No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient reconsent is required.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
MUGA/ECHO Test Results	
Laboratory Tests and Results: Baseline	
Adverse Events: Baseline	
Lymphoma Measurements: Baseline	
Supporting Documentation: Baseline	
Specimen Submission: Tissue (Baseline) [2,3]	
Specimen Submission: Blood (Baseline)[2]	
Patient Status: Baseline	
OP and Path Reports (see Section 17.0)[1]	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Upload Op and Path Reports via the Supporting Documentation: Baseline form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
2. If applicable.
3. ≤60 days after registration.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation/Clinical Follow-up
Treatment (Intervention)	X	X	
Treatment (Intervention): Dose Modifications, Omissions and Delays[2]	X[5]		
MUGA/ECHO Test Results[2]	X	X	X
Adverse Events: Solicited	X	X	X
Adverse Events: Other[2]	X	X	X
Lymphoma Measurements[2]	X[1]	X[1]	X[1]
Day 1 Laboratory Tests and Results	X		X
Day 15 Laboratory Tests and Results	X		
Supporting Documentation	X[1]	X[1]	X[1]

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation/Clinical Follow-up
Patient Status: Treatment (Intervention)	X	X	
Off Treatment		X	
Patient Status: Clinical Follow-Up/Observation			X
Laboratory Tests and Results			X
Adverse Event: Late[2]			X
Notice of New Primary[2]	X	X	X
Consent Withdrawal (choose appropriate form)[2] • Consent Withdrawal: Specimen Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-up	X	X	X
Lost to Follow-Up[2]	X	X	X
Deviation Form[2]	X	X	X

1. Upload a copy of documentation of CR/PR or PD in RAVE on the Supporting Documentation Form.
2. If applicable.

Follow-up Material(s)

CRF	Event Monitoring Phase/Survival Follow-up[1]				
	q. 6 months until PD[2]	At PD	After PD q. 6 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X	X	X	X	
Adverse Events: Late[3]					X
Supporting Documentation[2]		X			
Lost to Follow-Up[3]					X
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only[3] • Consent Withdrawal: Clinical Follow-Up Only[3] • Consent Withdrawal: All Follow-up[3]					X

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.

3. If applicable.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: Optional tumor biopsy slides and optional blood sample for banking for future use.

19.3 Other budget concerns: Nivolumab will be provided free of charge by Bristol-Myers Squibb. Brentuximab Vedotin will be provided free of charge by Seattle Genetics.

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ACCRU Informed Consent Template for Cancer Treatment Trials

(English Language)

***NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for ACCRU model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is [redacted]
- A blank line,_____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at [redacted] to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

ACCRU-LY-1601, A Phase II Trial of PET-Directed Therapy using AVD (doxorubicin, vinblastine, and dacarbazine) plus Brentuximab Vedotin Induction Chemotherapy, with or without Brentuximab Vedotin plus Nivolumab, Followed by Nivolumab Consolidation for Patients with Previously Untreated Non-bulky Limited Stage Hodgkin Lymphoma

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have non-bulky limited stage Hodgkin Lymphoma that has not been previously treated.

Why is this research study being done?

The purpose of this research study is to:

- Find out if doxorubicin, vinblastine and dacarbazine (AVD) plus brentuximab vedotin induction chemotherapy with or without brentuximab vedotin plus nivolumab followed by nivolumab consolidation therapy alone is helpful.
- Find out what effects, good and/or bad, this treatment has on you and your cancer
- Find out if novel agents used in this study (brentuximab vedotin and nivolumab) may safely and effectively replace the standard radiation therapy and/or reduce the amount of traditional chemotherapy drugs you receive

Brentuximab is an antibody attached to a chemotherapeutic drug targeted against Hodgkin lymphoma cells. Nivolimab is an antibody that enhances the immune system to better attack Hodgkin lymphoma cells. It has shown that both drugs induce high response rates in relapsed or refractory Hodgkin lymphoma, and they will be used for previously untreated Hodgkin lymphoma in this study.

The standard treatment for this type of cancer is 90% effective; however, the treatment being used in this trial does not include part of that standard treatment due to side-effects associated with bleomycin and radiation.

How many people will take part in the research study?

About 82 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and exam
- Pregnancy test, if necessary
- PET/CT scan of the chest, abdomen and pelvis
- Routine blood tests
- ESR to measure the level of inflammation
- Hepatitis B and Hepatitis C tests
- MUGA/echocardiogram scan
- Optional tumor tissue sample: The biopsy tumor tissue sample will be from your original biopsy. This tumor tissue is for future use only.
- Optional blood sample for future research only.

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical exam
- Pregnancy test, if necessary
- PET/CT of the chest, abdomen and pelvis
- Routine blood tests
- Thyroid function test
- PT and INR (blood clotting factors), if necessary
- MUGA/echocardiogram scan, if needed

If it is not known if you have hepatitis B or hepatitis C, you will need to have a blood test done. The researcher will tell you how to find medical help and counseling as needed, and you may not be able to take part in the study. Your health insurer or you will have to pay for the cost of the repeat test, any follow-up medical care, or counseling.

If the Hepatitis B or Hepatitis C test results are positive, it may be required that this result be reported to the State Department of Health. The tests results will also be put in your medical record.

You will receive AVD through a vein in your arm on Day 1 and Day 15 of each 28 day cycle. You will also receive brentuximab vedotin through a vein in your arm on Day 1 and 15 of each 28 day cycle within 1 hour of receiving AVD. This 28 day period of time is called a cycle. The cycle will be repeated 3 times. Depending on your status after having a PET scan, you will either:

1) receive brentuximab vedotin followed by nivolumab through a vein in your arm on day 1 every 14 days. This 14 day period of time is called a cycle. This cycle will be repeated 4 times. Then you will receive nivolumab alone through a vein in your arm on day 1 every 14 days. This 14 day period of time is called a cycle. This cycle will be repeated 8 times.

2) Receive nivolumab alone on day 1 every 14 days. This 14 day period of time is called a cycle. This cycle will be repeated 8 times. The chart below shows what will happen to you during Cycle 1 and

future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Study Chart

AVD + Brentuximab Vedotin
Cycle 1

Day	What you do
Up to 28 days prior to starting the study	• Medical history and exam • Pregnancy test, if needed • PET/CT of the chest, abdomen and pelvis • Routine blood tests • ESR • Hepatitis B and Hepatitis C tests • MUGA/ECHO • Optional tumor tissue sample: The biopsy tumor tissue sample will be from your original biopsy. • Optional blood sample
Day 1	• Exam (Day 1 only) • Pregnancy test if needed (Day 1 only) • Routine blood tests • Receive AVD and BV through a vein in your arm • Check for infusion reactions
Day 15	• Routine blood tests • Receive AVD and BV through a vein in your arm • Check for infusion reactions

AVD + Brentuximab Vedotin
Future Cycles (Cycles 2 and 3)

Day	What you do
Day 1	• Exam (Day 1 only) • Pregnancy test if needed (Day 1 only) • Routine blood tests • Receive AVD and BV through a vein in your arm • Check for infusion reactions
Day 15	• Routine blood tests • Receive AVD and BV through a vein in your arm • Check for infusion reactions
At the end of Cycle 3	• Exam • PET/CT of the chest, abdomen and pelvis • Routine blood tests

Brentuximab Vedotin + Nivolumab
All cycles

Day	What you do
Day 1	• Exam (Day 1,Cycles 1 and 3) • Pregnancy test if needed • Routine blood tests • Thyroid function tests • Receive BV and Nivolumab through a vein in your arm • Check for infusion reactions
At the end of Cycle 4	• PET/CT of the chest, abdomen and pelvis

Nivolumab
All cycles

Day	What you do
Day 1	• Exam (Day 1, Cycles 1, 3, 5, and 7 only) • Pregnancy test if needed • Routine blood tests • Thyroid function tests • Receive Nivolumab through a vein in your arm • Check for infusion reactions
4 weeks after Nivolumab is completed	• Exam • Pregnancy test if needed • Routine blood tests • Thyroid function tests
8 weeks after Nivolumab is completed	• Exam • Pregnancy test if needed • PET/CT of the chest, abdomen and pelvis • Routine blood tests • Thyroid function tests

How long will I be in the research study?

You will be asked to take the study drugs for approximately 9 months unless you stop study treatment early. After you are finished taking the study treatment, the study doctor will ask you to visit the office for follow-up exams 4 weeks after you stop study treatment and again 8 weeks after you stop study treatment. After this, there will be follow-up visits every 3 months or every 6 months depending on the status of your disease.

We would like to keep track of your medical condition for a total of 5 years. We would like to do this by checking on you and your medical condition every 6 months to see how you are doing. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the Doxorubicin include those which are:

Doxorubicin may cause all, some or none of the side effects listed. There is always the risk of very uncommon or previously unknown side effects that may happen.

More Likely:
- Feeling sick to the stomach
- Throwing up
- Hair loss
- Lowering of the white blood cell count
- Lowering of the platelet count which could lead to anemia
- Weakening of the heart muscle

Less Likely:
- Irritation of the mouth
- Discoloration of nail bed and creases in the skin
- Loss of appetite
- Diarrhea

Rarely:
- Alteration in the rhythm of the heartbeat
- Discoloration of the urine (red)
- Fever
- Allergic reactions
- Tissue injury it if infiltrates into the skin or other tissues upon administration
- Sudden death

In rare cases, acute leukemia may develop after treatment with doxorubicin, especially when it is given along with other cancer drugs.

Risks and side effects related to the Vinblastine include those which are:

Likely risks of Vinplastine:

- Lowered white blood cell count that may lead to infection
- Lowered platelet count that may lead to an increase in bruising or bleeding
- Lowered red blood cell count (anemia) that may cause tiredness or shortness of breath
- Hair loss
- Nausea
- Vomiting
- Fever
- Increased sensitivity to sunlight

Less likely risks of Vinblastine:

- Diarrhea
- Abdominal cramps
- Loss of appetite
- Constipation
- Shortness of breath
- Skin rashes
- Mouth and throat sores
- Metallic taste
- Numbness or tingling in the fingers or toes
- Abnormal liver function tests
- Raynaud's phenomenon

Rare, but serious risks of Vinblastine:

- Skin or tissue damage if leaks from the intravenous (IV) line
- Very high fever with sweating and dehydration

Risks and side effects related to the Dacarbazine include those which are:

Common side effects of dacarbazine (seen in more than 1 in 100 patients):

- A decrease in the numbers of white blood cells (leukopenia and neutropenia) may increase the risk of infections, including pneumonia and urinary tract infections. Infections in patients with low numbers of white blood cells in some circumstances can be life-threatening. You should immediately inform your doctor if you are feeling feverish, as this might be a sign that your body is fighting an infection.
- Decrease in the number of red blood cells (anemia) may result in a feeling of tiredness.
- A decrease in the number of platelets (thrombocytopenia) and this may result in an increased risk of bleeding and bruising.
- Loss of appetite
- Nausea and vomiting

Uncommon side effects of dacarbazine (seen in less than 1 in 100 patients):

- Confusion

- Involuntary changes in body movement or function, sensation, awareness or behavior (seizures)
- Numbness of the skin, or pins and needles sensation in the face
- Headache
- Blurred vision
- Facial flushing
- Hair loss (alopecia)
- Transient rash
- Flu-like symptoms (fever, chills, muscle aches), which may start approximately one week after treatment and may last up to three weeks
- Tiredness and weakness (lethargy)
- Increased sensitivity of the skin to sunlight (photosensitivity)

Rare side effects of dacarbazine (seen in less than 1 in 1,000 patients):

- Diarrhea
- Bruising
- Allergic reaction. If you experience any signs of allergy such as rash, shortness of breath, wheezing or trouble breathing during or after the dacarbazine infusion, you must immediately tell the study doctor, or doctor or nurse administering the infusion. A severe allergic reaction can be life threatening.

Very rare side effects of dacarbazine (seen in less than 1 in 10,000 patients):

- Redness of the skin, rash
- Itching
- Increase in liver enzymes measured in the blood tests. This may indicate that the liver function is affected. A very rare side effect may cause damage to the liver, which is caused by a blockage in the veins in the liver. This may require hospitalization and treatment. If you have increased liver enzymes measured in the routine blood tests, you may have more frequent blood tests to monitor this.
- Impaired kidney function

Risks and side effects related to the Brentuximab Vedotin include those which are:

Likely risks of Brentuximab Vedotin: *(events occurring greater than 20% of the time)*

- Feeling Tired (Fatigue)
- Fever (Pyrexia)
- Feeling sick to your stomach (Nausea)
- Abdominal pain
- Loss of weight
- Loose stools (Diarrhea)
- A low number of white blood cells, which are the infection fighting cells, which could put you at risk for infection (Neutropenia, Leukopenia)
- Abnormal nerve function in arms or legs
- Throwing up (Vomiting)
- Upper respiratory infection
- Peripheral Neuropathy: Some patients who received SGN-35 developed abnormal nerve function in their arms or legs (peripheral neuropathy). Peripheral neuropathy occurs when damage is done to nerves that carry movement information for muscle contraction and information such as touch, vibration, pain and temperature. Symptoms reported by these

patients included burning sensation, pain, weakness, numbness and tingling (feeling of pins and needles) of hands and/or feet and severe abnormal nerve function that caused difficulty walking.

- Infection Risk: Brentuximab vedotin may cause you to be less resistant to infections, including severe bacterial infections. It is very important that you notify your study physician if you develop a fever, sore throat, and/or painful sores (ulcers) around the mouth and/or anus. If you are unable to reach your study physician or other research team members, you should go to your nearest emergency room for treatment. If you have to go to the emergency room, be sure to mention your study physician's name and that you are participating in an anticancer treatment research study.
- Lung toxicity when brentuximab vedotin is given in combination with bleomycin (a type of chemotherapy) or on its own

Less likely risks of Brentuximab Vedotin: *(events occurring less than or equal to 20% of the time)*

- Cough
- Muscle pain
- Shortness of breath
- Chills
- Sensation of lightheadedness or vertigo (spinning sensation) (Dizziness)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding) (Thrombocytopenia)
- Back pain
- Difficulty passing stool (Constipation)
- Rash
- Hair loss (Alopecia)
- Joint pain (Arthralgia)
- Itching sensation (Pruritis)
- Inflammation of the pancreas
- Low blood sugar
- Abnormal liver function

Rare but serious risks of Brentuximab Vedotin *(events occurring less than 3% of the time)*

- Serious allergic reaction (wheezing/difficulty breathing, hives, itching, swelling) during or soon after SGN-35 treatment, which requires immediate medical attention and treatment discontinuation
- Severe painful rash that spreads to most of your skin (Stevens-Johnson syndrome/toxic epidermal necrolysis); Stevens-Johnson syndrome is a rare condition that could become life threatening and requires immediate medical attention. Seek emergency medical care if you experience any of the following signs or symptoms: unexplained widespread skin pain, blisters on your skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of your skin.
- Tumor lysis syndrome (TLS) is a potentially life-threatening complication. TLS usually occurs within a few days of the start of cancer treatment and may result in metabolic complications caused by the break-down of dying cancer cells. Potential complications may include nausea, vomiting, edema (swelling), shortness of breath, heart rhythm disturbances, and acute renal failure.
- Progressive multifocal leukoencephalopathy (PML) is a rare, serious brain infection caused by a certain virus. People with a weakened immune system can get PML. PML can result in death or severe disability. Tell your study doctor immediately if you have any of the following symptoms or if anyone close to you notices these symptoms: confusion or problems thinking, loss of balance or problems walking, difficulty speaking, decreased strength or weakness on one side of your body, blurred vision or loss of vision.
- Severe lung toxicity that may lead to hospitalization

Risks and side effects related to the Nivolumab (BMS-936558) include those which are:
Nivolumab may cause the side effects listed below. This information is based on data from subjects in other clinical trials with Nivolumab. In addition, there may be side effects that are not yet known that may occur. You should tell your doctor or nurse about any side affects you experience.

The most common side effects of Nivolumab are:

- Feeling tired (Fatigue)
- Weakness
- Skin problems: including rash, itchiness, redness, or dry skin
- Loose stools (Diarrhea)
- Loss of appetite
- Nausea (Feeling sick to your stomach)
- Vomiting (Throwing up)
- Joint pain or inflammation
- Fever and chills

Additional side effects may include:

- Liver abnormalities or inflammation
- Protein in the urine
- Decreased white blood cells which may affect your ability to fight infections.
- Shortness of breath
- Headache
- Cough
- Lung inflammation (see below for details)
- Bowel inflammation (diarrhea, blood or mucus in the stool, abdominal pain)
- Dry Mouth
- Allergic reaction during infusion of study drug
- Decreased phosphate in the blood
- Thyroid function abnormalities
- Muscle pain
- Arm or leg pain
- Postnasal drip
- Pituitary gland abnormalities
- Abdominal pain
- Heartburn
- Sensation of lightheadedness or vertigo (spinning sensation) (Dizziness)
- Hormone abnormalities
- Constipation
- Peripheral neuropathy

Less common side effects of Nivolumab include: pancreas inflammation, bone marrow production abnormalities, back pain, swelling of the arms or legs, bowel inflammation, fluid collection in the abdomen, injection site reaction, skin infection, constipation, trouble sleeping, night sweats, excessive sweating, hair loss, altered taste, irritability, mucosal inflammation, inflammation of the kidney, kidney failure, eye inflammation, muscle spasm, brain inflammation (meningitis or encephalitis), uncontrolled growth of activated lymphocytes and macrophages (hemophagocytic lymphohistiocytosis), loss of nerve

function (Guillian-Barre syndrome), nerve-associated muscle weakness (myasthenia gravis), muscle inflammation and breakdown (polymyositis and rhabdomyolisis), and a syndrome associated with muscle pain and stiffness in the neck, shoulders, and hips. Nivolumab should not be used in subjects with active autoimmune disease.

Although not common, death is also a possible risk.

The following reactions can be life threatening or have fatal adverse drug reactions: Pneumonitis, respiratory failure, diabetic ketoacidosis, myocarditis, toxic epidermal necrolysis, colitis, Rhabdomyolysis, encephalitis.

Lung Inflammation: It is possible that Nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in subjects treated with Nivolumab. While many subjects with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, or fatigue. These symptoms may require treatment with steroids, which may increase your risk of infections.

Solid organ and tissue transplant rejection has been reported in patients who have previously undergone transplantation and who were subsequently treated with programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitors, including BMS-936558. Treatment with BMS-936558 may increase the risk of rejection in solid organ and tissue transplant recipients.

Rapid-onset and severe graft vs host disease (GVHD), some with fatal outcome, has been reported in patients who had undergone prior allogeneic hematopoietic stem cell transplant (HSCT) and subsequently received PD-1/PD-L1 inhibitors. Complications of allogeneic HSCT after treatment with PD-1/PD-L1 inhibitors including BMS-936558, administered before allogeneic HSCT, may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of severe inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

As with any medication, allergic reactions are a possibility

The risks of drawing blood include pain, bruising or rarely infection at the needle site.

Reproductive risks: Sexually active female of reproductive capability i.e., WOCBP, has agreed to use a medically accepted form of contraception from time of registration to completion of study therapy through 24 weeks (6 months) after last dose of NVB or BV. Note: Females of non-child-bearing potential are those who are postmenopausal for > 1 year or who have had a bilateral tubal ligation or hysterectomy.

Male subjects agree to use an adequate method of contraception starting with the first dose of study therapy through 31 weeks after the last dose of study therapy. You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control

while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope the treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about this combination of drugs as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.
Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Academic and Community Cancer Research United (ACCRU)
- Levine Cancer Institute/Carolinas HealthCare System
- Bristol-Meyers Squibb
- Seattle Genetics
- Local IRB
- Government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agents, Brentuximab Vedotin and Nivolumab will be provided free of charge while you are taking part in this study. However, if you should need to take the study agent much longer than usual, the stock of free study agent that has been supplied could run out. If the free supply runs out, your study doctor will discuss with you how to get more drug from the manufacturer. You may be asked to pay for it.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [redacted] You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your

rights) at_____*(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

About Using Biological Samples for Research

We would like to collect and keep some of your tissue from your original biopsy for future research. No additional biopsies will be done to get this tissue. This collection of tissue for future research is optional. You can take part in the treatment portion of this study without taking part in the optional tissue collection. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the online booklet called "Providing Your Tissue for Research: What You Need To Know," to learn more about tissue research: [redacted]

We would also like to collect and keep some of your blood (about 2 teaspoons) for future research. This collection is optional. You can take part in the treatment portion of this study without taking part in the optional blood collection. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

Your tissue and blood may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us collect and keep tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and blood can be collected and kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and blood. Then any tissue and blood that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While ACCRU may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and blood is used for genetic research (about diseases that are passed on in families). Even if your tissue and blood is used for this kind of research, the results will not be put in your health records.

Your tissue and blood will be used only for research and will not be sold. The research done with your tissue and blood may help to develop new products in the future.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care or your participation in this study.

1. My tissue sample(s) may be collected and used for future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My tissue sample(s) may be collected and used for future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

3. My blood sample(s) may be collected and used for future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

4. My blood sample(s) may be collected and used for future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board_____.
ACCRU has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of ACCRU. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call ACCRU and ask for samples for their studies. ACCRU looks at the way that these studies will be done, and decides if any of the samples can be used. ACCRU sends the samples and some information about you to the researcher. ACCRU will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside ACCRU use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at ACCRU. Then ACCRU will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

I permit ACCRU to give my tissue sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

I permit ACCRU to give my blood sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

[redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all_____*[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Appendix II Revised response criteria for lymphoma

(Cheson, et al. J Clin Oncol. 2014;32(27):3059-68)

Response criteria	PET-CT-based response	CT-based response
Complete remission (CR)		
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5-PS**	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiological 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, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake	No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial remission (PR)		
Lymph nodes and extralymphatic sites	Score 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measureable nodes and extranodal sites
	At interim these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment these findings indicate residual disease	When no longer visible, 0 mm × 0 mm
		For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy, or an interval scan	Not applicable

No response or stable disease (SD)		
Target nodes/nodal masses, extranodal lesions	No response: score 4 or 5 with no significant change in FDG uptake from baseline, at interim or end of treatment	Stable disease: <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease (PD)		
Individual target nodes/nodal masses, extranodal lesions	Score 4, 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	PPD progression: An individual node must be abnormal with: • LDi >1.5 cm • Increase by ≥50% from PPD nadir An increase in LDi or SDi from nadir • 0.5 cm for lesions ≤2 cm • 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (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
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology. e.g. infection, inflammation. If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis if less than 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG avid foci	New or recurrent involvement

Measured dominant lesions: up to six of the largest dominant nodes, nodal masses and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body, and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs, e.g., liver, spleen, kidneys, lungs, etc., gastrointestinal involvement, cutaneous lesions of those noted on palpation. Non-measured lesions: any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant, measurable or which do not meet the requirements for measurability, but are still considered abnormal. As well as truly assessable disease which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites, e.g., gastrointestinal tract, liver, and bone marrow, FDG uptake may be greater than mediastinum with CMR, but should be no higher than surrounding normal physiologic uptake, e.g., with marrow activation due to chemotherapy or myeloid growth factors. SPD, sum of the product of the perpendicular diameters for multiple lesions; LDi, longest transverse diameter of a lesion; SDi, shortest axis perpendicular to the LDi; PPD, cross product of the LDi and perpendicular diameter. *, score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as inadequate response (to avoid under-treatment); **, PET five point scale (5-PS): 1, no uptake above background; 2, uptake ≤ mediastinum**; 3, uptake >mediastinum, but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma. Reprinted from reference (1).

Appendix III - Renal Impairment Guidelines

Group	Description	Estimated Creatinine Clearance (mL/min)
1	Normal renal function	80 mL/min
2	Mild renal impairment	50-80 mL/min
3	Moderate renal impairment	30-50 mL/min
4	Severe renal impairment	<30 mL/min
5	End-stage renal disease	Requiring dialysis

Cockcroft-Gault

$$\text{Estimated creatinine clearance (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

For females, use 85% of calculated creatinine clearance value.

Appendix IV - Child-Pugh Hepatic Impairment Score

Factor	1 point	2 points	3 points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	Class B	Class C
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Available at: [redacted] (Last updated August 4, 2015).

Appendix V – Unfavorable risk factors for Stage I/II HL

National Comprehensive Cancer Network (NCCN) guidelines define unfavorable factors for Stage I/II Hodgkin's Lymphoma (HL) as follows:

Bulky mediastinal disease (Mediastinal mass ratio [MMR, maximum width of mass/maximum intrathoracic diameter] greater than 0.33) or bulky disease greater than 10 cm

B symptoms (fever, night sweats, weight loss)

Erythrocyte sedimentation rate (ESR) > 50 mm/hr

More than two to three nodal sites of disease

Appendix VI– Deauville Score

SCORE	PET RESULTS	PET EVALUATION
1	No uptake	Negative
2	Uptake ≤ mediastinum	Negative
3	Uptake > mediastinum but ≤ liver	Negative
4	Moderately increased uptake compared to liver	Positive
5	Markedly increased uptake compared to liver	Positive

Appendix VII – Management of Algorithms for Nivolumab

- These general guidelines constitute guidance to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.

- Where applicable the Approved Label should be used for guidance around dose modifications and discontinuation

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

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

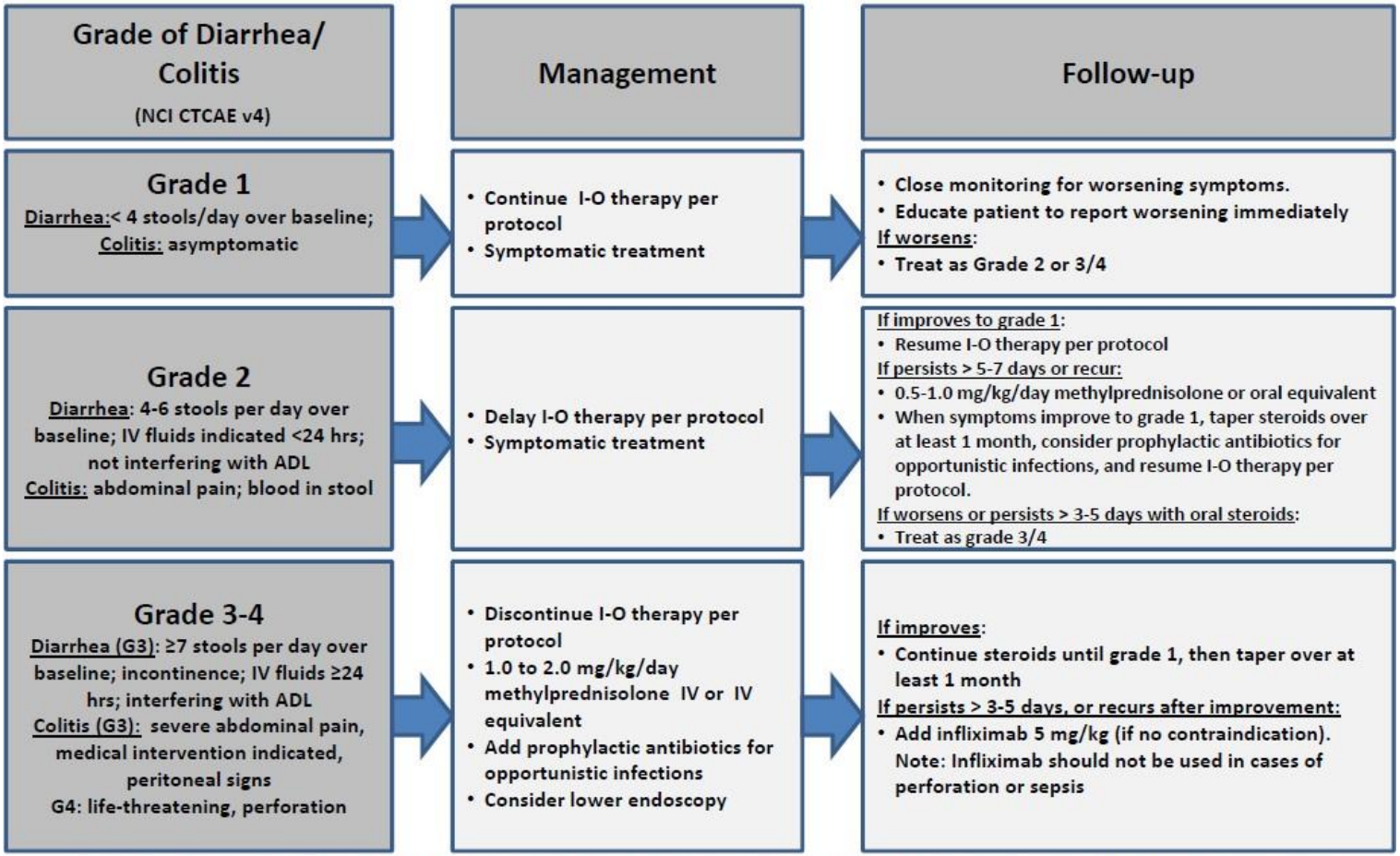
- Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

Investigators should refer to the most current version of the IB or Approved Label for current recommendations for management of a specific Adverse Event of interest.

GI Adverse Event Management Algorithm

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

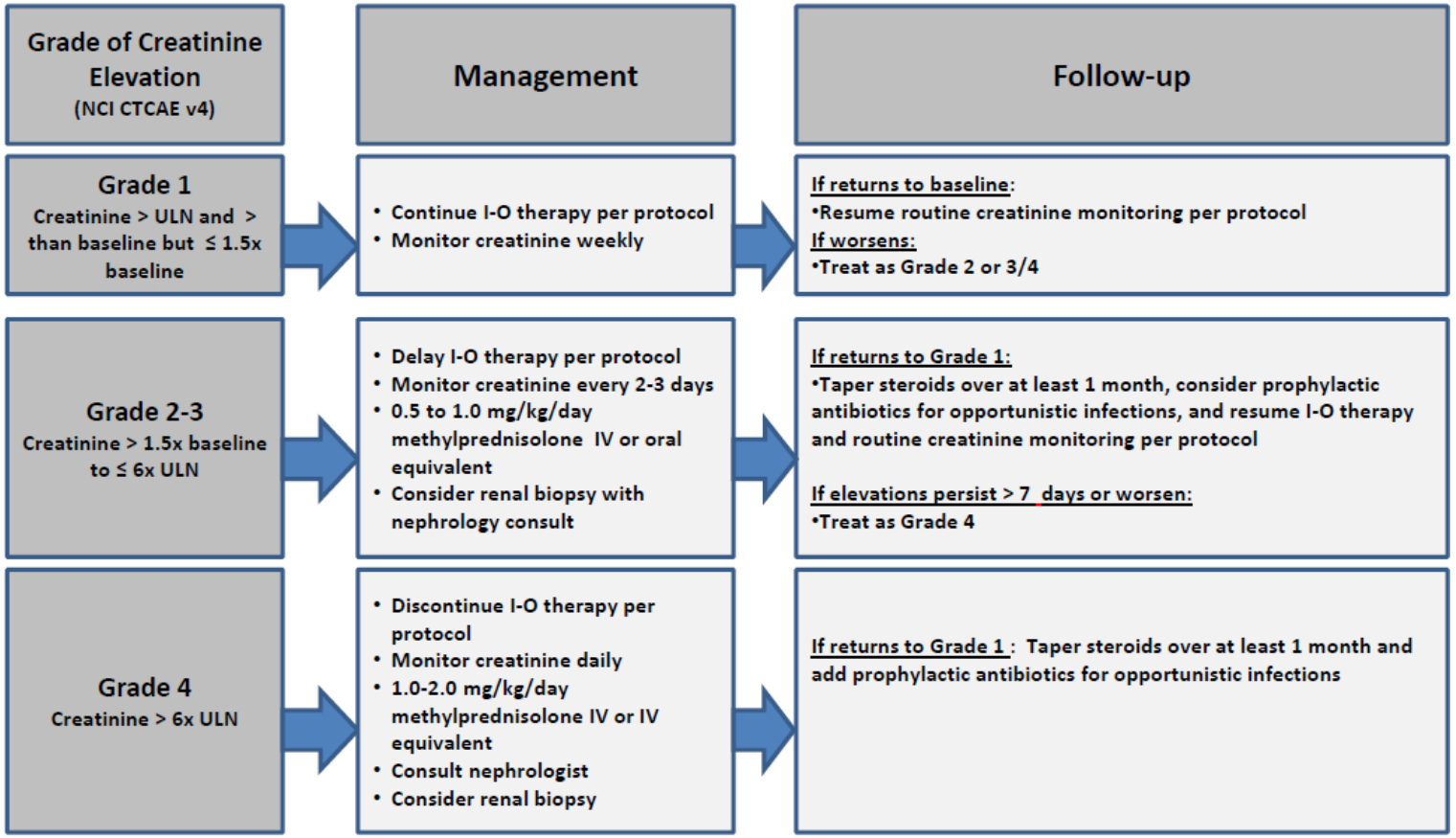


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

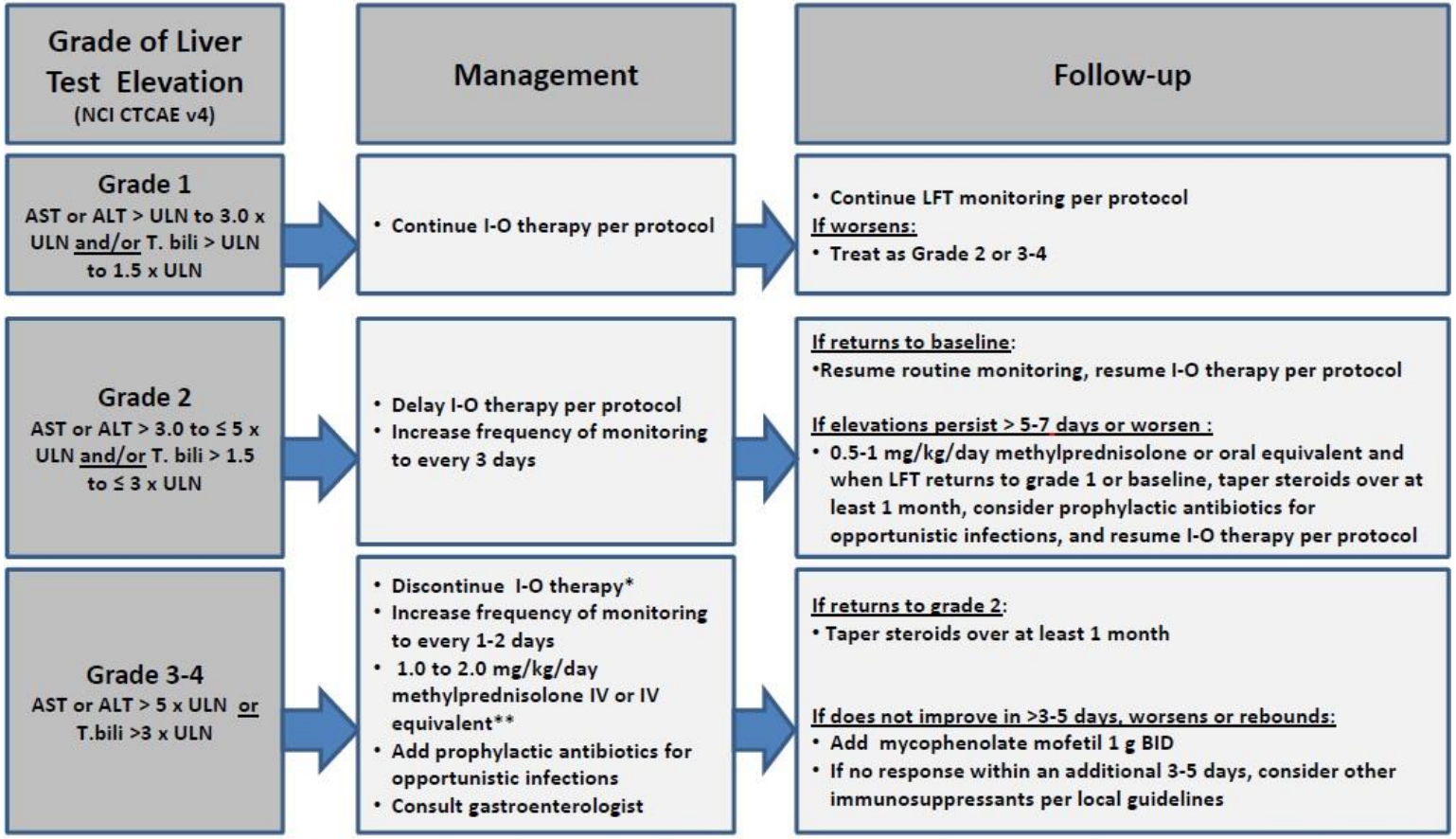
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new 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

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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

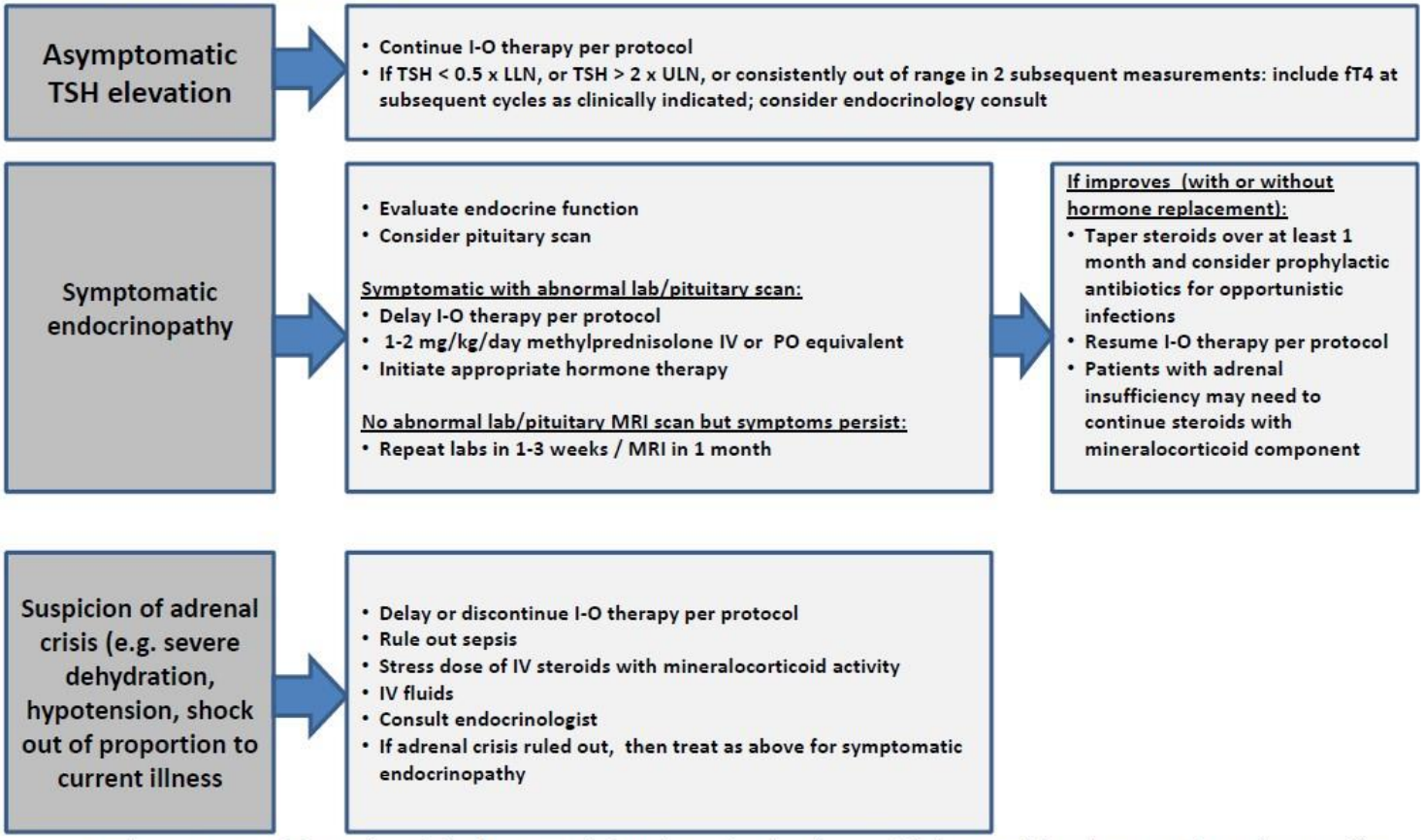
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

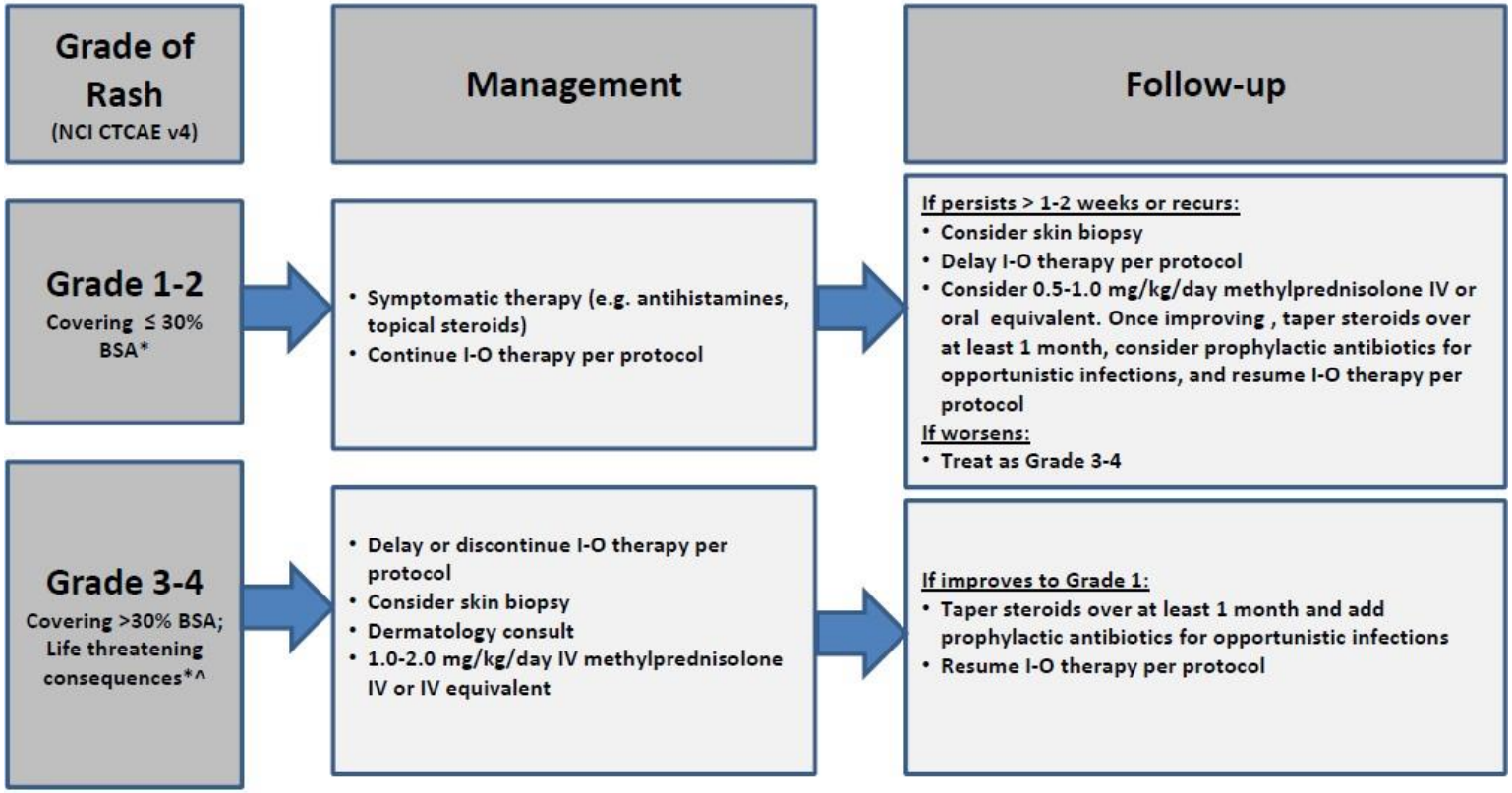


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

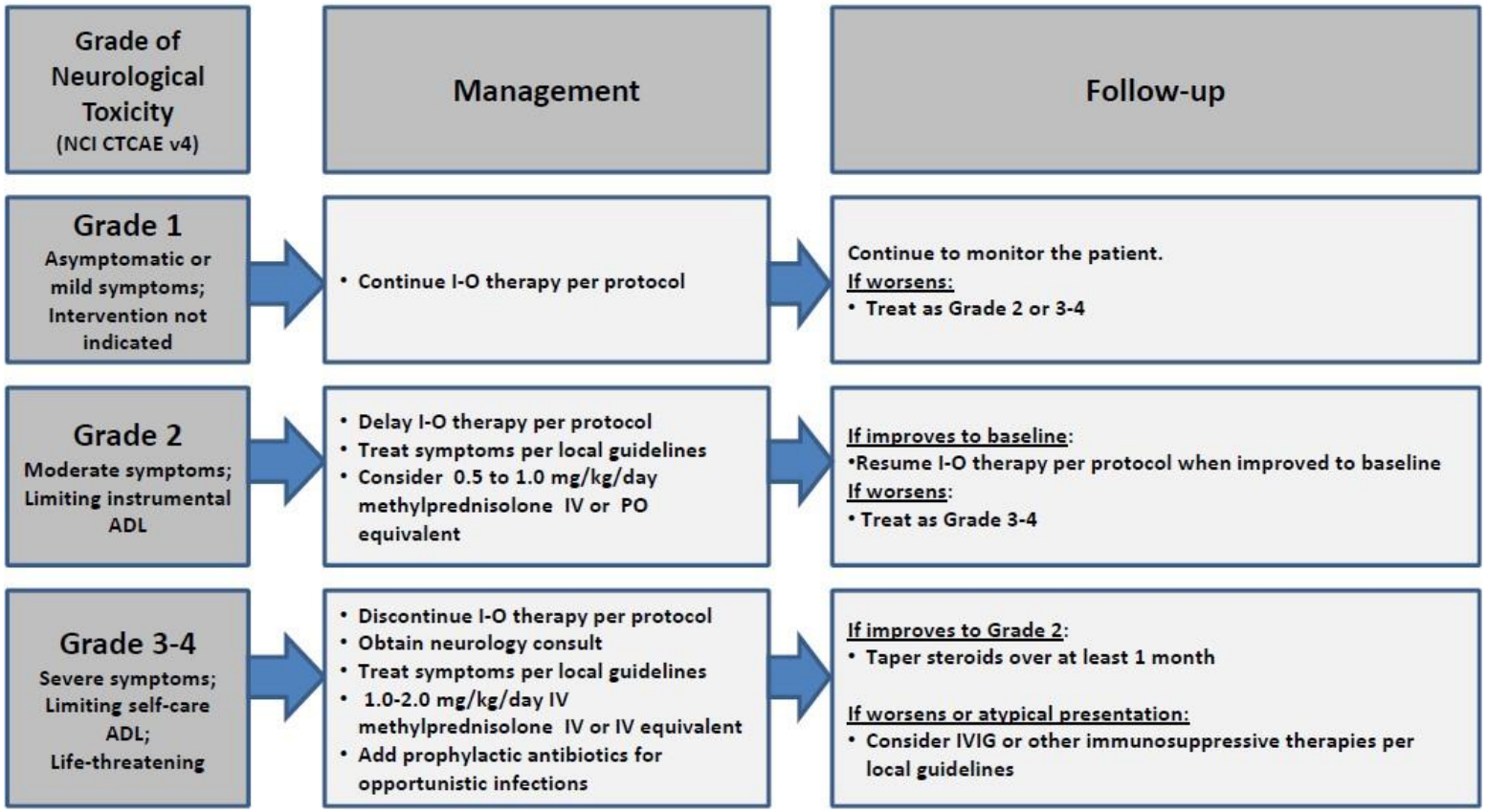


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016