Academic and Community Cancer Research United (ACCRU)

Phase II, Multi-center Trial of Nivolumab and Brentuximab Vedotin in Patients with Untreated Hodgkin Lymphoma Over the Age of 60 Years or Unable to Receive Standard Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD) Chemotherapy

For any communications regarding this protocol, please contact the person listed on the ProtocolRresource page This is a stand-alone document found on the ACCRU website (www.ACCRU.org).

Study Chairs

ACCRU: [redacted]

FDA IND Sponsor/Investigator: [redacted]

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Drug Availability

Drug Company Supplied: Brentuximab Vedotin (Adcetris)
Nivolumab (Opdivo)

IND# 128842 (For Combination of both drugs together)

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

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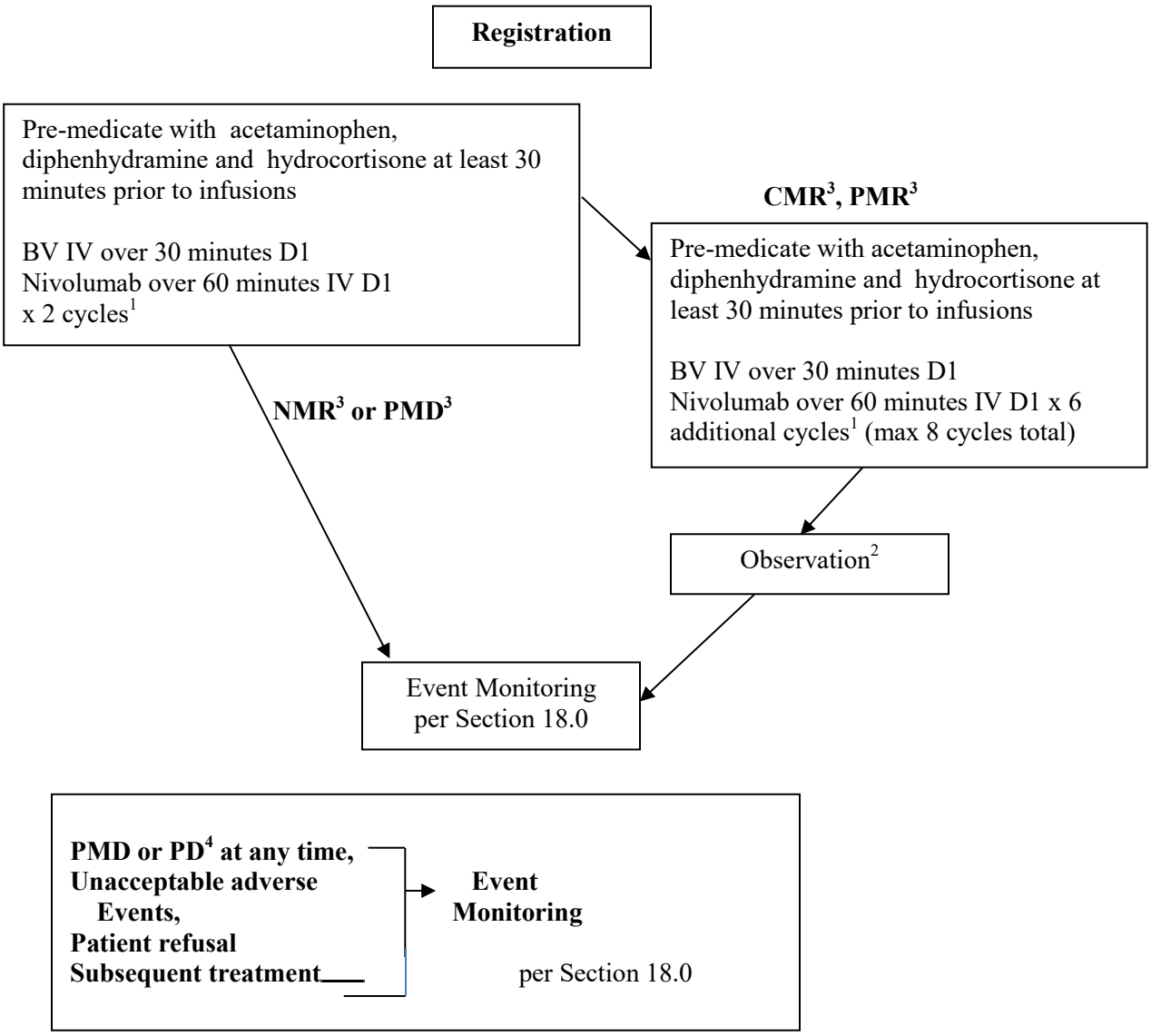
Schema



[1] Cycle length: Cycles 1-7 = 21 days, Cycle 8 = 6-8 weeks
[2] Every 30 days x 90days, then, every 90 days x 2.5 years, then every 6 months until 5 years from registration
[3]PET-CT based response criteria. See Section 11.0.
[4]Progressive disease by PET-CT or CT based response criteria (see Section 11.0). PET confirmation of progressive disease is per physician discretion.
Prior to discussing protocol entry with the patient, call the ACCRU Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

Generic name: Brentuximab Vedotin Brand name(s): Adcetris ACCRU Abbreviation: SGN35 Availability: Almac, Inc. (United States) Takekda Ireland (Non-U.S.)	Generic name: Nivolumab Brand name(s): Opdivo ACCRU Abbreviation: BMS936558 Availability: [redacted]

1.0 Background

1.1 Disease Background

Hodgkin lymphoma (HL) is predicted to affect over 9,000 patients in the United States in 2015, approximately 20% of which are greater than 60 years old [1]. While current front-line regimens such as adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) and Stanford V produce long-term remissions in younger patients (5-year overall survival (OS) 90%) [2], their efficacy is less in the elderly. In E2496, a phase III study of 45 patients 60 years or greater, ABVD and Stanford V regimens produced an overall response rate (ORR) of 68%, a complete response (CR) rate of 64%, and a 5-year OS of only 58% [3]. Furthermore, treatment related mortality (TRM) was 9% with increased rates of grade 3-4 neutropenia (82%) and anemia (24%) and grade 3-5 infections (11%) and pulmonary toxicity (24%). The age-related disparity in overall survival with a potentially curable lymphoma demonstrates the need for alternative, more tolerable, front line options for the elderly.

New biologic molecules have been developed recently to specifically target the malignant lymphocyte and its microenvironment with a goal of improving anti-tumor efficacy, while limiting toxicity. Brentuximab vedotin (BV) is an antibody drug conjugate (ADC) comprised of a chimeric anti-CD30 monoclonal antibody joined to a microtubule-disrupting agent, monomethyl auristatin E (MMAE), via a citrulline valine linker. BV gained its approval based on a phase II study demonstrating an ORR of 75% (CR 34%), median progression free survival (PFS) of 9.3 months, and a 3-year OS of 40.5 months in patients with relapsed and refractory HL following autologous transplant [4,5]. In a single-agent front-line phase II study of HL patients > 60 years-old treated with BV, the interim analysis of 27 patients reported an ORR 93%, a CR rate of 70% and PFS of 8.7 months. The drug was well tolerated with reports of > grade 3 adverse effects of neutropenia (22%), peripheral sensory and motor neuropathy (7% each) and rash (7%) [6]. It is currently under study in the ECHELON trial in combination with Adriamycin, vinblastine and dacarbazine, being compared with traditional ABVD.

Neoplastic Reed-Sternberg (RS) cells surrounded by a vast inflammatory cell infiltrate consisting of both T helper and regulatory cells pathologically characterize HL. Despite this immune cell infiltrate, there is lack of host mediated antitumor effect. Program death ligands (PDL) 1 and 2 inhibit T cell activity by interacting with program death receptor 1 (PD-1) on T cells. The amplification of chromosome 9p24 leads to over expression of PDL-1 and 2 on RS cells, which provides HL a mechanism to evade immune surveillance [7, Yamamoto, 2008 #2581]. Nivolumab (NIV), a fully human IgG4 monoclonal antibody which blocks PD-1 receptor restoring the cancer fighting ability of T cells, was first approved by the FDA in metastatic or unresectable melanoma [8]. In a phase I study of 23 heavily pretreated patients with relapsed/refractory HL, NIV demonstrated promising activity: ORR 87%, CR 17%, and 24-month PFS of 86%. The most common toxicities included rash (22%), thrombocytopenia (17%), stomatitis (13%), increased serum lipase (13%) and lymphopenia (13%), which were all manageable without any reports of grade 4 or 5 events [9]. Pembroluzimab, a humanized anti-PD-1 antibody, has also been studied in pre-treated HL revealing an ORR of 57% with CR rate of 20% [10].

Dual inhibition of the malignant lymphocyte and the microenvironment may be beneficial to patients with lymphoid malignancies, both in terms of efficacy as well as tolerability. In relapsed follicular lymphoma, the combination of pidiluzumab, a humanized anti-PD-1 antibody, and rituximab resulted in an ORR of 66% (CR 52%) and median PFS of 18.8 months. The median PFS was not reached in those who achieved a response and the regimen was deemed quite tolerable as there were no grade 3 or 4

adverse events reported [11]. The cytotoxic component of BV, MMAE, is derived from the dolastatin family of microtubule inhibitors. In immunocompetent mice (C57BL/6) and human HL models (L-540 cell line), in addition to triggering apoptosis, dolastatin-10 and MMAE were found to be strong inducers of dendritic cell (DC) maturation, resulting in T-cell stimulation and adaptive immunity activation [12]. In C57BL/6 mice, the combination of dolastatin-10 and anti-cytotoxic T-lymphocyte-associated protein 4(CTLA-4) and PD-1 antibodies was found to be synergistic, leading to an increase ratio of interferon gamma producing CD-8 effector T cells in the tumor and improvement in complete tumor regression rate from 8% to 58%. Based on these data, we propose that the combination of BV and NIV will provide an efficacious but tolerable regimen for elderly patients with previously untreated HL.

1.2 Brentuximab vedotin Background and Associated Known Toxicities

Cancer immunotherapy is based on the premise that tumors can be recognized as foreign rather than as self and, can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. This functions by aborting the emergence of tumors as they arise and/or causing tumor shrinkage where they are present. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response [13]. This evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of costimulatory pathways that affect the proliferation of cells involved in immunity. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system, either directly by stimulation of immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative costimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) [14]. Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulary receptors that also includes CD28, CTLA-4, ICOS, and BTLA [14].PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems [15,16].PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region [16,17]. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells [18].
Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus [19-21]. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain, and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes [22,23].Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-

cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1 [24-26]. This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies [27,28]. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro [16] Moreover, the expression of PD- L1 may protect the tumor cells from the induction of apoptosis by effector T cells [29].
Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by IHC) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness [28,30].

Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. In addition, in multivariate analysis, high expression of PD-L1 is correlated to have a worse overall survival rate compared with low expression levels of PD-L1 [31].
PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic option.

Brentuximab vedotin (ADCETRIS™, the first "A" of the experimental arm acronym) is an antibody-drug conjugate (ADC) composed of the anti-CD30 chimeric immunoglobulin G1 (IgG1) monoclonal antibody cAC10 and the potent antimicrotubule drug monomethyl auristatin E connected by a protease-cleavable linker. cAC10 binds to the CD30 antigen, which has a very low expression on normal cells but is found on the HRS cells of HL, on anaplastic large cell lymphoma (ALCL) cells, and on tumor cells of other varied lymphoproliferative disorders.

Brentuximab vedotin is approved in the United States as ADCETRIS™ for the treatment of patients with HL after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and for the treatment of patients with systemic ALCL after failure of at least 1 prior multi- agent chemotherapy regimen (1).

1.21 Nonclinical Experience

Brentuximab vedotin has the potential to target and selectively deliver a potent cytotoxic to tumor cells. It induces cell death of both HL and ALCL cell lines in vitro with subnanomolar concentrations producing 50% inhibition (IC50) and has demonstrated antitumor activity in xenograft models of the same tumors.

Multiple-dose brentuximab vedotin toxicity studies have been performed in monkeys and rats. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. In addition, lesions were seen in the kidneys, liver, and spleen in monkeys and in the liver and testes in rats.

Reversibility of toxicity was demonstrated for all of the findings with the exception of the testicular changes in rats. At the recovery sacrifice 4 weeks following the last dose of brentuximab vedotin, testicular changes (diffuse seminiferous tubule degeneration) were still evident. The no observed adverse effect level for brentuximab vedotin was defined at 1.0 mg/kg in monkeys and 0.5 mg/kg in rats. Human equivalent doses are 0.32 and 0.08 mg/kg, respectively.

1.211 In the L450cy tumor model [32], administration of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) plus brentuximab vedotin in tumor-bearing mice demonstrated significantly increased antitumor activity as compared to the mice treated with ABVD or brentuximab vedotin alone, suggesting a synergistic effect [33]. ABVD and brentuximab vedotin-treated animals demonstrated 0/8 and 4/9 durable responses, respectively, while the combination of brentuximab vedotin and ABVD resulted in 9/9 durable tumor regressions in all experimental animals. In addition, combination therapy was associated with a statistically significant tumor growth delay (TGD) relative to each treatment arm alone (combination vs brentuximab vedotin: $P < 0.0101$, combination versus ABVD: $P < 0.0001$). Improved efficacy in high tumor burden models suggests that combining brentuximab vedotin with ABVD may be associated with greater efficacy.

Similarly, when treatment was initiated when tumors reached 300 mm3 volume, the combination of brentuximab vedotin with ABVD significantly increased the TGD, resulting in durable responses in 5 of 10 animals. The delay in tumor growth induced by the combination treatment was highly significant relative to each individual treatment arm alone (combination versus brentuximab vedotin: $P < 0.05$, combination versus ABVD: $P < 0.001$).

Doxorubicin, vinblastine, and bleomycin had little if any single-agent antitumor activity in L540cy xenograft models and did not significantly improve antitumor activity of Brentuximab vedotin (ADCETRIS™) (1).

1.22 Clinical Experience

The safety and efficacy of brentuximab vedotin has been evaluated in more than 450 patients with HL, sALCL, and other CD30+ hematologic malignancies in 11 clinical studies. Clinical data have been collected from 2 completed phase 1 dose-escalation studies (SG035-0001 and SG035-0002), a pivotal phase 2 study in relapsed or refractory HL after ASCT (SG035-0003), a pivotal phase 2 study in relapsed or refractory systemic ALCL (sALCL) (SG035-0004), and a phase 1 drug-drug interaction study (SGN35-008A). Preliminary and final analyses of safety data indicate that brentuximab vedotin has a manageable safety profile in the studied populations.

1.221 In Study SG035-0001, a total of 45 patients with CD30+ hematologic malignancies (42 with HL, 2 with sALCL, 1 with angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously (IV) every 3 weeks. The primary objectives of the study were to establish a maximum tolerated dose (MTD) of brentuximab vedotin and to assess the associated toxicity profile. The most common adverse events (AEs) were fatigue (36%), pyrexia (33%), diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each). Notable serious adverse events (SAEs) considered at least possibly related to treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy. Numerous responses, including

complete remissions (CRs), were observed. The maximum tolerated dose (MTD) was determined to be 1.8 mg/kg administered IV over 30 minutes every 3 weeks.

1.222 In Study SG035-0002, a total of 44 patients with CD30-positive hematologic malignancies (including 38 with HL) were treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered IV weekly for 3 of 4 weeks. The primary objectives explored in this study were to establish the safety profile and MTD of weekly brentuximab vedotin monotherapy in patients with relapsed/refractory CD30+ hematologic malignancies.
Brentuximab vedotin (ADCETRIS™) Clinical Study Protocol C25003 Amendment 4, EudraCT: 2011-005450-60

1.223 Although this weekly regimen was designed to enable combination use with gemcitabine, efficacy with brentuximab vedotin monotherapy was deemed sufficient and the planned brentuximab vedotin/gemcitabine combination was not pursued. The most common AEs were peripheral sensory neuropathy (66%); fatigue (52%); nausea (50%); diarrhea (32%); arthralgia (27%); pyrexia (25%); and decreased appetite, myalgia, and upper respiratory tract infection (23% each). Treatment discontinuations due to AEs were observed in 30% of patients. The most frequent AE that led to dose modification or delay was peripheral sensory neuropathy. Acute infusion reaction AEs occurred in a total of 6 patients. Overall, these acute infusion reaction AEs were reported as less than Grade 2 in severity and resolved. Overall, 2 patients (14%) who had an acute infusion reaction also had antitherapeutic antibodies at any postbaseline visit.

1.224 In SG035-0003, a phase 2 single-arm, open-label study in patients with relapsed or refractory HL after ASCT, and SG035-0004, a phase 2 trial conducted in patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27weeks (9 cycles) and 20 weeks (6 cycles), respectively. Most patients (89%) in the 2 phase 2 studies were between the ages of 18 and 65 years. The primary endpoint of both studies was overall response rate (ORR) as assessed by an independent review facility (IRF). Key secondary endpoints included duration of response, CR rate per IRF, OS, and progression free survival (PFS). The key efficacy results in HL (SG035-0003) include ORR per IRF (75% [95% confidence interval (CI): 64.9-82.6%]), CR rate per IRF (34% [95% CI: 25.2 44.6%]), B symptom resolution rate (77%), and duration of response (DOR; 6.7 months). Of interest, for those patients achieving a CR, the median DOR was 20.5 months. Key efficacy endpoints in sALCL (SG035-0004) include ORR per IRF (88% [95% CI: 74.6-93.9%]), CR rate per IRF (53% [95% CI: 39.6-66.7%]), and B symptom resolution rate (82%).

1.225 Treatment-emergent AEs (TEAEs) occurring in ≥ 20% of patients in phase 2 were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events

were primarily mild to moderate in severity and reversible. Approximately half of patients had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an onset and severity pattern consistent with a cumulative effect. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively.
Brentuximab vedotin (ADCETRISTM)[SEP]Clinical Study Protocol C25003 Amendment 4, EudraCT: 2011-005450-60

1.226 These events were typically of short duration and well managed by brief dose delays with growth factor support in some cases. Infusion-related reactions occurred in approximately 10% of patients and were typically managed by dose interruption. Infusion-related reaction prophylaxis in subsequent treatment cycles was instituted at the discretion of the investigator. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥ Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 ALT and aspartate aminotransferase (AST).

1.227 In the phase 2 studies, 31% of patients had an SAE, 28% had an SAE of Grade 3 or higher, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAE preferred terms (2%) were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of sALCL patients experienced SAEs, including deaths within 30 days of last dose, relative to HL patients, likely due to the older age and more aggressive nature of the malignancy in this patient population.

1.228 A total of 9 deaths were reported within the safety evaluation period (within 30 days of the last dose of brentuximab vedotin) in 357 patients across the 6 phase 1 and phase 2 studies for which data are available. Two patient deaths (0.6%) were considered related to study treatment. One patient in Study SG035-0001 who received 3.6 mg/kg in phase 1 died due to febrile neutropenia and presumed septic shock. A second treatment-related death in Study SGN35-008A was attributed to pancytopenia, cytomegalovirus (CMV) infection, and intracranial hemorrhage. The remaining on-study deaths were primarily related to disease progression in sALCL patients.

1.229a Brentuximab vedotin has been shown to induce durable remissions in patients with HL both pre- and post-ASCT, and in patients with relapsed or refractory sALCL. PFS results comparing PFS with brentuximab vedotin to PFS from prior systemic therapy indicate that PFS is significantly prolonged with brentuximab vedotin for both HL and sALCL. A substantial number of HL and sALCL patients with B symptoms at baseline saw these symptoms resolve during treatment with brentuximab vedotin. In addition, the large majority of sALCL patients presenting with cutaneous lesions at baseline experienced resolution of these symptoms after receiving brentuximab vedotin.
Study SGN35-009 is a phase 1, 2-arm, open label, multicenter study to evaluate the safety of brentuximab vedotin when administered in combination with standard therapy (ABVD) or a modified standard

(doxorubicin (Adriamycin), vinblastine, dacarbazine [AVD]). To date, patients have received doses of 0.6, 0.9, or 1.2 mg/kg brentuximab vedotin with standard doses of ABVD or 1.2 mg/kg brentuximab vedotin with AVD, depending upon cohort assignment. The combination regimens are administered on Days 1 and 15 of each 28-day cycle for up to 6 cycles of therapy. Each regimen evaluated a dose limiting toxicity (DLT) period, defined as any Cycle 1 toxicity requiring a delay of ≥ 7 days in standard ABVD or AVD therapy. No DLTs were observed. Enrollment of an expansion cohort further testing 1.2 mg/kg brentuximab vedotin plus AVD is now complete and treatment of enrolled patients is ongoing within this cohort.

1.229b Of the 51 patients enrolled in Study SGN35-009, the mean age was 34.8 (range 18-59); 47% of patients had Stage IV disease at diagnosis, and 25% had a Hasenclever Hodgkin's Prognosis Score (IPS) ≥ 4. A recent review of interim safety data as of 07 February 2012 for all 51 enrolled patients included data from 25 patients in the brentuximab vedotin plus ABVD cohorts and 26 patients in the brentuximab vedotin plus AVD cohorts. The most commonly reported TEAEs were nausea, neutropenia, peripheral sensory neuropathy, fatigue, vomiting, constipation, alopecia, pyrexia, bone pain, decreased appetite, diarrhea, and insomnia, each reported in 25% or more patients. Peripheral neuropathy events have been reported in 25 patients (49%); 1 patient had Grade 3 peripheral motor and sensory neuropathy, but no other patient's peripheral neuropathy event exceeded Grade 2. In the brentuximab vedotin plus ABVD cohorts, Grade ≥ 3 events included neutropenia (n = 20, 80%), febrile neutropenia (n = 5), pulmonary toxicity (n = 5), anemia (n = 4), dyspnea (n = 3), pulmonary embolism (n = 3), syncope (n = 3), and anorectal cellulitis, cough, fatigue, hypokalemia, hyponatremia, leukopenia, pericardial effusion, rash, and respiratory failure (n = 1 each). In the brentuximab vedotin plus AVD cohorts, Grade ≥ 3 events included neutropenia (n = 17, 65%), anemia (n = 3), febrile neutropenia (n = 2), and decreased appetite, dyspnea, elevated ALT, fatigue, leukopenia, peripheral sensory and motor neuropathy, Pneumocystis jiroveci pneumonia, SIADH, syncope, and tooth abscess (n = 1 each).

1.229c Interim efficacy data as of 07 February 2012 demonstrate that all patients who completed frontline therapy on study for whom response assessment results are available achieved a CR at the end of treatment, including 18 patients from the ABVD cohorts and 6 patients from the AVD cohorts. Additionally, an exploratory analysis of interim fluorodeoxyglucose (FDG) positron emission tomography (PET) results after 2 cycles of therapy was performed by independent radiology review using the Deauville criteria.(8) Of 37 patients, 36 (97%) had a negative interim PET after Cycle 2 by central review, including 22 of 22 (100%) negative in the ABVD cohorts and 14 of 15 (93%) negative in the AVD cohorts.

1.3 Nivolumab Background and Associated Known Toxicities

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes [34]. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2),

results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

1.31 Nonclinical Studies

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family.2,3 Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro.4,5,6 Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1.2 In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-□release [35].

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents [36].

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted [37]. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 µg•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice [38]. Approved v 15.0 930038243 16.0 18 Investigator Brochure[SEP]BMS-936558/MDX1106 nivolumab.

1.32 Effects in Humans

The PK, clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, and clear-cell renal cell carcinoma (RCC) in addition to other tumor types. Clinical activity and safety information presented in this Investigator Brochure (IB) focuses primarily on that obtained from Phase 2/3 studies (CA209063, CA209017, CA209057, ONO-4538-05, and ONO-4538-06) in subjects with advanced or metastatic squamous (SQ) and nonsquamous (NSQ) NSCLC, Phase 2/3 studies (CA209037, CA209066, CA209067, and CA209069) in subjects with unresectable or metastatic melanoma, and a Phase 2 study (CA209010) in subjects with advanced

or metastatic clear-cell RCC. Data are also provided from Phase 1 studies MDX1106-03, CA209012, CA209016, and CA209039 and from Phase 1 safety cohort of CA209143. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

Nivolumab is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma and previously treated, metastatic squamous NSCLC, the EU for treatment of previously treated, unresectable or metastatic melanoma, and Japan for treatment of unresectable melanoma.

1.33 Clinical Pharmacokinetics

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

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials.

1.34 Clinical Efficacy

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab or other agents in several tumor types, including NSCLC, melanoma, RCC, and some lymphomas [9,11,39]. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC and in subjects with unresectable or metastatic melanoma. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.

1.4 Safey in Subjects with Relapsed or Refractory Hematologic Malignancies

CA209039 Nivolumab, at 1 or 3 mg/kg, has an acceptable safety profile in subjects with relapsed or refractory hematologic malignancy, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to

discontinuation. The following were the key safety findings for 105 subjects treated with nivolumab monotherapy in CA209039 as of 15-Apr-2015:

- The most frequently reported drug-related AEs (> 10% of subjects) were fatigue (16.2%) and rash (10.5%). The majority were Grade 1-2 in severity.
- The most frequently reported drug-related SAE was pneumonitis (4.8%).
- Drug-related AEs leading to discontinuation were reported for 14.3% of subjects. The most frequently reported AE leading to discontinuation were pneumonitis (2.9%).
- The most frequently reported drug-related select AE categories were skin (19.0%), GI (9.5%), and pulmonary (9.5%). The most frequently reported (≥5% of total treated subjects) drug-related select AEs were rash (10.5%), pneumonitis (9.5%), pruritus (9.5%), and diarrhea (8.6%). Drug-related select AEs were mostly Grade 1-2 in all categories.
- Most deaths were due to disease progression. One death was reported due to study drug toxicity (The subject with non Hodgkin's lymphoma [small lymphocytic lymphoma] in the 3 mg/kg treatment group died due to Grade 5 pneumonitis with onset 10 days after the subject received the only dose of nivolumab).

1.41 Clinical Activity of Nivolumab in Lymphoma

In a broad phase II study, Ansell et al treated 23 patients with classical HL who had been heavily pretreated [9]. Nivolumab at a dose of 3 mg/kg was administered q 2 weeks until CR< tumor progression, or toxicity. Of these, 78% had progressed following a prior autologous stem cell transplant, and 78% following brentuximab vedotin. An objective response was achieved in 87%, including 17% with a CR. The rate of progression-free survival at 24 weeks was 86%. Therapy was discontinued in 6 patients to go to stem cell transplantation, with disease progression in 4, and toxicity in 2.

From the same study Lesokhin et al reported 29 patients with a variety of histologies of B-NHL with responses in 36% of diffuse large B-cell NHL (9% CR), 40% of follicular NHL (10% CR) [40].

1.5 Rationale

Given the impressive activity of both Brentuximab Vedotin and nivolumab in patients with relapsed and refractory Hodgkin Lymphoma, and their lack of overlapping toxicities, the combination is worthy of study. Given the poor results and tolerability of traditional chemotherapy in older patients with Hodgkin Lymphoma, as described above, this combination can be considered for first-line therapy.

2.0 Goals

2.1 Primary

2.11 The primary objective of the study is to determine the efficacy based on overall rmetabolic response rate (PMR + CMR) of Brentuximab Vedotin /Nivolumab in previously untreated Hodgkin Lymphoma patients 60 years of age or older, or those considered unsuitable for standard chemotherapy because of a low cardiac ejection fraction (<50%) or impaired pulmonary or renal function.

2.2 Secondary

2.21 The complete metabolic response (CMR) rate

2.22 Safety and tolerability of the regimen in this patient population

2.23 Duration of response (DOR)

2.24 Progression-free survival (PFS)

2.25 Overall survival (OS)

2.3 Correlative Research

2.31 T-cell/cytokine– peripheral blood specimens will be used to assess T-cell activation and cytokine up regulation as measures of treatment effect. This goal will be exploratory in nature and reported descriptively.

2.32 Biomarkers- intratumoral cell populations, genetic variability, serum cytokines and T-cell activation will be evaluated to identify potential biomarkers that correlate with response to therapy. This goal will also be exploratory in nature.

3.0 Patient Eligibility

Prior to discussing protocol entry with the patient, call the [redacted] for dose level and to ensure that a place on the protocol is open to the patient.

3.1 Registration – Inclusion Criteria

3.11 Classical Hodgkin Lymphoma determined by local hematopathology review

3.12 One of the following:

- Age ≥ 60 years
- Age <60 years but unsuitable for standard chemotherapy because of a cardiac ejection fraction of <50%, a pulmonary diffusion capacity <80%, or a creatinine clearance ≥30 and <60 mL/min, or refused standard chemotherapy despite efforts to convince them otherwise.

Cockcroft-Gault Equation:

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

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

3.13 Requirement for systemic chemotherapy: all stages except IA (not bulky disease), if involved field is considered Radiotherapy (RT) curative.

3.14 Previously untreated with either chemotherapy, radiation therapy or either brentuximab vedotin or nivolumab, or another check point inhibitor.

3.15 ECOG Performance Status (PS) 0, 1, or 2 (Appendix II)

3.16 The following laboratory values obtained ≤ 7 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm^3, unless secondary to bone marrow involvement.
- Leukocytes ≥ 3,000/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin >9.0 g/dL – unless determined by treating physician to be disease related
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤ 2.5 x ULN
- Alanine Transaminase (ALT) ≤ 2.5 x ULN
- Creatinine ≤2.0 mg/dL
- Amylase and/or lipase ≤1.5 x ULN

3.17 Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to registration

Note: Women of child-bearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.
Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.18 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.*

3.19a Ability to understand and willingness to sign an informed written consent.

3.19b Provide blood and tissue samples for mandatory correlative research purposes (see sections 4.0, 14.0 and 17.0).

3.2.1 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 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.

3.23 Active, known or suspected autoimmune disease. Note: 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

3.24 Use of systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications $\leq$ 14 days of registration. Note: Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3.25 Immunocompromised patients, patients with known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) and currently receiving antiretroviral therapy, patients with a prior history of known or suspected autoimmune disease, active Hepatitis B virus surface antigen (HBV sAg+), active Hepatitis C (if Ab+ then PCR+) indicating acute or chronic infection, and/or history of interstitial lung disease.

3.26 Allergy to Brentuximab Vedotin and/or Nivolumab

3.27 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.

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

3.29a Have had prior chemotherapy or radiotherapy for Hodgkin lymphoma

3.29b Have received either of the study drugs

3.29c <60 years who are considered candidates for standard chemotherapy

3.29d ≥ Grade 2 peripheral neuropathy

3.29e Other active malignancy ≤2 years prior to registration, unless treated with curative intent. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer.

3.29f Active CNS involvement or leptomeningeal metastases involvement.

3.29g Known history of pancreatitis.

4.0 Test Schedule

Tests and procedures		Active Monitoring Phase			
	Baseline ≤14 days of Registration	Prior to each new cycle[10] </= 3 days (starting at cycle 2)	Restaging End of Cycle 8 (6-8 Weeks after Day 1 of Cycle 8)	End of Treatment if discontinued early (at PD or PMD, withdrawal, or removal)	Observation (Every 30 days x 90 days, , then every 90 days x 2.5 years, then every 6 months until 5 years from registration) +/-14Days
History and exam	X	X[1]	X	X	X
B Symptoms[9]	X	X	X	X	X
ECOG PS	X	X	X	X	X
Height (baseline only), Weight	X	X	X	X	X
Adverse event assessment	X	X	X	X	X
Cardiac ejection fraction	X[14]				
ECG	X				
Pulmonary function studies (including oxygen saturation)[12]	X				
HBV sAg and HCV Ab or HCV RNA	X				
Comprehensive metabolic panel: (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, Albumin, bicarbonate	X[4]	X	X	X	
INR[R, 13]		X	X	X	X
TSH (with Free T4 and Free T3)	X[4]	X[11]	X	X	
Hematology: CBC/differential	X[4]	X	X	X	X
Erythrocyte sedimentation rate	X				
Uric Acid	X				
Pregnancy Test[3]	X	X	X	X	X
PET-CT	X[14]	X[2]	X	X	
CT scan Chest/Abd/Pelvis					X[5]
Mandatory Research blood samples (See section 14.0)[R, 6]		X[15]	X	X	X[8]
Mandatory Tissue sample[7, R]	X				

(Footnotes on next page)

1 If on physical exam there are any palpable lymph nodes present: Tumor (bidiminsional)-measurements by physical exam to be done at end of every cycle, prior to next cycle.
2 End of cycle 2, prior to Cycle 3 (≤ 5 days)
3 For women of childbearing potential only. A serum or urine pregnancy testing is required ≤ 24 hours before registration, then every other cycle. (more frequently if required by local standard). After discontinuation from nivolumab, these should be repeated at approximately 30 days and approximately 70 days [or more frequently if required by local standard].
4 Must be obtained ≤7 days prior to registration.
5 CT scan is every 3 months during the first year of observation, then as clinically indicated.
6 Must be drawn on Day 1 of each cycle before treatment Cycles 1-8, at restaging 6-8 weeks post Cycle 8 Day 1, end of treatment if discontinued early (PD or PMD, withdrawal or removal), and at time of PD or PMD.
7 To be submitted within ≤14 days following Registration; see 17.0 Pathology Considerations/Tissue Biospecimens
8 Only at time of PD or PMD
9 Unexplained persistent fever > 38° C(or >100.4° F) in previous month, recurring drenching night sweats during the previous month, and/or unexplained weight loss >10% of body weight in the previous six months
10 If tests have been done ≤ 14 days prior to registration they need not be repeated for the first cycle.
11 Thyroid function testing should be done every third cycle day 1 (≤ 3 days) for subjects receiving nivolumab.
12 Oxygen saturation by pulse oximetry at rest (also specify supplemental oxygen level, if applicable) should be assessed at baseline
13 ONLY if clinically indicated
14 Must be obtained ≤28 days prior to registration.
15 Research blood draw to be done prior to every cycle, including Cycle 1.
R Research funded (see Section 19.1)

5.0 Stratification Factors: None

6.0 Registration Procedures

6.1 Safety Analysis Phase

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office [redacted] for dose level and to ensure that a place on the protocol is open for the patient.

6.11 Registration Procedures

To register a patient, fax [redacted] a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Phase II Cohort

6.21 To register a patient, access the ACCRU web page at [redacted] go to the Application section and 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]

The instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training."

Prior to initiation of protocol study intervention, this process must be completed in its entirety and a 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 ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted] click on "Registration, Installation & Entry Instructions".

6.3 Safety Analysis Cohort and Phase II Cohort

6.31 Correlative Research

A mandatory correlative research component is part of this study. The patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0).

6.32 Prior to accepting the registration, 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

6.33 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using online ACCRU Regulatory Management Systems (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 is required until the study has been closed through your IRB.

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

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her 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 sample(s) to outside researchers.

6.35 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist or hematologist.

6.36 Treatment cannot begin prior to registration and must begin ≤14 days after registration.

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

6.38 All required baseline symptoms (see Section 10.54) must be documented and graded.

6.39a Study drug is available on site.

6.39b Blood draw kit is available on site. Kits must be used for this study.

7.0 Protocol Treatment

7.1 Safety Analysis Phase: Since this combination has not been studied to date, the first 6 patients treated at dose level 1 will be used as an early safety analysis per Section 16.4. If 2 or more patients experience a dose-limiting toxcitity (DLT) as defined below, then the starting dose level will be adjusted and additional cohorts may be evaluated at dose levels -1 and -2 in the safety analysis phase as described in section 16.4. A conference call will

be held weekly amongst the investigators to discuss patients on study or proposed for accrual. Investigators are to contact the ACCRU Operations Office (507-266-0800 as soon as any DLT occurs.

7.11 Safety Analysis Dose Levels

Dose level	Brentuximab Vedotin	Nivolumab
-2	1.2 mg/kg IV Day 1	Omit
-1	1.8 mg/kg IV Day 1	Omit
***1**	1.8 mg/kg IV Day 1	3 mg/kg IV Day 1

***starting dose level**

7.12 Definition of Dose Limiting Toxicity (DLT)

For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event occurring during the first cycle of treatment that is possibly, probably, or definitely related to study treatment and that meets one of the following:

- Any ≥Grade 4 non-hematological organ toxicity (except for Grade 4 nivolumab related diarrhea, pneumonitis, LFT elevations, that improve within 7 days)
- Any ≥Grade 4 hematological toxicity (excluding asymptomatic Grade 4 elevations in amylase or lipase)

7.2 Treatment Schedule - Use actual weight

7.21 Pretreatment medication

Agent	Dose Level	Route	Day	Cycle Length
Acetaminophen[1]	650 mg	PO	Day 1	Cycles 1-7 (21 days) Cycle 8 (6-8 weeks)
Diphenhydramine[1]	25-50 mg	IV infused or PO at least 30 minutes prior to brentuximab Vedotin and Nivolumab infusions	Day 1	Cycles 1-7 (21 days) Cycle 8 (6-8 weeks)
Hydrocortisone[1] (or other steroid equivalent)	100 mg	IV infused at least 30 minutes prior to brentuximab Vedotin and Nivolumab infusions	Day 1	Cycles 1-7 (21 days) Cycle 8 (6-8 weeks)

1. If Brentuximab Vedotin is omitted there are no premedications to be given with just Nivolumab.

7.22 Treatment Schedule

Agent	Dose Level	Route	Day	Cycle Length
Brentuximab vedotin	1.8 mg/kg (cap at 180 mg) in 100 to 250 mL NS to final concentration 0.4 mg/mL to 1.8 mg/mL	IV infused over 30 minutes, before nivolumab	Day 1	Cycles 1-7 (21 days) Cycle 8 (6-8 weeks)
Nivolumab	3 mg/kg in 100 cc NS	IV infused over 60 minutes. 1 hour after completion of Brentuximab vedotin	Day 1	

7.222 The dosing calculations should be based on the actual body weight at baseline. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 9.Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/mL (10 mg/mL) Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 21 days during treatment (with the exception of Cycle 8). After therapy completion, the patient must return to the institution, every 30 days x 90 days, then every 60 days x 180 days, then every 90 days x 2 years, then every 6 months until 5 years post registration, during observation (Active Monitoring Phase) until the patient goes to event monitoring per Section 13.0.

7.4 Patients will be treated for a planned maximum of 8 cycles.

7.5 A PET-CT scan will be performed within 5 days prior to starting cycle 3. Patients who

are in CMR or PMR continue treatment for a total of 8 cycles as tolerated. Those with NMR or PMD at the first interim PET-CT (within 5 days prior to starting cycle 3), or who experience PD or PMD any time thereafter go off treatment to event monitoring and are treated as per their primary hematologist/oncologist.

7.6 For this protocol, the patient must return to the consenting institution for evaluation at least every 21 days (+/- 3 days) during protocol treatment. Protocol treatment may not be administered by a local medical doctor (LMD).

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

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

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2*)

Brentuximab Vedotin	
	Starting Dose 1.8 mg/kg IV Day 1
1st dose reduction	1.2 mg/kg IV Day 1
2nd dose reduction	Discontinue

Nivolumab	
	Starting Dose 3.0 mg/kg IV Day 1
1st dose reduction	Discontinue

Note: If either drug is discontinued, the patient may continue treatment with the other drug. If both drugs are discontinued, the patient will go to event monitoring per Section 18.0.

8.2 Recommended Brentuximab Vedotin (BV) and Nivolumab Dose Modifications for Treatment-Associated Toxicity

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
AT TIME OF RETREATMENT			
Investigations	Platelet count decreased	Brentuximab Vedotin (BV) and Nivolumab	**Grade 3:** Hold both BV and nivolumab until grade 2 or better, then reinstitute BV at 1.2 mg/kg and resume nivolumab at same dose.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Investigations	Alanine aminotransferase Increased, Aspartate aminotransferase Increased, and/or Blood bilirubin increased **NOTE:** increased bilirubin does not factor into dose modifications if secondary to Gilbert's syndrome.	Brentuximab Vedotin (BV) and Nivolumab	**Grade 2 (>3 to 5 x ULN) AST or ALT elevations:** Omit dosing for nivolumab;continue BV at the same dose level. Nivolumab may be resumed if the value improves to Grade 1 (**≤3 x ULN**) or better. **Grade 2 Bilirubin elevations (>1.5 to 3 x ULN):** Omit dosing for nivolumab; continue BV at the same dose level. Nivolumab may be resumed if the bilirubin improves to **Grade 1 (>ULN to 1.5 x ULN)** or better. **Grade 2 (>3 to 5 x ULN) AST or ALT elevations WITH Grade 2 Bilirubin elevations (>1.5 to 3 x ULN):** Hold both nivolumab and BV until ALT/AST value improves to Grade 1 (**≤3 x ULN**) or better **and** bilirubin value improves to **Grade 1 (>ULN to 1.5 x ULN)** or better. **Grade 3 (AST or ALT, OR Bilirubin elevations)**: **Discontinue nivolumab;** hold dosing for BV until toxicity is ≤ **Grade 2** or has returned to baseline, then resume at the same dose level. **Grade 4 (AST or ALT, OR Bilirubin elevations)**: **Discontinue both nivolumab and BV.** Patient should go to event monitoring, per Section 18.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Investigations	Creatinine Increased	Nivolumab	Patients will be monitored for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (**Grade 4**) serum creatinine elevation and permanently **Discontinue** nivolumab; continue BV at the same dose level. For severe (**Grade 3**) or moderate (**Grade 2**) serum creatinine elevation, withhold nivolumab and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently **Discontinue** nivolumab; continue BV at the same dose level.
Investigations	Neutrophil (ANC) count decreased	Brentuximab Vedotin (BV) and Nivolumab	**≥Grade 3;** hold both BV and nivolumab until resolved to grade 1 (or baseline). At this point myeloid growth factors can be used at investigator's discretion. If not resolved to ≤Grade 1 or better within 28 days, discontinue nivolumab and BV. Patient should go to event monitoring per Section 18.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Amylase and/or lipase increase	Brentuximab Vedotin (BV) and Nivolumab	**Grade ≥ 3:** Hold BV and nivolumab until resolved to ≤Grade 2, then resume at same dose, per protocol. If there is clinical or radiographic evidence of pancreatitis, refer to pancreatitis AE actions (below).
Immune System Disorders	Immune system disorders-other	Nivolumab	If patient experiences immune-mediated rash **Grade 3**: Omit nivolumab dose until symptoms resolve and management with coritcosteroids is complete, and then restart at the same dose level. If reoccurance, discontinue nivolumab (continue brentuximab vedotin per protocol). **Grade 4:** Permanently discontinue nivolumab (continue BV per protocol). For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, omit nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to **Grade 1** or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event (continue BV per protocol).
Infections and Infestations	Encephalitis infection	Brentuximab Vedotin (BV) and Nivolumab	**Discontinue** Nivolumab if patient experiences immune-mediated encephalitis. Continue BV at same dose per protocol.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Nervous system disorders	Peripheral sensory neuropathy or peripheral motor neuropathy	Brentuximab Vedotin (BV)	**Grade 2** Reduce BV by 1 dose level and resume treatment; if already at 1.2 mg/kg, continue dosing at that level. **Grade 3** Omit BV until toxicity is ≤ Grade 2, then consult with PI **Grade 4** Discontinue BV. Continue Nivolumab at same dose per protocol.
Gastrointestinal disorders	Pancreatitis	Brentuximmab Vedotin and Nivolumab	**Grade 2** Omit nivolumab until resolution, maximum 3 weeks. If > 3 weeks, discontinue nivolumab ONLY (continue BV per protocol). **Grade 3 or Grade 4**, Discontinue BV . Hold nivolumab until grade 1 or better, then reintroduce. If it recurs, then discontinue nivolumab and patient should go to event monitoring, per Section 18.
Gastrointestinal disorders	Diarrhea	Brentuximab Vedotin (BV) and Nivolumab	**Grade ≥2**: Hold both BV and nivolumab until resolution to baseline grade **Grade 3**: Hold both BV and nivolumab and start corticosteroids until resolution to baseline grade. **Grade ≥4: Discontinue BV and Nivolumab.** Patient should go to event monitoring, per Section 18.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Gastrointestinal disorders	Colitis	Brentuximab Vedotin (BV) and Nivolumab	**Grade ≥2**: Hold both BV and nivolumab until resolution to baseline grade **Grade 3**: Hold both BV and nivolumab and start corticosteroids until resolution to baseline grade. **Grade ≥4: Discontinue BV and Nivolumab.** Patient should go to event monitoring, per Section 18.
General disorders and administration site conditions	Fatigue	Brentuximab Vedotin (BV) and Nivolumab	**Grade 3:** Hold both BV and nivolumab until grade 2 or better
Endocrine Disorders	Adrenal insufficiency Hypothyroidism, Hyperthyroidism, Endocrine Disorders-Other (i.e. Hypophysitis, diabetes)	Nivolumab	**Grade ≥3**: Omit nivolumab until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete, and then restart at the same dose level. If reoccurence, discontinue. (continue BV per protocol). Nivolumab should be continued in the presence of hormone replacement therapy, as long as no symptoms are present.
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Brentuximab Vedotin (BV) and Nivolumab	**Grade ≥2**: Hold both BV and nivolumab and start corticosteroids until resolution to baseline grade. **Grade ≥3**: **Discontinue BV and nivolumab** and initiate treatment with high doses of corticosteroids. Patient should go to event monitoring, per Section 18.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Respitory, thoracic and mediastinal disorders	Cough	Brentuximab Vedotin (BV) and Nivolumab	**Grade ≥2**: Hold both BV and nivolumab and start corticosteroids until resolution to baseline grade. **Grade ≥3**: **Discontinue BV and nivolumab** and initiate treatment with high doses of corticosteroids. Patient should go to event monitoring, per Section 18.
Respiratory, thoracic and mediastinal disorders	Dsypnea	Brentuximab Vedotin (BV) and Nivolumab	**Grade ≥3**: Hold both BV and nivolumab up to four weeksuntil resolution to baseline grade. If no resolution patient should go to event monitoring, per Section 18.
All other hematologic and non-hematologic	All other hematologic and non-hematologic	Brentuximab Vedotin (BV) and Nivolumab	**Grade ≥ 2**: Hold both BV and Nivolumab up to four weeks until resolution to Grade 1 or baseline. If no resolution patient should go to event monitoring, per Section 18.

* Located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

** 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 restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors is discouraged but if necessary should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendation for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006; 24:3187-3205, 2006.

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 anti-diarrheal, 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 As there is potential for hepatic toxicity with nivolumab or nivolumab combinations, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab-containing regimen.

9.6 Please refer to Appendix V for additional Adverse Event Management Algorithms

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure. 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, 5 days or 10 days 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 10.52and 18.0).

10.11 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**.

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. If patient is hospitalized, please follow normal reporting criteria. These events must still be reported via Routine Reporting (see Section 10.52). *

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not require expedited reporting.
Investigations	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood count	≤Grade 4
	Lymphocyte count decreased	≤Grade 4
Blood and lymphatic system disorders	Anemia	≤Grade 4

*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.

10.334 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.

10.3341 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 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 [provided upon request from BMS].

10.3342 Seattle Genetics Reporting: Based on the estimated date of conception, all pregnancies that occur from time of informed consent to within 6 months of last study drug dose, including any pregnancies that occur in the partner of a male study patient, are required to be reported to Seattle Genetics within 48 hours of becoming aware of such pregnancy. Email or fax the Seattle Genetics Pregnancy Report Form to [redacted] (USA only toll free). The Seattle Genetics Preganancy Report Form can be found posted with the protocol on the ACCRU website.

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 a SAE. Congenital anomalies or birth defects, as defined by the ‘serious’ criterion above should be reported as SAEs.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 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.	7 Calendar Days	24-Hours; 1 Calendar Day
Not resulting in Hospitalization ≥ 24 hrs.	Not required	

Note: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.32

Expedited AE reporting timelines are defined as:

- "24-Hour; 1 Calendar Day" - 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.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

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

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- 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 5, 2011

- Follow site-specific reporting guidelines.
- Submit the ACCRU Adverse Event Expedited Report Form to the ACCRU SAE Coordinator via fax [redacted] The ACCRU SAE Coordinator will forward to Bristol-Myers-Squibb and Seattle Genetics.
- ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU SAE Coordinator will also fax or e-mail to Seattle Genetics at: Facsimile [redacted] or Email: [redacted]
- 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 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]

10.53 Serious Adverse Event Collection and Reporting
Following the subject's written consent to participate in the study, all SAEs, related or not related to study drug, must be collected, including those thought to

be associated with protocol-specified procedures. All SAEs must be collected that occur after discontinuation of dosing (please refer to test schedule). All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure. SAEs, whether related or not related to study drug, and pregnancies must be reported to ACCRU within 24 hours and the ACCRU SAE coordinator will report to BMS within 1 business day. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

10.54 Baseline and Adverse Events Evaluations

Pre-treatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class	**Adverse event/Symptoms**	**Baseline**	**Each evaluation**
Nervous System Disorders	Peripheral motor neuropathy	X	X
Investigations	Creatinine increased	X	X
Respiratory, thoracic and mediastinal disorders	Pneumonitis	X	X
	Dyspnea	X	X

10.55 **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)

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

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

10.553 Grade 5 AEs (Deaths)

10.5531 Any death within 100 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5532 Any death more than 100 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.

10.56 Late Occurring Adverse Events

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).

11.0 Treatment Evaluation

Lugano Classification Response Criteria

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 post cycle 2 of chemotherapy and 6-8 weeks post cycle 8 of chemotherapy. During observation, CT scan should be obtained every 3 months during the first year 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). Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (eg, hepatic nodules) may be included in the six representative, measured lesions. A measurable extranodal lesion should have an LDi greater than 1.0 cm. 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).

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.

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 extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† 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	Individual target nodes/nodal masses must regress to ≤ 1.5 cm in LDi 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 lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not Applicable
Progressive disease	**Progressive metabolic disease (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. A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (eg, hepatic nodules) may be included in the six representative, measured lesions. A measurable extranodal lesion should have an LDi greater than 1.0 cm. 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

12.1 Group: Age ≥60 years old vs. Age < 60 years old and unable to receive standard ABVD chemotherapy

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients will be evaluated for response after 2 cycles of treatment. Patients who are NMR or PMD after 2 cycles of treatment will discontinue treatment and go to the event-monitoring phase per Section 18.0. Patients who are CMR or PMR will continue treatment per protocol.

13.2 Patients who develop progressive disease by either PET-CT based (PMD) or CT based (PD) response criteria (see Section 11.0) at any time while receiving therapy or during observation will go to the event-monitoring phase per Section 18.0.

13.3 Patients who go off protocol treatment for unacceptable adverse events, subsequent treatment or refusal will go to the event-monitoring phase per Section 18.0.

13.4 Observation: The patient will be observed every 30 days x90 days then every 90 days x 2.5 years, then every 6 months until 5 years from registration. If the patient develops disease progression (see section 13.2) or receives subsequent treatment before disease progression while in observation, they will go directly to the event monitoring phase per section 18.0.

13.5 Patients who achieve a PMR or CMR will receive a maximum total of 8 cycles of treatment. After 8 cycles, they go to observation per Section 13.4 above.

13.6 Early Safety Analysis Phase Only: If a patient fails to complete the first cycle (21 days) of treatment for reasons other than toxicity, the patient will be regarded as in evaluable and will be replaced.

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 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 being processed and submitted by participating site**	**Cycles 1-8 Day 1 Pre-treatment**	**6-8 weeks after Day 1 of Cycle 8**	**End of Treatment, If discontinued early(At PMD or PD, withdrawal or removal)**	**At time of PMD or PD**	**Additional processing required at site after blood draw?**	**Storage /shipping conditions[1]**
Mandatory	SST (Marble top)	8.5 ml (1)	Whole blood	X	X	X	X	No	Refrigerated / Do not Freeze
Mandatory	EDTA (purple top)	10 mL (2)	Whole blood	X	X	X	X	No	Refrigerated / Do not Freeze

After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see below for detailed shipping instructions.)

14.2 **Kits *will* be used for this study** and will be contain supplies for collecting, processing and shipping specimens.

14.21 Participating institutions may obtain kits by e-mailing [redacted] E-mail requests should include the site address, contact information and number of kits being requested.

14.22 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. Please allow 3 to 4 business days to receive the kits.

14.23 Any questions concerning sample collection and [redacted]

14.24 Peripheral Blood
Draw 8.5 mL of peripheral blood into one SST (marbled) collection tube and 20 mL of peripheral blood into two lavender top EDTA tubes. It is important to thoroughly mix the samples with the anticoagulant agent by gently inverting the tubes not less than five times.

14.3 Shipping and Handling

14.31 **Samples are to be collected Monday through Thursday ONLY.** Samples are to be shipped the same day they are collected. **NOTE:** Friday and Pre-Holiday shipments should be avoided.

Samples are to be shipped to:

[redacted]

Please e-mail [redacted] to notify the laboratory when specimens are being shipped. The message should include the study name, sample type(s), FedEx airbill tracking number, contact name and telephone number.

14.4 Study Methodology and Storage Information

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

14.411 DNA extraction and storage of DNA for future pharmacogenetic assays (e.g., for genetic polymorphisms such as PD-L1/2, EZH2, MEF2B, ARID1A, CARD11, FOXO1, CREBBP and EP300 that may correlate with efficacy and tolerability. Dr. Stephen Ansell's laboratory Stabile 6-28 will initially analyze a portion of the DNA for the presence of using standard laboratory protocols. Remaining DNA will be stored frozen at -70ºC by Dr. Stephen Ansell's Lab, according to patient consent information) 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.)

14.412 A portion of the serum/plasma will initially be analyzed for the presence of Cytokines and T-Cells in Dr. Stephen Ansell's laboratory using standard laboratory protocols. According to patient consent information remaining serum/plasma will be stored frozen at -70ºC by Dr. Stephen Ansell's Lab, 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.)

14.414 As part of ongoing ACCRU research, we will collect serum/plasma for future research studies, according to patient consent information on molecular determinants of efficacy and tolerability. Samples will be stored frozen at -70ºC by Dr. Stephen Ansell's Lab until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

14.5 Return of Genetic Testing Research Results

For this study, DNA specimens are only being banked and no specific genetic testing is being performed. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sough 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.

14.51 Peripheral blood assays

14.511 Serum cytokine analysis: Serum cytokine levels have been shown to be prognostic in Hodgkin lymphoma [Marri]. Samples will be subjected to multiplex ELISA (Invitrogen, Camarillo, CA) to measure 30 serum cytokines in pre-treatment blood samples. Luminex-200 system version 1.7 will be used for reading plates and MasterPlex QT1.0 system (MiraiBio) will be used to analyze data. Cytokines will include epidermal growth factor (EGF), eotaxin, basic fibroblast growth factor (FGF-b), granulocyte macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), IFN-α, IFN-ϒ, interleukin 1 receptor antagonist (IL-1RA), IL-1β,IL-2, IL-2R , IL-4, 5, 6, 7, 8, 10,12,13,15,17, Inducible protein-10 (IP10/CXCL10), monocyte chemotactic protein 1(MCP-1), monokine induced by interferon γ, (MIG/CXCL9), MIP-1α (CCL3), MIP1β (CCL4), regulated on activation normal T-cell expressed and secreted (RANTES),TNF-α and vascular endothelial growth factor (VEGF). Internal control serum will be included in all assays to control for interassay variation.

14.512 Flow cytometry: To define changes in peripheral blood cell populations after treatment with brentuximab vedoton and nivolumab, peripheral blood ononuclear cells will be stained with fluorochrome-conjugated antibodies to human CD69 (R&D Systems), CD3 (clone HIT3a), CD19 (clone 4G7), PD1 (clone EH12.1), CD14 (clone M5E2), CD163 (clone GH1/61), CD21 (clone B-ly4), CD273 (clone M1H18), CD274 (clone M1H1), TIM3 (clone 344823), and CD23 (clone EBVCS-5; all obtained from BD Biosciences) and the data will be analyzed using CellQuest software (Becton Dickinson).

15.0 Drug Information

IND number128842 (for combination of both drugs)

- Investigator brochures will be available on the ACCRU website.

15.1 Brentuximab vedotin (SGN-35, Adcetris®)

15.11 **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.

15.12 **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.

15.13 **Preparation and storage**:
Vials containing brentuximab vedotin must be stored under refrigeration at 2-8°C.

If an excursion occurs, refer to the study-specific Stability Data document which has stability data for each product supplied by Seattle Genetics that used in the study. If the excursion is between the Acceptable Low Temperature and the Acceptable High Temperatures (the green range) and does not exceed the Maximum out of Range Time, the excursion does not need to be reported. If the excursion is outside of either the acceptable temperature range (the red range) or time range, the product should be quarantined and the excursion should be reported to Seattle Genetics.

Report excursions using FM-244 Investigational Product Quality Complaints and Temperature Excursions Form. Found as a free standing document on the ACCRU Website.

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 an infusion 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.

15.14 **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.

15.15 **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 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 increases 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.

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. Unless otherwise specified in the clinical study protocol, the recommended starting dose in patients with hepatic impairment or severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. 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.

15.16 **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.

15.17 **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, abdominal pain, constipation
Hematologic & oncologic: Neutropenia, anemia, thrombocytopenia
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

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.

See the current version of the Investigator's Brochure for more comprehensive toxicity data.

15.18 **Drug procurement:**

15.181 Brentuximab vedotin will be provided in 50mg vials free of charge from Seattle Genetics for investigational use to Almac, Inc. Each participating ACCRU treating location will order the drug from Seattle Genetics/Almac, Inc. E-mail or Fax the Drug Order Request Form (found on the ACCRU website) to:

Note: Allow 7 business days to process drug order requests.

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of Brentuximab Vedotin and Nivolumab and will use the appropriate Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 **Nursing Guidelines**

15.191 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.

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

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

15.194 Rash is common. Rarely patients can devlope Steven's Johnson Syndrome or TENS. Instruct patient to report any rash. Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.

15.195 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.

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

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

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

15.199a Monitor for respiratory symptoms (cough, URI). Treat symptomatically and monitor for effectiveness. 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.

15.199b Assess patients medications. Patients who are taking medications that are CYP3A4 inhibitors (i.e ketoconazole) should be closely monitored for adverse reactions. 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.

15.199e 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.

15.199g 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.

15.199h Pancreatitis is possible with nivolumab. Instruct patients to report abdominal pain, nausea and vomiting to the study team.

15.199i 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.

15.199j Monitor renal function as patients may experience acute interstitial nephritis. Report any increase of levels to the study team.

15.2 **Nivolumab (Opdivo®, BMS-936558)**

15.21 **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.

15.22 **Formulation**: Available for injection 10mg/ml (4mL, 10mL, 24mL) in a single-use vial [contains in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), polysorbate 80, and water for injection]

15.23 **Preparation and storage**: When the dose is based on patient weight (ie, 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 not 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. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions"

15.24 **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.

15.25 **Pharmacokinetic information**:
Distribution: Vd: 8 L
Half-life elimination: ~27days
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).

15.26 **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.

15.27 **Known potential toxicities**: (from package insert): Consult the package insert for the most current and complete information.

Very common known potential toxicities (>10%):
Cardiovascular: Edema (≤13%), peripheral edema (≤13%), hypertension (11%)
Central nervous system: Fatigue (≤59%), malaise (≤46%), headache (16% to 23%), dizziness (≤14%), peripheral neuropathy (≤14%; grade 3: <1%)
Dermatologic: Skin rash (1% to 40%; immune-mediated: 9% to 16%), pruritus (10% to 28%), vitiligo (≤11%)
Endocrine & metabolic: Hyperglycemia (19% to 46%), hyponatremia (19% to 41%), increased serum triglycerides (32%), hyperkalemia (11% to 30%), increased thyroid stimulating hormone level (≥10% to 26%), hypocalcemia (10% to 26%), increased serum cholesterol (21%), hypercalcemia (2% to 19%), thyroiditis (≤12% to 18%; including immune-mediated events), hypomagnesemia (14% to 17%), hypokalemia (14% to 16%), thyroid dysfunction (15%), hypothyroidism (≤12%; including immune-mediated events)
Gastrointestinal: Diarrhea (1% to 43%), nausea (20% to 34%), abdominal pain (13% to 34%), increased serum lipase (20% to 33%), decreased appetite (14% to 28%), vomiting (12% to 28%), constipation (10% to 23%), increased serum amylase (13% to 19%)
Genitourinary: Urinary tract infection (2% to 17%)
Hematologic & oncologic: Anemia (26% to 50%; grades 3/4: 3% to 8%), lymphocytopenia (27% to 42%; grades 3/4: ≤11%), leukopenia (11% to 38%; grades 3/4: ≤5%), thrombocytopenia (15% to 37%; grades 3/4: 1% to 3%), neutropenia (13% to 37%; grades 3/4: 4% to 5%)
Hepatic: Increased serum alkaline phosphatase (10% to 37%), increased serum aspartate aminotransferase (22% to 33%), increased serum alanine aminotransferase (23% to 32%), increased serum bilirubin (11% to 14%)
Immunologic: Graft versus host disease (20%; within 14 days of stem cell infusion), antibody development (11%; neutralizing: <1%)
Neuromuscular & skeletal: Asthenia (≤57%), musculoskeletal pain (20% to 42%), back pain (21%), arthralgia (10% to 21%)
Renal: Increased serum creatinine (12% to 42%)
Respiratory: Upper respiratory tract infection (2% to 44%), cough (≤36%), productive cough (≤36%), dyspnea (≤27%), dyspnea on exertion (≤27%), bronchopneumonia (≤13%), pneumonia (≤13%), nasal congestion (11%)
Miscellaneous: Febrile reaction (35%; events without an infectious cause that required steroids), fever (≤29%; may include tumor-associated fever), infusion-related reaction (≤14%)

Cardiovascular: Pulmonary embolism (2% to 3%)
Central nervous system: Neuritis (<10%), peripheral nerve palsy (peroneal: <10%), insomnia (9%)
Dermatologic: Erythema of skin (10%), xeroderma (7%)
Endocrine & metabolic: Weight loss (7% to 8%), hyperthyroidism (3% to 6%; including immune-mediated events), adrenocortical insufficiency (1%; including immune-mediated events), increased gamma-glutamyl transferase
Gastrointestinal: Intestinal perforation (<10%), stomatitis (<10%), colitis (including immune-mediated events: ≤6%)

Hepatic: Hepatitis (immune-mediated: 2% to 3%)
Immunologic: Sjogren's syndrome (<10%)
Infection: Sepsis (≥2%, systemic inflammatory response)
Neuromuscular & skeletal: Myopathy (<10%), rheumatism (spondyloarthropathy: <10%)
Renal: Acute renal failure (≥2%), nephritis (≤1%; immune-mediated), renal insufficiency (≤1%; immune-mediated)
Respiratory: Interstitial pulmonary disease (6%), pneumonitis (≤6%; including immune-mediated events), pleural effusion (1% to 5%), respiratory failure (≥2%)

Frequency not defined:
Central nervous system: Migraine
Dermatologic: Acneiform eruption, bullous dermatitis, dermatitis, erythematous rash, exfoliative dermatitis, maculopapular rash, morbilliform rash, palmar-plantar erythrodysesthesia, psoriasiform eruption, pustular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
Endocrine & metabolic: Dehydration
Gastrointestinal: Abdominal distress
Neuromuscular & skeletal: Limb pain

Rare known potential toxicities (<1%), postmarketing, and/or case reports: Demyelinating disease (immune-mediated), diabetic ketoacidosis, duodenitis (immune-mediated), encephalitis (limbic/lymphocytic/viral; may be immune-mediated), facial nerve paralysis (immune-mediated), gastritis (immune-mediated), Guillain-Barré syndrome, hepatic sinusoidal obstruction syndrome, hypophysitis (including immune-mediated events), immunological signs and symptoms (hemophagocytic lymphohistiocytosis) (Hantel 2018), iritis (immune-mediated), lymphadenitis (immune-mediated; histiocytic necrotizing lymphadenitis [Kikuchi lymphadenitis]), motor dysfunction (immune-mediated), myasthenia (myasthenic syndrome), myocarditis (immune-mediated), myositis (immune-mediated), neuropathy (autoimmune; immune-mediated), pancreatitis (immune-mediated), pituitary insufficiency (immune-mediated), pneumonia due to Pneumocystis jirovecii, polymyalgia rheumatica (immune-mediated), rhabdomyolysis (immune-mediated), sarcoidosis (immune-mediated), sixth nerve palsy (abducens nerve palsy; immune-mediated), type I diabetes mellitus (immune-mediated event), uveitis (immune-mediated), vasculitis, Vogt-Koyanagi-Harada syndrome

15.28 **Drug procurement:** Investigational nivolumab is provided free of charge to patients by Bristol-Myers Squibb Research and Development.

15.281 Nivolumab will be provided free of charge from Bristol-Myers Squibb for investigational use to Clinical Research Services, a division of Rx Crossroads by McKesson. Each participating ACCRU treating location will order the drug from Clinical Research Services, a division of Rx Crossroads by McKesson.
Fax the Drug Order Request Form (found as a stand alone document) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of Nivolumab and will use the appropriate Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29 **Nursing Guidelines**

15.291 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 off 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.

15.292 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.

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

15.294 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.

15.295 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.

15.296 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.

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

15.298 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.

15.199a Monitor renal function as patients may experience acute interstitial nephritis. Report any increase of levels to the study team.

15.199b 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 it is crucial that they stay in touch with their transplant team during treatment.

15.199c Patients who have undergone allogeneic 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 is a phase II study of nivolumab and brentuximab vedotin in patients with untreated Hodgkin lymphoma ≥ 60 years old or under 60 and unable to receive standard ABVD chemotherapy. The study is designed to assess the overallmetabolic response rate using a single stage phase II study design with an interim analysis. Accrual will be halted after 6 patients to assess safety (see Section 16.4). We do not plan to halt accrual during the interim analysis (see Section 16.214).

16.11 Primary Endpoint: The primary endpoint of this trial is the rate of overall metabolic response. A metabolic response is defined as a patient who has achieved an objective status of PMR or CMR at the end of cycle 8. Throughout Section 16.0, metabolic response will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation or are replaced in the safety analysis phase per Section 13.6. If the safety analysis determines that a reduction to the starting dose is warranted, only patients treated at the final dose level will be included when evaluating the decision rules in Sections 16.211 and 16.212. Patients treated at other dose levels will be summarized separately.

16.2 Statistical Design:

16.21 Decision Rule:

In a single-agent front-line phase II study of HL patients ≥ 60 years-old treated with brentuximab vendotin, the interim analysis of 27 patients reported rate of 93%[6] . This study will look at responses maintained until the end of cycle 8 and will utilize an updated response criteria that assesses metabolic response (Cheson 2014). Considering these factors, along with heterogeneity of disease in patients with HL and a broader eligibility criteria that includes patients < 60 years old with other co-morbidities, an overall metabolic response rate of greater than 65% for brentuximab vendotin with the addition of nivolumab would be of interest for this study.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 65%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 80%. The following one–stage design with an interim analysis is based on a two-stage Simon optimum design and requires 56 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 65%.

16.211 Interim Analysis: Enter 25 evaluable patients into the study. If 17 or fewer successes are observed in the first 25 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of successes is at least 18, we will continue accrual.

16.212 Final Decision Rule: Enter an additional 31 evaluable patients into the study. If 40 or fewer successes are observed in the first 56 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 41, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.213 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 Section 16.313.

16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 25 patients to become evaluable, unless undue toxicity is observed. Given the limited

overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.22 Sample Size: The one stage study design with an interim analysis to be used is fully described above. A minimum of 25 and a maximum of 56 evaluable patients will be accrued onto this phase II study at the final dose level determined in the safety analysis phase, unless undue toxicity is encountered. An additional one or two cohorts of 6 patients will be accrued if the early safety analysis determines that a reduction to the starting dose is warranted for up to 12 additional evaluable patients. We anticipate accruing up to an additional 7 patients (2 safety analysis, 5 phase II) to account for ineligibility, cancellation, major treatment violation, or other reasons (i.e. replacement of a safety analysis patient) for a total of 75 patients overall.

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 25-30 evaluable patients per year. At this rate, it will likely take about 3 years to enroll all patients. The maximum total study duration is expected to be approximately 3.5 years, or until the last patient accrued has been observed for at least 6 months.

16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.65	0.70	0.75	0.80
Then the probability of declaring that the regimen warrants further study is…	0.10	0.29	0.59	0.85
And the probability of stopping at the interim analysis is…	0.69	0.49	0.27	0.11

16.25 Other considerations: 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

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with ACCRU Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint of this trial is the rate of overall metabolic response. A metabolic response is defined as a patient who has achieved an objective status of PMR or CMR at the end of cycle 8. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will

be evaluable for metabolic response, unless they are determined to be a major violation or are replaced in the safety analysis phase per Section 13.6. If the safety analysis determines that a reduction to the starting dose is warranted, only patients treated at the final dose level will be included when evaluating the decision rules in Sections 16.211 and 16.212. Patients treated at other dose levels will be summarized separately.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.

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 any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.32 Secondary Outcome Analyses

16.321 The complete metabolic response rate will be estimated by the total number of complete metabolic responses (CMR) divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true complete metabolic response rate will be calculated.

16.322 Duration of response is defined for all evaluable patients who have achieved a response as the date at which the patient's objective status is first noted to be a CMR or PMR to the earliest date progression (PMD or PD) is documented. If a patient has not had disease progression, they will be censored on the date of their last disease assessment The distribution of duration of response will be estimated using the method of Kaplan-Meier.

16.322 Progression-free survival is defined as the time from registration to the earliest date of documentation of disease progression (PMD or PD) or death due to any cause. If a patient is alive and has not had disease progression, they will be censored on the date of their last disease assessment. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

16.323 Overall survival time is defined as the time from registration to death due to any cause. If a patient is still alive, they will be censored on the date of their last follow-up. The distribution of overall survival will be estimated using the method of Kaplan-Meier.

16.324 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). Adverse events will be assessed using CTCAE version 4.0 per Section 10.0. 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.

16.33 Correlative Outcome Analyses: Due to the small overall sample size, the results of these analyses will be considered exploratory and hypothesis-generating in nature.

16.331 Biomarkers including intratumoral cell populations, genetic variability, serum cytokines, and T-cell activation will be evaluated both before and during treatment. Baseline values and changes in these parameters over time will be both graphically

and quantitatively summarized and explored. Standard paired comparisons methodologies (paired t-tests, Wilcoxon signed rank tests and Fisher's exact tests for interval, ordinal and nominal level data, respectively) will be used to assess changes in these variables before and after therapy. In addition, baseline values and changes over time in each measure will be explored in relation to clinical outcome to explore any differences between responders and non-responders and by depth of response (CMR vs. PMR) to identify potential biomarkers.

16.4 Early Safety Analysis: An early safety analysis will be performed after the first 6 patients have been accrued to the study at dose level 1 and observed for one cycle. If 2 or more of the first 6 patients experience a DLT as defined in Section 7.12, then the starting dose level will be adjusted and additional cohorts may be evaluated at dose levels -1 and -2 as described below. Accrual will be halted while evaluating each cohort in the early safety analysis.

16.41 Dose level +1: Six evaluable patients will be accrued onto dose level +1 and observed until they complete one cycle treatment. If 0 or 1 out of 6 patients experience a DLT, accrual will continue in the phase II portion at dose level 1. If 2 or more patients experience a DLT on dose level +1, the toxicity level for dose level +1 will be considered unacceptable and six additional patients will be treated on dose level -1.

16.42 Dose de-escalation to Dose level -1: If dose level +1 has an unacceptable level of toxicity, six evaluable patients will be accrued onto dose level -1. If 0 or 1 out of 6 patients experience a DLT on dose level -1, accrual will continue in the phase II portion at dose level -1. If 2 or more patients experience a DLT, the toxicity level for dose level -1 will be considered unacceptable and six additional patients will be treated on dose level -2.

16.43 Dose escalation to Dose level -2: If dose level -1 has an unacceptable level of toxicity, six evaluable patients will be accrued onto dose level -2. If 0 or 1 out of 6 patients experience a DLT on dose level -2, accrual will continue in the phase II portion at dose level -2. If 2 or more patients experience a DLT, the toxicity level for dose level -2 will be considered unacceptable and accrual to the study will be temporarily closed, evaluated and potentially amended.

16.5 Data & Safety Monitoring:

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

16.52 Adverse Event Stopping Rules (to include all patients treated at the dose level determined in the early safety analysis): The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping 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 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

- if after the first 15 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

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.

16.6 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 [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3.5 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 6 months.

16.7 Inclusion of Women and Minorities

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

16.72 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.

16.73 The geographical region served by ACCRU has a population which includes approximately 5-7% minorities. Based on prior ACCRU studies involving similar disease sites, we expect about 5-7% of patients will be classified as minorities by race and about 50% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	36	37	0	73
Ethnic Category: Total of all subjects*	37	38	0	**75**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	1	0	1
Black or African American	1	1	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	36	36	0	72
Racial Category: Total of all subjects*	37	38	0	**75**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens:

17.1 Tissue Biospecimen Submission

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**
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (**OR (10) 5 micron** unstained slides with corresponding H&E)**	Mandatory	Within ≤14 days following registration	Correlative biomarkers, tumor genetic variability and Banking	Section 17.31

17.2 Paraffin Embedded Tissue Blocks/Slides

17.3 Submit one formalin fixed paraffin-embedded (FFPE) tissue block Biopsy material obtained at the time of recurrence is preferred, but if not available, biopsy material obtained at the time of initial diagnosis of Hodgkin Lymphoma may be submitted *OR* Please submit biopsy material from each surgery.) **A corresponding H&E slide for each submitted block must be provided** to permit quality assessment of each tissue block.

17.31 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut (11) 5 micron unstained slides and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** H&E stain the first slide (i.e., slides labeled 1, 11, etc.). These H&E slides will be reviewed centrally under the research base's protocol for assessing tissue quality. **Do not bake or place covers slips on the slides.**

17.32 The following materials below are mandatory and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide (OR (10) 5 *micron* unstained slides with corresponding H&E(s)).

17.33 [redacted] to notify Mayo Clinic Reference Laboratory when the specimen(s) are being shipped.

17.34 Specimens should be shipped to the following address:

[redacted]

17.4 Tumor Assays

17.41 Immunohistochemistry (IHC): Previous studies of tumor biomarkers have shown that the tumor microenvironment in Hodgkin lymphoma is very important. These studies have shown that the number, phenotype and distribution of intratumoral immune cells predicts response to therapy. To confirm the prognostic or predictive role of immune cells in patients with Hodgkin lymphoma treated with brentuximab vedotin and nivolumab, we will use submitted paraffin-embedded tissue to measure the T-cell and macrophage infiltrate and correlate cell numbers and location with patient response and progression – free survival. As described above, serial 5-µm paraffin-embedded sections will be used for IHC. The tissue will be deparaffinized with three changes of xylene and cleared through graded series of ethanol. Endogenous peroxidase will be quenched by incubation in 50% methanol/H_2O_2 and after rinsing with tap water; all sections will be pretreated for 30 minutes with 50 mmol/L EDTA using a steamer and cooled for additional 5 minutes.

All staining will be done automatically on DAKO Autostainer using the following antibodies to CD11c (Leica Microsystems 5D11), CD14 (Cell Marque EPR 3653), CD163 (DAKO 1F8), CD68 (DAKO PG-M1), CXCL13 (R&D Systems 53610), FOXP3 (Abcam 236AE/7), CD3 (R&D Systems), PD-L1 (405.9A11), PD-L2 (366C.9E5) and PD-1 (Abcam NAT). The sections will be viewed with an Olympus BXFA51 microscope and pictures taken with an Olympus DP71 camera.

17.42 Fluorescence in situ hybridization (FISH): FISH will be performed on Hodgkin lymphoma tissue sections to assess copy number on chromosome 9p24.1. The bacterial artificial chromosome probes (CHORI; www.chori.org) RP11-599H2O, which maps to 9p24.1 and includes *CD274* (encoding PD-L1, labeled with Spectrum Orange), and RP11-635N21, which also maps to 9p24.1 and includes *PDCD1LG2* (encoding PD-L2, labeled with Spectrum Green), will be cohybridized. A control centromeric probe, Spectrum Aqua–labeled *CEP9* (Abbott Molecular) that maps to 9p11-q11, will be hybridized according to the manufacturer's recommendations. Malignant Reed–Sternberg cells will be identified by means of nuclear morphologic features, and all such cells will be analyzed. Nuclei with a target:control probe ratio of at least 3:1 will be classified as amplified, those with a probe ratio of more than 1:1 but less than 3:1 will be classified as relative copy gain, and those with a probe ratio of 1:1 but with more than two copies of each probe will be classified as polysomic for chromosome 9p.

17.43 Molecular Signature: We will define the intratumoral molecular signature predictive of response to therapy in patients with Hodgkin lymphoma. We will use a previously described gene expression profile and optimize it for use in paraffin-embedded tissue [Sriedl et al]. The coefficients and the capture-based hybridization pipeline designed for formalin-fixed, paraffin-embedded tissues (FFPET) will be used. The genes include *CSFR1, PD-L1, PD-L2, EZH2, MEF2B, ARID1A, CARD11, FOXO1, CREBBP* and *EP300*. In addition, gene signatures downstream of specific mutations will be explored using a paraffin-based approach that follows gene set enrichment analysis of mutated cases. The signature(s) will be used to explore their ability to select cases with inferior outcomes.

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 Brentuximab vedotin and Nivolumab will be provided by Seattle Genetics and Bristol-Myers Squibb respectively, at no charge.

19.3 Tests to be research funded:

19.31 Mandatory blood and tissue samples for research.

[redacted]