A PHASE I/II STUDY OF GEMCITABINE, BENDAMUSTINE, AND NIVOLUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Patient Eligibility (See Protocol for Full Criteria)

Histologically confirmed classical Hodgkin lymphoma that is recurrent or refractory after at least one prior therapy.
No history of severe pneumonitis
Measurable Disease
Prior stem cell transplant is permitted but no active GVHD
Non-pregnant and non-nursing

Initial Required Laboratory Values

ANC $\geq$ 1000/μL*
Platelets $\geq$ 75,000/μL*
Creatinine Clearance ≥50mL/min
Bilirubin $\leq$ 2.0mg/dL
AST/ALT $\leq$ 2.0 x ULN
*Except in instance of bone marrow involvement

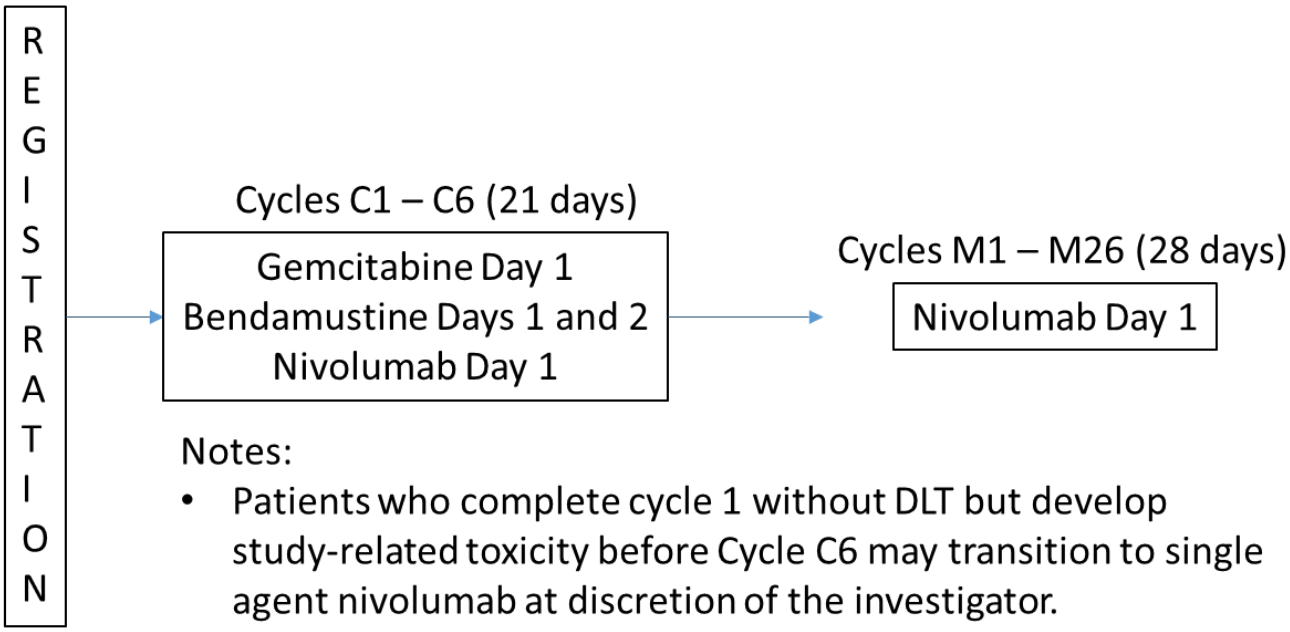
Staging and Entry Parameters

History and physical examination.
CBC with differential
Creatinine, bilirubin, AST, ALT, ESR
PET/CT scan

TREATMENT SCHEMA FOR COMBINATION CYCLES

Phase I Dose Escalation Schema Cycle Length: 21 days			
Dose level	Gemcitabine (mg/m^2) IV over 30 minutes day 1	Bendamustine (mg/m^2) IV over 30 minutes days 1 and 2	Nivolumab (mg) on day 1
-3	800	75	140
-2	800	90	140
-1	800	90	240
1	1000	90	240
2	1000	120	240

NOTE: Maintenance dosing will be nivolumab monotherapy 480mg IV day 1 of 28 day cycle.



Notes:

- Patients who complete cycle 1 without DLT but develop study-related toxicity before Cycle C6 may transition to single agent nivolumab at discretion of the investigator.
- Patients will receive nivolumab 480mg on day 1 of all maintenance cycles regardless of dose level during the combination phase.

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1.0 INTRODUCTION

1.1 RELAPSED HODGKIN LYMPHOMA

Most patients with classical Hodgkin lymphoma will be cured with combination chemotherapy, with long-term progression-free survival (PFS) ranging from 75% to 82% for patients treated with ABVD or brentuximab vedotin + AVD.[1,2] However, this approach is not curative in all patients, and patients who relapse will require additional therapies. Currently, patients with relapsed Hodgkin lymphoma who are fit receive intensive salvage therapies including ICE, GVD, or others followed by autologous stem cell transplantation (ASCT).[3-5] Despite the use of high dose therapy, up to 50% of patients who complete stem cell transplantation will relapse and still others will either be poor candidates for ASCT or will not achieve adequate disease control to proceed to transplant. As a result, alternative approaches are needed for the subset of patients who are not cured with currently available therapies.

During the past few years, 3 agents have been approved for management of relapsed Hodgkin lymphoma: brentuximab vedotin, nivolumab, and pembrolizumab. Brentuximab vedotin (BV) is a CD30-directed antibody drug conjugate with an overall response rate (ORR) of 75% in patients with relapsed classical HL who had progressed after ASCT.[6] This agent has also been evaluated as post-transplant maintenance therapy in patients with high risk relapsed disease undergoing ASCT (based on extranodal site of relapse, early relapse, or poor response to salvage therapy), and use of BV post-transplant was associated with an improvement in PFS (median 43 months vs 24 months) when compared to those patients who did not receive BV. Most recently, BV has been evaluated in combination with AVD in the upfront setting, where there was a statistically improved modified PFS when compared to the standard, ABVD.[2] As a result of these studies, BV has been integrated into the standard approach to patients with HL. However, BV is not effective in all patients, is not curative, and can be associated with significant toxicities including neuropathy, neutropenia, and others. As a result, most patients who receive BV for management of relapsed disease will require additional therapies.

1.2 PD1 Inhibition in Hodgkin Lymphoma

The pathology of classical HL includes rare Reed-Sternberg cells surrounded by an immune infiltrate, and the role of the immune system in the development and progression of HL has been well-described. The programmed death-1 (PD-1) pathway has been identified as a critical component of disease progression in HL, as Hodgkin RS cells commonly overexpress PD-1 ligand and have been shown to have amplification of chromosome 9p24.1, where genes encoding PD-1 and PD-1 ligand reside.[7] This is felt to suppress the surrounding immune cells and permit the Hodgkin RS cell to continue to grow and proliferate, and these findings result in a rationale for targeting of the PD-1 axis in classical HL.

Two PD-1 antibodies have been approved for use in relapsed/refractory classical Hodgkin Lymphoma: pembrolizumab and nivolumab. Nivolumab was initially evaluated in a phase 1 study across lymphoid malignancies, where the ORR ranged from 15-40% based on underlying histology, which included both T-cell and B-cell NHL.[8] A separate study in classical Hodgkin Lymphoma demonstrated an even higher ORR of 87% with a CR rate of 17%.[9] As a result, a phase 2 study of nivolumab in classical HL was conducted which included patients relapsed after autologous stem cell transplantation, with variable prior exposure to brentuximab vedotin.[10] The ORR in this study was 66%, and subsequent follow-up for this study has now been published and has identified durable remissions. In addition, as opposed to conventional chemotherapy, patients with classical HL who receive nivolumab have been able to safely receive therapy beyond radiographic progression.[11] As a result, the management of patients receiving checkpoint inhibitors requires careful clinical assessment in addition to radiographic restaging. Despite the fact that radiographic response may not fully reflect disease activity in HL patients receiving checkpoint inhibitors, the majority of patients will not achieve a CR and nearly all will eventually have true relapse requiring additional therapy. However, the use of PD1 antibodies in patients in combination with chemotherapy in HL has been limited, and it is possible that achievement of a CR with combination therapy followed by maintenance with nivolumab may significantly prolong remissions for patients with relapsed/refractory disease.

1.3 Gemcitabine and Bendamustine in Relapsed/Refractory Hodgkin Lymphoma

Despite the proliferation of novel therapies in relapsed/refractory HL, current non-transplant therapies are not curative, and many patients require additional lines of treatment. In addition, brentuximab vedotin is now being utilized more frequently in the front-line setting and as post-transplant consolidation for high-risk patients with relapsed/refractory disease and so may be less useful in the setting of a post-transplant relapse.

Gemcitabine has been utilized in relapsed/refractory HL in a number of settings, both before and after ASCT.[5,12,13] For example, in combination with vinorelbine and doxil, the ORR is 75% in patients with relapsed/refractory HL. Additional chemotherapy agents such as bendamustine have also been evaluated in HL, both as monotherapy as in combination.[14,15] As a single agent, the ORR is 53%, although the median duration of response is only 5 months.

We have previously reported outcomes for a phase I study utilizing a combination of gemcitabine and bendamustine in relapsed/refractory Hodgkin lymphoma. In our phase I study, there were no DLT's identified and the maximum tolerated dose was established at gemcitabine 1000mg/m^2 on day 1 and bendamustine 120mg/m^2 on days 1 and 2 of a 21 day cycle. This regimen was used prior to autologous or allogeneic transplant in many patients, but those patients who did not proceed with transplant had a shortened progression-free survival. We have now completed a phase 2 study of this combination, with 22/24 evaluable patients responding. Encountered toxicities were generally manageable and included primarily myelosuppression as well as nausea/vomiting, and

pulmonary complications (see Table 1). Two patients experienced severe pulmonary complications, including one with a biopsy-proven gemcitabine-associated pneumonitis who recovered fully after discontinuation of treatment and another patient who developed an infectious pneumonia. In addition to the double, bendamustine and gemcitabine have been combined in a triplet with vinorelbine in relapsed/refractory HL with an ORR of 83%, and most patients moving forward with autologous stem cell transplantation after 4 cycles of therapy.[14]

TABLE 1. GRADE 3/4 TOXICITIES FROM GEMCITABINE AND BENDAMUSTINE PHASE 1 / 2 STUDY

GRADE 3	**GRADE 4**
LYMPHOPENIA (N=5) THROMBOCYTOPENIA (N=2) PNEUMONITIS (N=1) ATRIAL FIBRILLATION (N=1) RENAL INSUFFICIENCY (N=1) HYPOALBUMINEMA (N=1) HYPOTENSION (N=1) PNEUMONIA (N=1) RASH (N=1) VOMITING (N=1) INSOMNIA (N=1) HYPOKALEMIA (N=1)	THROMBOCYTOPENIA (N=1) LYMPHOPENIA (N=7) PULMONARY TOXICITY (N=1)

1.4 Prior Experience with Nivolumab and Chemotherapy in Solid Tumors

Gemcitabine and nivolumab have been previously combined in patients with solid tumors. In a phase 1 study in pancreatic cancer, gemcitabine (100mg/m^2) was safely administered with nab-paclitaxel and nivolumab, with 3/6 patients achieving a PR and no DLT's identified. Gemcitabine, cisplatin, and nivolumab were evaluated in squamous cell lung cancer as well, with manageable toxicity and a 33% ORR. Toxicities encountered when combined with chemotherapy have been manageable and expected. For example, when combined with a platinum doublet in patients with chemotherapy-naïve non-small cell lung cancer, the most common drug-related adverse event was fatigue, while other toxicities including pneumonitis (7.1% of patients), anemia (5.4%), febrile neutropenia (3.6%), and rash (3.6%). The most common drug-related AE's leading to treatment discontinuation included pneumonitis and hypersensitivity, and no AE-related deaths were described.

In a Japanese study of nivolumab in combination with chemotherapy in patients with relapsed/refractory non-small lung cancer, 6 patients were treated with gemcitabine

and cisplatin in combination with nivolumab. Among those 6 patients, 2 patients discontinued therapy due to toxicity (due to endocrine dysfunction and hypersensitivity). One other patient experienced atrial fibrillation.

1.5 Rationale for Current Study

The use of immunotherapy in HL has resulted in significant improvements in outcome for patients relapsed/refractory disease, and nivolumab-containing approaches are now also being assessed in the frontline setting. However, nivolumab as a single agent results in a complete response in the minority of cases and as a result requires continuous therapy. In addition, most patients will experience radiographic progression within a year and many of those patients will require treatment discontinuation. By inducing a deep remission with combination chemotherapy, we are hoping to significantly prolong remission duration and benefit of the PD-1 antibody by introducing maintenance therapy in the setting of remission rather than in the presence of a high tumor burden. This should hopefully overcome the challenges associated with nivolumab monotherapy where the CR rate is modest. In the phase 1/2 study of the combination of gemcitabine and bendamustine, this regimen was highly active but frequently required a consolidation approach to maintain remission. However, not all patients are candidates for transplantation or others may have already progressed after transplantation. As a result, we wish to pursue a maintenance strategy with nivolumab that may prolong the remission. In addition, continuation of nivolumab after completion of chemotherapy should allow for improved immune activity that may be compromised during chemotherapy but can recover afterwards and contribute to anti-tumor activity.

In this study, we will be able to evaluate the benefit of such an approach which can then be utilized for future studies. We will identify any safety concerns associated with administration of the combination followed by monotherapy maintenance. As an exploratory aim, we will also be able to compare our findings to the historical response rates and duration of responses seen with nivolumab monotherapy and with gemcitabine/bendamustine cominbations in HL.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To evaluate the toxicity and determine the maximum tolerated dose (MTD) of combined gemcitabine, bendamustine, and nivolumab in patients with relapsed/refractory classical Hodgkin lymphoma.

2.1.2 To determine the efficacy of bendamustine, gemcitabine, and nivolumab in patients with relapsed/refractory classical Hodgkin lymphoma.

2.2 Secondary Objectives

2.2.1 To evaluate the duration of response, progression-free survival, and overall survival for patients with relapsed/refractory classical Hodgkin lymphoma who receive gemcitabine, bendamustine, and nivolumab, including those who receive nivolumab maintenance.

3.0 ELIGIBILITY CRITERIA

3.1 Histologically documented Classical Hodgkin lymphoma that is recurrent or refractory after standard chemotherapy. Core biopsies are acceptable if they contain adequate tissue for primary diagnosis and immunophenotyping. Bone marrow biopsies as the sole means of diagnosis are not acceptable. At least one biopsy-proven relapse is required for enrollment, but patients who have multiply relapsed disease do not require repeat biopsy if not clinically indicated.

3.2 Prior Treatment: Patients must have relapsed or progressed after at least one prior therapy.

3.2.1 Patients with relapsed or refractory disease following autologous stem cell transplantation arepermitted. Due to the risk of treatment-refractory GVHD, patients who have previously completed an allogeneic transplant are excluded..

3.2.2 Patients may have received gemcitabine, bendamustine, or nivolumab in the past but may not have discontinued therapy due to toxicity felt to be related to that specific drug.

3.3 Age $\geq$ 18 years of age.

3.4 ECOG Performance Status 0-2.

3.5 Measurable disease must be present either on physical examination or imaging studies. Non-measurable disease alone is not acceptable.

3.5.1 Measurable Disease

Lesions that can be accurately measured in at least two dimensions as ≥ 1.0 x 1.0 cm by computerized tomography (CT), PET/CT (positron emission tomography/CT), or magnetic resonance imaging (MRI). If identified by PET/CT, there must be at least one lesion that demonstrates abnormal FDG avidity, consistent with active disease. Ultrasound or physical examination alone may not be utilized to confirm measurable disease.

3.5.2 Non-measurable Disease

All other lesions, including small lesions (less than 1.0 x 1.0 cm) and truly non-measurable lesions.

Lesions that are considered non-measurable include the following:

- Bone lesions (lesions if present should be noted)
- Ascites

- Pleural/pericardial effusion
- Lymphangitis cutis/pulmonis
- Bone marrow (involvement by Hodgkin lymphoma should be noted)

3.6 Non-pregnant and non-nursing. Due to the teratogenic potential of these agents, pregnant or nursing patients may not be enrolled. Women and men of reproductive potential should agree to use an effective means of birth control.

3.7 Patients with HIV infection are eligible. Patients with HIV infection must meet the following: No evidence of co-infection with hepatitis B or C; CD4+ count $\geq$ 400/mm^3 no evidence of resistant strains of HIV; on anti-HIV therapy with an HIV viral load < 50 copies HIV RNA/mL. Patients with HIV must have ongoing follow-up with an infectious disease specialist and must have been evaluated within 90 days of cycle 1 day 1.

3.8 Patients with a history of hepatitis C are eligible as long as the hepatitis C has been treated and cleared and they have no evidence of hepatic dysfunction related to hepatitis C. Patients must have been seen by a hepatologist within 6 months of cycle 1 day 1.

3.9 Patients who test positive for hepatitis B core antibody may enroll on the study as long as they test negative for both hepatitis B surface antigen and hepatitis B DNA, and if they have no evidence of hepatic dysfunction that is felt to be related to hepatitis B.

3.10 Patients must have adequate pulmonary function, defined as the following:

3.10.1 No history of drug-related, radiation-induced, or autoimmune pneumonitis requiring hospital admission.

3.10.2 Baseline pulse oximetry reading of ≥92% on room air.

3.10.3 Patients with a history of asthma or COPD must have no oxygen requirement, must have not had a hospital admission for COPD/asthma exacerbation within the past 2 years, and must not have received systemic steroids (≥10 mg prednisone for more than 7 days) for asthma/COPD within the past 2 years.

3.11 Patients may not have an auto-immune disease requiring systemic immunosuppression, biologic therapy, and/or steroid use (≥10mg daily of prednisone or equivalent). Patients with hypothyroidism or type 1 diabetes mellitus that are on chronic hormonal therapy and which are well-controlled are eligible.

3.12 Patients with current or prior CNS involvement with lymphoma are not eligible.

3.13 Required Initial Laboratory Data:

Granulocytes	≥ 1000/µl
Platelet count	≥ 75,000/µl
Creatinine Clearance	≥50 mL/min

Bilirubin	≤ 2.0 mg/dL
AST/ALT	≤ 2.0 x upper limits of normal

4.0 REQUIRED DATA

Guidelines For Pre-Study Testing

To be completed within 16 DAYS before cycle 1, day 1:

- All bloodwork, history and physical exam.

To be completed within 42 DAYS before cycle 1, day 1:

- Scan of any type that is utilized for tumor measurement per protocol.

Tests & Observations	**Screening**	**Cycle 1 Days 1, 8, and 15**	**Day 1 of Cycles 2+**	**Post Treatment Follow up***
Physical Examination	X	X	X	X
Height/Weight/Body Surface Area	X		X	
Performance Status	X	X	X	
Drug Toxicity Assessment	X	X	X	X
Concomitant Medications	X	X	X	
Pulmonary Function Tests (w/ DLCO)	X			
Pulse Oximetry	X	X	X	
Laboratory Studies				
CBC with differential	X	X	X	X
Serum Creatinine, BUN	X	X	X	X
Serum Electrolytes (Na, K, Cl, CO2)	X	X	X	X
Liver Function Tests	X	X	X	X
ESR	X			X
Serum or Urine Pregnancy Test#	X		X	
TSH	X		A	
Free T3 and Free T4	X			
Hepatitis B Core Antibody Total	X			
Hepatitis C Antibody	X			
Restaging/Disease Evaluation				
PET/CT, CT (with IV contrast), or MRI scan (neck, chest, abdomen, pelvis)	B		C	X**
Bone Marrow Aspirate and Biopsy	D			D
Histologic Review	E			

* Patients who have discontinued study therapy but have not started a subsequent treatment should be evaluated every 3 months for 2 years from discontinuation of study therapy.

** Patients who discontinue study therapy but have not started a subsequent treatment should complete restaging every 6 months for 2 years after discontinuation of therapy.

Women of childbearing potential (defined per institutional standard).

A. TSH should be drawn at baseline, at the beginning of cycles C3 and C6, and at the beginning of cycles M3, M6, M9, M12, M15, M18, M21, and M24. T3 and T4 is required at baseline for all patients but only should be checked as clinically indicated after the initial screening.
B. PET/CT preferred at the time of study registration and at re-staging after cycles C2, and C6. PET/CT, CT (with IV contrast), or MRI may be utilized according to physician preference during maintenance cycles and follow-up. CT or MRI should include neck, chest, abdomen, and pelvis.
C. Restaging studies should occur for patients on therapy after cycles C2 and C6 (PET/CT preferred after C2 and C6), and subsequently after cycles M3, M6, M9, M12, M18, and M26.
D. Bone marrow biopsy and aspirate is only required for patients with suspected involvement at the discretion of the treating physician and should only be performed if felt to be necessary as part of the patient's routine care. Patients who do undergo bone marrow biopsy and aspirate and who are found to have involvement with Hodgkin lymphoma should repeat the procedure at time patient achieves a CR.
E. Pathology review at the treating center is required prior to enrollment if a biopsy confirming relapse has not previously been evaluated at the treating center.

NOTE: All study treatments may be adjusted +/- 3 days to account for circumstances including holidays, weather, clinic closures, or any other condition which prevents the patient from being treated on schedule. However, growth factor must be administered no later than 72 hours after completion of day 2 bendamustine during combination cycles. While on treatment, "day 1" laboratory values may be obtained up to 48 hours prior to initiating therapy. Scheduled scans while on treatment may be obtained +/- 7 days from day 1 of the required combination cycles and +/- 14 days of required maintenance cycles. Patients who are off treatment and in follow-up should be evaluated +/- 30 days from the scheduled time point and required scans should also occur +/- 30 days from the scheduled time point.

5.0 REGISTRATION PROCESS

After each subject at participating subsites signs consent, the Central Subject Registration Form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/ HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form.

The Eligibility Checklist is to be printed from OnCore and verified by 2 people, of which one *MUST* be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator or designee (Fax 404-778-0417) within 14 days after

pre-registration but no later than 2 business days before scheduled treatment visit. In cases where it is not feasible to provide within 2 days before the first treatment visit due to a rapid screening, the subsites shall provide Winship with the eligibility checklist and source documentation as soon as possible. This must be reviewed prior to initiating therapy. Eligibility will be confirmed by the site investigator or co-investigator and the Multi-site coordinator or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria.

The clinical management system being used for this study is The Online Collaborative Research Environment (OnCore). OnCore will be used to record all study related information for all registered subjects, including their assigned patient ID and assigned dose cohort. All data must be entered no later than 30 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The Multi-site coordinator will provide OnCore training and request access to the appropriate staff at the participating sites.

6.0 TREATMENT PLAN

6.1 Phase 1 Study

6.1.1 Dose Escalation Schema and Treatment Plan

Phase I Dose Escalation Schema Cycle Length: 21 days

Dose level	Gemcitabine (mg/m^2) IV over 30 minutes day 1	Bendamustine (mg/m^2) IV over 30 minutes days 1 and 2	Nivolumab (mg) on day 1
-3	800	75	140
-2	800	90	140
-1	800	90	240
1	1000	90	240
2	1000	120	240

NOTE: Maintenance dosing shall be Nivolumab monotherapy 480mg IV on day 1 of a 28 day cycle (cycles M1-M26).

In the phase I trial, three patients will be enrolled at each dose level starting at dose level 1(See above dose escalation schema) using a standard 3+3 dose escalation phase I design. If one patient experiences a dose limiting toxicity (DLT), this dose level will be expanded to 6 patients. The dose where 2 or more DLT's are observed will be declared the maximum administered dose and will have exceeded the maximum tolerated dose (MTD). If 2 or more DLT's are observed at a given dose level, the previous dose level will be expanded to a total of 6 patients and if 1 or

fewer DLT's is observed at this level, this will be the maximum tolerated or recommended phase 2 dose (RP2D). If 2 or more DLTs are observed at dose level 1, the next cohort of 3 patients will be accrued to dose level (-1). If dose escalation reaches dose level 2, this dose level will expand to 6 patients to ensure patient safety. If 1 or fewer patients experience DLT at dose level 2, this will be used as the RP2D, and the trial will proceed to phase II. All patients treated within a dose level must complete one cycle of therapy prior to dose escalation to the next level. Patients who do not complete prescribed treatment for the first cycle of therapy for reasons other than toxicity will be replaced on that dose level for the purposes of DLT determination but will still be followed for safety endpoints and can continue study therapy if they have not experienced a DLT and are felt to be suitable candidates to continue.

A combination cycle will be defined as one 21-day treatment period and patients may continue to receive bendamustine and gemcitabine for a maximum of 6 combination cycles. Nivolumab will be administered in combination with gemcitabine and bendamustine up to cycle 6, then as monotherapy thereafter. Patients who experience toxicity that is felt to be related to gemcitabine and/or bendamustine during cycles 1-6 MAY initiate maintenance therapy early (i.e, before completing 6 cycles of combination treatment) if they are felt to be benefiting from nivolumab and have completed at least 1 full cycle of therapy without a DLT. These patients must not discontinue gemcitabine or bendamustine due to a potential immunologic or any pulmonary toxicity. Potential additional immunologic toxicities could include colitis, hepatitis, or adrenal insufficiency. Any questions regarding a patient's eligibility to proceed with monotherapy in this situation should be directed to the study chair. Response will be assessed after cycles 2 and 6 during the combination phase and then as directed in Section 4.0 during the maintenance phase. BM biopsy will be repeated in those patients with evidence of a complete response and pre-treatment bone marrow involvement.

The treatment schedule for maintenance dosing shall be nivolumab 480mg IV day 1 of each 28-day cycle. The nivolumab dose shall be 480mg during maintenance regardless of the dose received during combination. If this dose/schedule is not felt to be safe by the treating investigator, the patient should be removed from study therapy prior to initiation of maintenance.

This study is not designed to be utilized prior to autologous or allogeneic transplantation but in some instances, proceeding to an alternative therapy may be in the patient's best interest and is permitted. All patients who are not experiencing frank, clinical progression and/or unacceptable toxicity, should complete at least 2 cycles of combination therapy prior to proceeding to any subsequent therapies. All patients who discontinue study therapy to proceed to transplantation or any other alternative therapies shall be considered for the planned safety assessments and, as able, shall be considered for response assessment. Any patient who receives any alternative anti-cancer treatment outside of the study shall be permanently removed from the study and may not receive any subsequent combination or nivolumab monotherapy as part of the study.

6.1.2 Definition of Dose limiting toxicity during the Phase 1 Trial

Table 3. Definition of Dose Limiting Toxicity
Grade 3 febrile neutropenia > 7 days
Grade 4 infection or febrile neutropenia
Grade ≥2 pulmonary toxicity
Any grade ≥3 non-hematologic toxicity except nausea/vomiting, alopecia, or asymptomatic non-hematologic laboratory abnormalities that are correctible within 72 hours.
Grade ≥3 rash/cutaneous toxicity.
Any dose delay of > 14 days due to therapy-related toxicity (including delay of initiation of cycle 3).
Any Grade 5 toxicity

Dose limiting toxicity (DLT) will be defined during cycles 1 and 2 of the phase I trial (ie, for the first 6 weeks of treatment). Patients with a DLT during this window will be immediately removed from the study. Toxicities during cycles 3-6 or that do not meet criteria for dose limiting toxicity will be managed according to section X.

Note: All toxicities encountered during the first 2 cycles will be considered for the purposes of identification of a DLT. However, toxicities that develop that are clearly and unequivocally unrelated to study therapy will not be considered a DLT. This determination will be made by the study chair alone or in consultation with the treating physician of the patient, other co-investigators, and other resources as indicated. Should this occur, the reason for not considering a toxicity to be a DLT shall be clearly documented.

6.1.3 Planned interim safety analysis during phase 1 study.

In addition to the monitoring for DLT during cycles 1 and 2 for all patients enrolled on the phase 1 study, we will also plan a second safety evaluation after 6 patients have completed 4 cycles of combination therapy (regardless of dose level). If any of the first 6 patients discontinue study therapy for any reason prior to completion of cycle 4, their data will still be included in this safety analysis. However, the safety analysis will not occur until 6 patients have completed 4 cycles of therapy.

If any of the following occur prior to the completion of 4 cycles of therapy, the study will temporarily hold further accrual and a determination will be made by the principal investigator, in collaboration with the Winship Cancer Institute Data Safety Monitoring Committee regarding the need to adjust the treatment regimen/schedule, eligibility criteria, or other aspect of the study to improve safety:

a) ≥ 20% of patients experience grade ≥ 3 pneumonitis at least possibly related to study therapy and not felt to be infectious

b) ≥ 20% of patients experience grade ≥ 3 transaminase elevation (ALT or AST) at least possibly related to study therapy

c) ≥ 20% of patients experience grade ≥ 3 rash at least possibly related to study therapy

d) ≥20% of patients experiencing grade ≥3 or unmanageable lesser-grade immune mediated adverse reaction.

6.2 Phase II Study

The phase 2 portion of the study shall commence upon determination of the recommended phase 2 dose (RP2D). For phase 2, gemcitabine, bendamustine, and nivolumab will be administered for up to 6 cycles at the RP2D, and nivolumab will subsequently be administered as a monotherapy for up to 26 additional 28-day cycles. Gemcitabine shall be administered prior to bendamustine on day 1 of each cycle, and nivolumab shall be administered last on any days in which multiple therapies are being administered. Patients will receive pegfilgrastim within 72 hours of completion of bendamustine for cycles 1-6. Pegfilgrastim will not be required during monotherapy/maintenance.

Response will be assessed by PET/CT (preferred), CT of the chest, abdomen, and pelvis, or MRI after cycles 2 and 6 and again as specified in Section 4.0 above during the maintenance phase. Patients without evidence of disease progression may continue combination therapy for a maximum of 6 cycles of therapy followed by up to 26 cycles of nivolumab. Given the evidence that radiographic progression does not always reflect true symptomatic progressive disease when PD1 antibodies are administered in Hodgkin lymphoma, patients who are receiving nivolumab monotherapy who experience radiographic progressive disease MAY, at the discretion of the treating physician, remain on single agent therapy if they are felt to be clinically benefitting, for up to a total of 26 maintenance cycles. It is less clear whether a similar phenomenon occurs in patients receiving nivolumab in combination with chemotherapy. As a result, patients who experience evidence of progression during combination therapy but who are having unequivocal clinical benefit may continue combination treatment in consultation with the study chair.

This study is not designed to be utilized prior to autologous or allogeneic transplantation but in some instances, proceeding to an alternative therapy may be in the patient's best interest and is permitted. All patients who are not experiencing frank, clinical progression and/or

unacceptable toxicity, should complete at least 2 cycles of combination therapy prior to proceeding to any subsequent therapies. All patients who discontinue study therapy to proceed to transplantation or any other alternative therapies shall be considered for the planned safety assessments and, as able, shall be considered for response assessment. Any patient who receives any alternative anti-cancer treatment outside of the study shall be permanently removed from the study and may not receive any subsequent combination or nivolumab monotherapy as part of the study.

6.3 Study-therapy related deaths

Deaths of any subjects while on active therapy or within 30 days of treatment shall be assessed immediately. In the event that the death is not clearly unrelated to study therapy (ie, disease progression), accrual shall cease until a full accounting of the event can be obtained and any needed amendments can be developed to address the event and prevent it from occurring in the future. This may include dose reductions of any or all therapies, introduction of additional supportive care therapies, inclusion of more frequent laboratory or clinical assessments, or any other measures deemed appropriate by the study chair in consultation with co-investigators and other study personnel.

6.4 Criteria to temporarily hold study accrual

In addition to the safety parameters identified above for DLT monitoring and the early stopping rules presented for the phase 1 study, we will have several additional criteria that shall be applied throughout the study and which will result in temporary holding of accrual. If any of these criteria are met at any time (phase 1 or phase 2 portions), the study shall hold accrual until appropriate modifications can be made to the protocol to ensure future safety of patients.

- Any study-related death at any time on treatment or within 30 days of discontinuing treatment
- ≥ 5 subjects experiencing therapy-related grade ≥ 3 pneumonitis, transaminase elevation, or cutaneous toxicity
- ≥5 subjects experiencing therapy-related grade ≥4 toxicity
- ≥10 subjects who are unable to complete the 6 cycles of combination therapy (dose modifications are permitted; this criterion only applies to patients who must discontinue chemotherapy entirely)
- The study chair may suspend accrual at any time if a significant safety concern is identified. This would include unexpected toxicities associated with transplantation after completion of study therapy. This therapy is not specifically designed to be used pre-transplant but any study-related complications related to transplantation (autologous or allogeneic) will be captured and considered as indicated.

6.5 Order of Drug Administration

Gemcitabine shall be administered first on day 1, followed by bendamustine in all patients, at all dose levels. Bendamustine will be administered alone on day 2. Nivolumab shall be the final drug administered on all days in which multiple agents are being administered.

6.6 Criteria for Retreatment – Combination Phase (Cycles 1-6)

On the phase I and phase II trials, patients without evidence of symptomatic disease progression may continue combination therapy for up to 6 cycles. To start a cycle, the following criteria must be met. In addition, please note the criteria for nivolumab discontinuation in Section 7.3. Any patient who requires discontinuation of nivolumab shall be permanently removed from study therapy:

1) The absolute neutrophil count must be $\geq$ 1000/μL and the platelet count must be $\geq$75,000/mm^3
2) Therapy-related immune-mediated toxicities and symptomatic endocrinopathies must be resolved to ≤ grade 1. NOTE: Any steroids utilized to manage immune-mediated toxicities must be decreased to 10mg or less of prednisone (or equivalent) for at least 5 days prior to initiating the next cycle.
3) Asymptomatic, therapy related endocrinopathies must be ≤ grade 2.
4) All other treatment-related non-laboratory, non-immune mediated toxicities must be resolved to $\leq$ grade 2.
5) Asymptomatic laboratory abnormalities (hematologic and non-hematologic) that are ≤grade 3 and can be readily corrected do not require a dose delay.
6) Patients with liver function test abnormalities (ALT, AST, Alkaline phosphatase) that are ≥ Grade 3 must be delayed until recovery to Grade ≤1.
7) Any grade 4 toxicity that is at least possibly related to study therapy requires a dose delay.

Patients who require a treatment delay of > 21 days shall be removed from combination therapy but MAY continue monotherapy if felt to be clinically benefitting and the toxicity is felt to be most likely related to gemcitabine/bendamustine. Patients requiring a delay of ≤21 days but for whom continued combination therapy is felt to be unsafe may also continue monotherapy at the discretion of the investigator if they are felt to be clinically benefitting.

6.7 Criteria for Retreatment – Maintenance Phase

In order for patients to initiate a maintenance cycle of single agent nivolumab, the following criteria must be met. In addition, please note the criteria for nivolumab discontinuation in Section 7.3. Any patient who requires discontinuation of nivolumab shall be permanently removed from study therapy:

1) The absolute neutrophil count must be $\geq$ 1000/μL and the platelet count must be $\geq$75,000/mm^3
2) Therapy-related immune-mediated toxicities and symptomatic endocrinopathies must be resolved to ≤ grade 1. NOTE: Any steroids utilized to manage immune-mediated toxicities must be decreased to 10mg or less of prednisone (or equivalent) for at least 5 days prior to initiating the next cycle.
3) Asymptomatic, therapy related endocrinopathies must be ≤ grade 2.
4) All other treatment-related non-laboratory, non-immune mediated toxicities must be resolved to $\leq$ grade 2.
5) Asymptomatic laboratory abnormalities (hematologic and non-hematologic) that are ≤grade 3 and can be readily corrected do not require a dose delay.
6) Any grade 4 toxicity that is at least possibly related to study therapy requires a dose delay.

Patients requiring a dose delay of > 21 days due to toxicity must be removed from study therapy and cannot be retreated without discussion with the principal investigator.

6.8 Treatment Duration and Staging

Re-staging should be performed after cycles 2 and 6 of combination therapy and subsequently subsequently after cycles M3, M6, M9, M12, M18, and M26 during maintenance. Patients will receive a minimum of two cycles of therapy, unless rapid disease progression or dose-limiting toxicity is noted. Patients without evidence of progressive disease may continue to receive Gemcitabine and Bendamustine for a total of 6 cycles. Nivolumab monotherapy can be continued for up to 26 cycles.

Any patient who experiences toxicity felt to be related to study therapy that is considered to make further therapy unsafe shall be removed form study therapy. Any patient with symptomatic progressive disease shall also be removed from therapy.

**Patients who experience radiographic progression while on the combination therapy should be removed from treatment, but patients with radiographic progression after completion of the combination portion of the study MAY remain on monotherapy if they are felt to be clinically benefitting. These patients should continue to have imaging assessments as set forth in the protocol but may complete up to the full 26 cycles of therapy in the absence of symptoms that are felt to be related to disease progression or unacceptable toxicity.

7.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

The following dose modifications will apply to all patients in the phase 1 trial during cycle 1-2 who do not meet the criteria for dose limiting toxicity (see Section 6.1.2), to all patients receiving cycles 3+ in the phase I trial, and to all patients receiving therapy on the phase 2 trial.

Any patient who requires a dose reduction shall NOT be re-escalated at any point in the study.

Given the demonstrated safety and efficacy of single-agent nivolumab as well as nivolumab administered in combination with other agents, this combination is primarily of interest only if we can safely combine the chemotherapy backbone with a known therapeutic dose of nivolumab. As a result, we will prioritize maintaining the active dose of nivolumab, and there shall be NO dose reductions of nivolumab. If a dose reduction is required, BOTH gemcitabine and bendamustine shall be reduced per Table 4 below.

During the combination phase of the study, toxicities may be encountered that could be related to both gemcitabine/bendamustine and nivolumab. These may include hepatic, pulmonary, hematologic, or other toxicities.

While on combination therapy, any toxicity which may be immune-mediated should be managed per the algorithms described in the appendix, and patients meeting the criteria specified below in Section 7.3 shall discontinue nivolumab and study treatment. All therapy shall be held until resolution of the immune-mediated toxicity.

Other non-hematologic toxicities that require a dose hold shall be managed as documented below in Section 7.2 with a dose modification of the gemcitabine/bendamustine per Table 4. In such case, nivolumab shall also be held until recovery of the toxicity and all therapies shall be re-initiated at the same time.

7.1 Hematologic Toxicity: The following dose modifications should be made for febrile neutropenia, nadir blood counts, and blood counts obtained within 2 days prior to each subsequent cycle. If more than one of these applies, use the most stringent (i.e., the greatest dose reduction) but only one dose reduction shall occur per cycle.

Example: If a patient has a nadir platelet count of 20,000 during a cycle and an ANC of 750 at the time of the next cycle, only one dose reduction is required at that time. If any of these hematologic toxicities recur after reinitiation of therapy, a second dose reduction would be indicated.

7.1.1 Febrile Neutropenia

If febrile neutropenia (defined as temperature ≥ 38.5°C [101 F] concomitant with an ANC < 500/ µl) develops in a given cycle, dose reduce bendamustine and gemcitabine one level below the current dose according to Table 4. These dose reductions will be applied to the next and all subsequent cycles.

7.1.2 Nadir Blood Counts

In patients with a platelet count < 25,000/μl or a ANC < 250/μl at any time during the cycle, dose reduce bendamustine and gemcitabine one dose level below the current dose according to Table 4. These modifications will apply to the next and all subsequent cycles.

- Treatment should be held until the patient has an ANC ≥ 1000/μl and a platelet count ≥ 75,000/μl.
- Treatment delays > 3 weeks will lead to study removal.
- Once the ANC or platelet count has improved, therapy can be re-instituted at the next lowest dose level.
- No dose modifications are required for leukopenia, lymphopenia, or anemia that occurs during a cycle.

7.1.3 Blood Counts on Day 1 of Cycle

In patients with a platelet count < 75,000/μl or a ANC < 1000/μl obtained on a planned day 1 of each cycle of therapy, dose reduce bendamustine and gemcitabine one dose level below the current dose according to Table 4. These dose reductions will apply to the next and all subsequent cycles.

- Treatment should be held until the patient has an ANC ≥ 1000/μl and a platelet count ≥ 75,000/μl.
- Treatment delays > 3 weeks will lead to study removal.
- Once the ANC or platelet count has improved, therapy can be re-instituted at the next lowest dose level.

Table 4. Gemcitabine and Bendamustine Dose Reductions

Gemcitabine dosing (reduce one level below current dose)	Bendamustine dosing (reduce one level below current dose)
1000 mg/m^2	120 mg/m^2
800 mg/m^2	90 mg/m^2
600 mg/m^2	75 mg/m^2
Discontinue Gemcitabine	Discontinue Bendamustine

7.2 Non-Hematologic Toxicity

If a dose delay is required due to treatment-related non-hematologic toxicity, therapy should be held until the patient meets criteria to reinitiate therapy. At that time, treatment should be reinitiated with a dose reduction per Table 4. Nivolumab will not be dose reduced.

There will be no required dose reductions for mid-cycle non-hematologic toxicities that have resolved by the completion of the cycle if a patient meets criteria to receive the next cycle of treatment. However, an investigator MAY dose reduce any patient experiencing a grade 3-4 non-hematologic toxicity during a cycle if they feel it is in the patient's best interest. In addition, a patient experiencing a mid-cycle grade 3-4 non-hematologic toxicity while on combination therapy MAY, at the discretion of the investigator, discontinue combination therapy and move to nivolumab monotherapy.

Patients who discontinue and/or dose reduce gemcitabine and bendamustine due to toxicity, may NOT re-escalate these therapies.

7.3 Immune Mediated Toxicities and Criteria for Discontinuation of Nivolumab

Nivolumab, like other PD1 antibodies, is associated with the development of immune mediated toxicities including rash, diarrhea, pneumonitis, endocrinopathy, hepatitis, and others. Presumed immune-mediated toxicities shall be managed per Appendix attached, and investigators are encouraged to consult the Nivolumab investigator brochure for further information.

Any patient experiencing a nivolumab-mediated immunologic toxicity shall be managed according to the algorithm whenever possible, including the use of corticosteroids. Patients who are felt to be unable to continue nivolumab therapy will be removed from study treatment.

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

- ♦ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- ♦ Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
- ♦ Concurrent AST or ALT > 3 x ULN AND total bilirubin >2x ULN

NOTE: Any patient who requires discontinuation of nivolumab for the above reasons shall be removed from all study therapy, regardless of timing (during combination or monotherapy).

7.4 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, **all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification**. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration.

8.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

8.1 Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

8.2 Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

8.3 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

8.4 Gemcitabine

Availability

Gemcitabine

Preparation

Gemcitabine may be prepared per institutional standard

Storage and Stability

Gemcitabine solutions are stable for 24 hours at controlled room temperature. Unopened vials are stable until the expiration date indicated on the package when stored at controlled room temperature.

Administration

Administer IVPB over 30 minutes

Toxicities

Myelosuppression, nausea, vomiting, diarrhea, stomatitis, transient elevation in transaminases, mild proteinuria and hematuria, fever, rash, dyspnea, edema, flu-like symptoms, irritation at site of injection.

8.5 Bendamustine

Please refer to the FDA-approved package insert for bendamustine for product information and a complete list of adverse events.

AVAILABILITY

Bendamustine will be obtained commercially for enrolled patients. The bendamustine brand (Treanda, Bendeka, or other) shall be determined per institutional preference/standard and is not mandated by this protocol.

STORAGE &STABILITY

Once diluted with 0.9% Sodium Chloride, the final admixture, is stable for 24 hours when stored refrigerated (2-8°C or 36 – 47°F) or for 3 hours when stored at room temperature (15 – 30°C or 59 – 86°F) and room light.

PREPARATION

Bendamustine will be prepared per package insert and institutional standards.

ADMINISTRATION

Bendamustine will be administered intravenously over 30 minutes on days 1 and 2.

TOXICITY

Myelosuppression: In the randomized study of bendamustine in CLL, myelosuppression was observed, including grade 3/4 neutropenia (24%), febrile neutropenia (3%), red blood cell transfusions (20%), and platelet transfusions (<1%). Hematologic nadirs are expected in the third week of treatment.

Infection: Infections, including pneumonia and sepsis have occurred in patients receiving bendamustine. Cases of infection-associated hospitalization, septic shock, and death have been reported. Patients who develop myelosuppression are at higher risk of infection.

Infusion Reactions and Anaphylaxis: Common infusion reactions include fever, chills, pruritus, and rash, but rare cases of anaphylactic and anaphylactoid reactions have

been reported. Infusion reactions seem to be more common in the second and subsequent cycles of therapy. Patients should be monitored for signs and symptoms suggestive of infusion reactions.

Tumor Lysis Syndrome: Tumor lysis syndrome associated with bendamustine treatment has been reported in patients in clinical trials and in spontaneous reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death.

Dermatologic Toxicity: Skin reactions, including rash, toxic skin reactions, and bullous exanthema has been reported. Reports of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. When skin reactions occur, they may be progressive and increase in severity with further treatment.

Other Adverse Reactions: Other frequent adverse reactions include fever, nausea, vomiting, asthenia, fatigue, malaise, weakness, dry mouth somnolence, cough, constipation, headache, mucositis, and stomatitis. Worsening hypertension, including hypertensive crisis has been reported rarely.

8.6 Nivolumab

Please refer to the FDA-approved package insert for nivolumab for product information and a complete list of adverse events.

AVAILABILITY

Nivolumab will be provided by BMS for patients enrolled on this study.

STORAGE &STABILITY

The product does not contain a preservative. After preparation, nivolumab can be stored at room temperature for no more than 8 hours from the time of preparation (which includes time for administration). Or, prepared nivolumab infusion may be stored under refrigeration for no more than 24 hours from the time of infusion preparation.

PREPARATION

Withdraw the required volume of nivolumab and transfer into an intravenous container.

Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1mg/mL to 10mg/mL.

Mix diluted solution by gentle inversion. Do not shake.

Discard partially used vials or empty vials of nivolumab.

ADMINISTRATION

Nivolumab shall be administered over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not co administer other drugs through the same line. Flush the line at the end of infusion.

Nivolumab shall be administered last on all days when it is co-administered with gemcitabine or bendamustine.

TOXICITY

See package insert and investigator brochure for details regarding toxicity.

Toxicity related to nivolumab is frequently immune-mediated and includes the following:

- Pneumonitis
- Colitis
- Hepatitis
- Endocrinopathies (including thyroid, adrenal, and pancreatic dysfunction)
- Nephritis/renal dysfunction
- Cutaneous reactions
- Encephalitis

Nivolumab is also rarely associated with infusion reactions as well as increased risk of graft-versus-host disease and febrile syndrome when administered around the time of an allogeneic transplant.

9.0 Ancillary Therapy

9.1 Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the study case report forms.

9.2 Treatment with *hormones or other chemotherapeutic agents* may not be administered except for steroids given for nausea, adrenal failure, or immune-mediated toxicities or hormones administered for non-disease-related conditions (e.g., insulin for diabetes). Use of dexamethasone and other steroidal antiemetics is permitted.

9.3 *Palliative radiation therapy* may not be administered. Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur) prior to study initiation, provided other measurable disease is present.

9.4 Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol:

9.4.1 Erythropoietin (EPO)

Use of erythropoietin (EPO) is **permitted** at the discretion of the treating physician.

9.4.2 Filgrastim (G-CSF) and sargramostim (GM-CSF)

1. As all patients will receive pegfilgrastim with each cycle, filgrastim (G-CSF) and sargramostim (GM-CSF) treatment as prophylactic treatment is prohibited **unless a patient did not receive pegilgrastim as scheduled.**
2. The use of filgrastim or sargramostim may be indicated in patients who did not receive pegfilgrastim during a cycle a cycle, or who experience a clinical scenario with a high risk of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSF's in this setting. The use of CSF (filgrastim or sargramostim) must be documented and reported on flow sheets.
3. If filgrastim or sargramostim are used, they must be obtained from commercial sources.

10.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

For the purposes of this study, patients will be restaged using PET/CT, CT, or MRI scan after cycles 2 and 6 of induction therapy, and after cycles M3, M6, M9, M12, M18, and M26 during the maintenance phase.

If a patient experiences a delay in treatment, every attempt should be made to keep the restaging scans paired with the beginning of the cycle when it is due when possible. For example, if cycle M4 is delayed two weeks, the restaging scan should also be delayed 2 weeks. Windows for scans are provided and should be based on the date in which the required cycle took place, regardless of delays. Unavoidable and/or unexpected delays (such as due to laboratory toxicities on day 1 of a cycle, weather, or unrelated

emergencies preventing treatment) are expected, and if they occur and result in a scan being obtained outside of a defined window, this should be documented but a repeat scan is not required.

10.1 Definitions of Response

Response to therapy will be determined using the Lugano Classification (2014) for the purposes of determining the ORR.[16] However, as an exploratory endpoint the LYRIC criteria, which take into account the possibility of an Indeterminant Response may be incorporated into the clinical decision making regarding appropriateness of continuing therapy for patients with radiographic PD.[17]

PET/CT based response will include utilization of the 5-point Deauville score[18]:

1 – No uptake above background

2 – Uptake present but ≤ mediastinal blood pool

3- Uptake > mediastinum by ≤ normal section of 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

10.1.1Complete Response (CR):

If PET/CT is used (preferred):

- Deauville Score of 1, 2, or 3 with or without a residual mass
- No new lesions (Defined as any new FDG-avid lesion that is consistent with lymphoma rather than another etiology)
    - New lesions of uncertain etiology should be confirmed by either biopsy or subsequent scan prior to being considered progression
- No evidence of FDG-avid disease in the bone marrow

If CT alone is used:

- Target nodes / nodal masses must regress to ≤1.5cm in longest diameter
- No extralymphatic sites of disease
- Organ enlargement regressed to normal
- No non-measured lesions
- No new lesions
    - New node > 1.5cm 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
- Regrowth of previously resolved lesions

- Bone marrow is normal by morphology

10.1.2 Partial Response (PR):

If PET/CT is used (preferred):

- Deauville score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size.
- No new lesions (Defined as any new FDG-avid lesion that is consistent with lymphoma rather than another etiology)
  - New lesions of uncertain etiology should be confirmed by either biopsy or subsequent scan prior to being considered progression
- Bone marrow: residual uptake higher than normal but reduced compared to baseline. In the presence of a nodal response, consider a bone marrow biopsy and/or interval scan if there remains uptake in the bone marrow.

If CT alone is used:

- ≥ 50% decrease in the sum of the product of diameters for up to 6 target measurable nodes and extranodal sites
- Lesions too small to measure on CT shall be assigned a diameter of 5mm x 5mm
- Lesions that are no longer visible shall be considered 0mm x 0mm
- For nodes that are > 5mm x 5mm, use the actual measurement
- Spleen must have regressed by > 50% in length beyond normal
- No increase in non-measured lesions
- No new lesions
  - New node > 1.5cm 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
  - Regrowth of previously resolved lesions

10.1.3 Stable Disease (SD):

If PET/CT is used:

- Deauville score of 4 or 5 with no significant change in FDG uptake from baseline
- No new lesions (Defined as any new FDG-avid lesion that is consistent with lymphoma rather than another etiology)
    - New lesions of uncertain etiology should be confirmed by either biopsy or subsequent scan prior to being considered progression
- Bone marrow: No change from baseline

If CT is used:

- < 50% decrease from baseline in the sum of the product of the diameters of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
- No increase consistent with progression in non-measured lesions and/or organ enlargements
- No new lesions
    - New node > 1.5cm 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
    - Regrowth of previously resolved lesions

10.1.4 Progression (PD) or Relapse:

If PET/CT is used (preferred):

- Deauville score of 4 or 5 with an increase in intensity of uptake from baseline in individual target nodes/nodal masses and/or new FDG-avid foci consistent with lymphoma.
- Bone marrow: New or recurrent FDG-avid foci

If CT is used:

- An individual node must have a Longest diameter > 1.5cm and an increase in 50% from the product of the proximal diameter nadir and an increase in the longest or shortest diameter from the nadir of 0.5cm for lesions ≤2cm and 1.0 cm for lesions > 2cm
- Splenic length increased by > 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, then it must increase by at least 2cm from baseline.
- New or clear progression of previous non-measured lesions
- Any new nodal lesion:
    - New node > 1.5cm 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
    - Regrowth of previously resolved lesions

10.2 Consideration of an Indeterminant Response

For the purposes of defining the efficacy endpoint of this study, patients who experience PD according to the criteria above will be considered to have PD. However, given the propensity for tumor flare, pseudoprogression, and other radiographic findings of progression that exist in patients receiving this class of therapy in the absence of clinical symptoms consistent with progression, patients who experience PD but who are clearly benefitting from treatment will be allowed to continue.

These patients will be considered to have an Indeterminant Response, defined as having one of the following:

1) Increase in overall tumor burden (as assessed by the sum of the product of the diameters of ≥ 50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration.

2) Appearance of new lesions or growth of one or more existing lesion(s) ≥ 50% at any time during treatment; occurring in the context of lack of overall progression (< 50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment.

3) Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size of number.

Patients who experience radiographic PD will be assessed for the possibility of an indeterminant response and this will be recorded for all patients. Note: patients do NOT have to achieve one of these criteria to be permitted to continue therapy in the context of radiographic PD as long as the patient is clearly benefitting from therapy as assessed by the investigator.

11.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

11.1 Duration of Treatment

All patients not experiencing significant toxicity (including DLT) or frank, symptomatic disease progression shall receive at least 2 cycles of therapy. Thereafter, selected patients may discontinue study therapy to proceed with off-study consolidation approaches as felt appropriate by their treating physician (ie, autologous transplant).

NOTE: Patients who discontinue study therapy to proceed with alternative treatment such as transplantation will be permanently removed from the study treatment and may not receive combination therapy or nivolumab monotherapy as part of the study.

11.1.1 CR, PR, or SD

All patients achieving CR, PR, or SD may continue study therapy until the development of unacceptable toxicity, the patient or treating physician feels that treatment should be discontinued for any reason, or the patient has completed all prescribed therapy.

11.1.2 Disease Progression

Any patient who experiences confirmed PD during the first 6 cycles of therapy shall be removed from study therapy unless they are showing unequivocal benefit from treatment and are not experiencing undue toxicity. These patients may continue on study therapy until they have symptomatic progression of disease. Ideally all patients who have not experienced unacceptable toxicity will complete at least 2 cycles of therapy and will have their first disease assessment but patients with frank, clinical evidence of progressive disease may be removed from the study at any time.

Patients experiencing PD during the monotherapy phase of the study shall be managed based on the scenarios below:

a) Patients with radiographic evidence of progression but no clinical symptoms may, at the discretion of the treating investigator, continue on study therapy until they have completed the prescribed treatment. These patients shall be considered PD for the purposes of data analysis but may continue therapy if felt to be benefitting.

b) Patients with radiographic evidence of progression with associated symptoms MUST be removed from study therapy. In addition, any patient who experiences PD with or without symptoms and who is felt to no longer be benefitting from study therapy shall be removed from study therapy.

11.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy shall be discontinued.

12.0 STATISTICAL CONSIDERATIONS

12.1 Phase 1 Trial

We will use the standard 3 + 3 phase I dose escalation design with 3-6 patients being treated at each dose level. Dose limiting toxicity [DLT] will be defined according to Table 2. The DLT observation period will be the first two cycles; i.e. the first two cycles will be used to determine DLT and inform does escalation decision. For the purposes of DLT determination, the first two cycles shall end when the first chemotherapy is infused on cycle 3, day 1. A patient who must delay cycle 3 for any reason will still be considered for DLT until they have actually initiated cycle 3 therapy. Patients who do not complete 2 cycles of therapy for reasons other than toxicity will be replaced on that dose level for the purposes of dose determination but may still continue therapy and be considered for safety and efficacy analyses.

The maximum tolerable dose [MTD] is defined as the highest dose level where at most one of 6 patients experience DLT. Three patients will be enrolled at each dose level, starting at dose level 1. If one patient experiences a DLT, this dose level will be expanded to 6 patients. The dose where 2 or more DLTs are observed will be declared the maximum administered dose and will have exceeded the MTD. The previous dose level will be expanded to a total of 6 patients and if 1 or fewer DLTs are observed at this level, this will be the maximum tolerated or recommended phase 2 dose (RP2D). There will be no intra-patient dose escalation. If 2 or more DLTs are observed at dose level 1, the next cohort of patients will be accrued to dose level (-1). If dose escalation reaches dose level 2, this dose level will expand to 6 patients to ensure patient safety. If 1 or fewer patients experiences DLT at dose level 2, this will be used as the recommended phase 2 dose and the trial will proceed to phase 2. A phase 2 study will be conducted in patients with relapsed or refractory Hodgkin lymphoma at the phase 1 determined MTD. Those 6 patients at RP2D in the phase 1 study will be included in the responses evaluated as part of the phase 2 study of this trial.

In addition to the monitoring for DLT during cycle 1-2 for all patients enrolled on the phase 1 study, we will also plan a second safety evaluation after 6 patients have completed 4 cycles of combination therapy. If any of the first 6 patients discontinue study therapy for any reason prior to completion of cycle 4, their data will still be included in this safety analysis. However, the safety analysis will not occur until 6 patients have completed 4 cycles of therapy.

If any of the following occur prior to the completion of 4 cycles of therapy, the study will temporarily hold further accrual and a determination will be made by the principal investigator, in collaboration with the Winship Cancer Institute Data Safety Monitoring Committee regarding the need to adjust the treatment regimen/schedule, eligibility criteria, or other aspect of the study to improve safety:

a. ≥ 20% of patients experience grade ≥ 3 pneumonitis at least possibly related to study therapy and not felt to be infectious

b. ≥ 20% of patients experience grade ≥ 3 transaminase elevation (ALT or AST) at least possibly related to study therapy

c. ≥ 20% of patients experience grade ≥ 3 rash at least possibly related to study therapy

d. ≥20% of patients experiencing grade ≥3 or unmanageable lesser-grade immune mediated adverse reaction.

e.

12.2 Phase 2 Trial

For the phase 2 portion of the study, we will enroll patients at the MTD/RP2D as determined by the phase 1 study. We will utilize a 2 stage Simon MiniMax design for phase 2 with CR rate as the primary endpoint. For this study, we will use the historical CR rate of 25% (from the phase 1/2 study of gemcitabine/bendamustine) to evaluate the efficacy of this regimen and determine the interest in moving the combination forward. The goal CR rate for this study shall be 45%.

Patients will be enrolled and evaluated for best response achieved through cycle 6. Patients who discontinue study therapy prior to cycle 6 but who had a response reported will use that response for the primary endpoint (ie, a patient achieving a CR after 2 cycles who discontinues therapy to move forward . CR rate will be determined by dividing the number of CR's (per Lugano criteria) by the total number of evaluable patients. Evaluable patients will include patients who receive any dose of study therapy at any time. Patients who discontinue study therapy due to progression as well as those who discontinue for other reasons prior to the first restaging assessment will be considered as non-responders for the purposes of the primary endpoint.

In order to have 80% power to detect an improvement in CR rate from 25% to 45%, we will enroll a total of 36 patients to the phase 2 portion of the study. The first stage of the 2-stage design will include enrollment of 17 patients, and the study will continue to the second stage if ≥ 5 patients achieve a CR. If 4 or fewer patients achieve a CR, the study will end at the conclusion of the first stage.

In order to reach both planned primary endpoints (phase 1 and phase 2) we will require a minimum of 26 patients (9 in phase 1 and 17 in phase 2) and a maximum of 54 patients (18 in phase 1 and 36 in phase 2).

Planned secondary analyses will include overall response rate (total number of patients achieving a PR or CR as best response through cycle 6 divided by total number of patients treated); duration of response (determined from date of best response to progression or death), progression free survival (determined from date of 1st dose of study drug to progression or death), and overall survival (determined from date of 1st dose of study drug to death from any cause). We will also capture the time to next treatment as well as the time from progression to discontinuation of study therapy for patients who continue to receive therapy post progression.
We will determine all of the above endpoints using Lugano criteria of response and to determine progression of disease. However, as an exploratory endpoint, we will also utilize recently published Lyric guidelines for evaluation of immunotherapies.

Survival endpoints will be evaluated using the Kaplan-Meier method and will presented in tables and graphs.

We will also evaluate toxicities which will be presented in tabular form as appropriate based on grade and attribution.

As discussed above, we will also continuously monitor for immune-mediated toxicities throughout the study as well as any study-related deaths which shall result in a temporary holding of accrual while any further amendments or supportive measures are implemented. This is discussed in detail above.

12.3 Statistical Analysis

After study complete, DLTs will be listed per dose level. Because the intent is to find a desirable dose that meets the tolerability criteria based on DLT rate while demonstrating clinical activity based on response rate, descriptive statistics (n, frequency and percentage) will be reported. Corresponding listings of data will be generated. DLT rate by dose level will be calculated as proportion (Patients with DLT/Total patients) along with 95% confidence intervals using the Clopper-Pearson method. Chi-square test or Fisher's exact test will be used to compare the probability of DLT between the different dose levels, respectively.

Other adverse events (toxicity) will be listed and summarized overall and by dose level. Adverse events will also be listed by severity, seriousness, and by system organ class. The number and percentage of subjects who experience AEs will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. No formal statistical comparison between the dose levels will be performed. AEs will be presented with and without regard to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity grades 1 through 5, will be described. Additional summaries will be provided for AEs that are observed with higher frequency.

Planned secondary analyses will include overall response rate (total number of patients achieving a PR or CR as best response through cycle 6 divided by total number of patients treated); duration of response (determined from date of best response to progression or death), progression free survival (determined from date of 1st dose of study drug to progression or death), and overall survival (determined from date of 1st dose of study drug to death from any cause). We will also capture the time to next treatment as well as the time from progression to discontinuation of study therapy for patients who continue to receive therapy post progression. We will determine all of the above endpoints using Lugano criteria of response and to determine progression of disease. However, as an exploratory endpoint, we will also utilize recently published Lyric guidelines for evaluation of immunotherapies.

Response rate (ORR or CBR) will be calculated as proportion (Responders/Total patients) along with 95% confidence intervals using the Clopper-Pearson method. Chi-square test or Fisher's exact test will be used to compare the efficacy in term of response rate between the different groups stratified by dose level or other factors, respectively. Logistics regression model will be further employed to test the adjusted effect of dosage on the response rate after adjusting for other clinical factors and demographic factors.

Overall survival (OS) and progression free survival (PFS) rates of two patient groups stratified by dose levels or other factors will be estimated with the Kaplan-Meier method and compared between different groups using the log-rank test, respectively. The PFS and OS of each patient group at specific time points, such as 6 moths, 1 year, 3 year, and 5 year, etc. will be also estimated alone with 95% CI. Cox proportional hazards models will be further used in the multivariable analyses to assess adjusted effect of dose levels on the patients' OS and PFS after adjusting for other factors. Interaction terms between these factors will also be tested for statistical significance. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics. Violations of the proportional hazards assumptions will be addressed by use of time-dependent covariates or extended Cox regression models.

13.0 Adverse Event Identification and Reporting

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be recorded and reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all AEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any AE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS . The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
    - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
    - The MedWatch form is available at: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
-
- Worldwide.Safety@bmsaepbusinessprocess@bms.com
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.
    - Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of

the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to the FDA and their local IRB, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on either CIOMS or MedWatch form & pregnancies must be reported on a Pregnancy Surveillance Form or can be submitted on the aforementioned SAE form to BMS.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to Emory University IRB, which in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

DEFINITIONS

SERIOUS ADVERSE EVENTS

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

Adverse Events at Subsites:

For participating subsites, adverse events collected at weekly treatment visits is to be entered into OnCore no later than 14 calendar days after data collection.

Site investigators must also report all SAEs and unanticipated problems to the sponsor-investigator within 24 hours of the participating site becoming aware of the event. The participating site will submit the MedWatch Form 3500A to the Winship regulatory staff and will also enter the data into OnCore within the specified timelines above. The Emory sponsor must review and sign off on the event and return to the Winship regulatory staff. Regulatory will review the assessment to determine IRB and/or FDA reporting requirements.

The Winship Cancer Institute Data Safety Monitoring Committee

The study will also be followed by the Winship Cancer Institute Data Safety Monitoring Committee to allow for local review and confirmation of proper study execution and safety measures.

Patient safety, study efficacy and compliance will be reviewed at the Winship Cancer Institute Lymphoma Working Group meeting. The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will also oversee the conduct of this study (every 6 months or annually – depending on the risk level of the protocol). This committee will review pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The Committee reserves the right to conduct additional audits if necessary. The Principal Investigator (PI) or designee is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study. The PI or designee will also notify the DSMC of study status within 2 months before the next scheduled review is due.

Procedures to assure data integrity and protocol adherence

Imaging and clinical data will be analyzed in a quarterly meeting of investigators, clinical research coordinators and regulatory personnel.

Adverse event reporting will utilize NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and is detailed in section 13 above.

Study Team Oversight: The study progress in terms of enrollment, activity of current patients under active treatment, observed toxicities will be reviewed in the weekly Emory Lymphoma Working Group. Here there will be random and selected case report form and chart review. Special and problematic items requiring additional attention will be addressed in separate sessions of the Lymphoma Working Group occurring up to weekly including selected study investigators, clinical research coordinators and regulatory personnel.

Training of investigators, clinical research coordinators and regulatory personnel at all sites will be performed by one of the site investigators utilizing the written protocol and a summary of pertinent treatment activities. Completion of the training of investigators, clinical research coordinators and regulatory personnel will be documented on a study training log.

On-site Audits
Regulatory authorities, the IRB and BMS may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support given reasonable notice at all times for these activities.

Monitoring plan of Subsite(s):

At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spread sheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spread sheet will be shared with the Emory PI via e-mail monthly. Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the principal investigators at each site. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy and the PI at Emory will communicate with participating sites via monthly email as needed. Chart reviews will be performed on selected cases by the participating site staff to confirm that the data collection is accurate.

Winship's Multi- Site Coordinator will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (annually once onsite and three times remotely) until subject follow-up is terminated.. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies.

16.0 References

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APPENDIX: Suggested algorithms for common immunologic toxicities related to nivolumab.

NOTE – the algorithms below do not take the place of clinical judgment and are meant as suggested approaches.

PULMONARY:

Grade 1:

- May continue nivolumab treatment
- Monitor every 2-3 days with clinical exam
- Re-image (Chest X-Ray or CT Chest as indicated) at least every 3 weeks if not resolved
- If worsens, treat as if grade 2

Grade 2:

- Withhold nivolumab treatment
- Initiate 1-2mg/kg/day prednisone (or equivalent) followed by 1 month steroid taper
- Workup: Consider pulmonary and/or infectious disease consultation, bronchoscopy w/ biopsy, and repeat imaging every 1-3 days as indicated.
- Steroids should be tapered prior to consideration of restarting nivolumab. Patients should only be rechallenged with nivolumab in consultation with the study chair.

Grade 3-4:

- Permanently discontinue nivolumab and remove from study therapy
- Initiate prednisone 1-2mg/kg/day (or equivalent) and taper steroids over 6 weeks.
- Consider inpatient hospitalization, pulmonary/infectious disease consultation, and bronchoscopy w/ biopsy.
- Consider non-corticosteroid immunosuppression if symptoms worsen after 2 days.

GASTROINTESTINAL

Grade 1:

- Continue nivolumab treatment
- Administer symptomatic treatment as indicated
- Monitor closely for worsening symptoms and counsel the patient to contact the clinical team immediately with worsening symptoms.
- If worsens, treat as if grade 2

Grade 2:

- Withhold nivolumab
- Treat with symptomatic measures
- If grade 2 colitis for > 5 days, initiate 0.5-1mg/kg/day of prednisone (or equivalent) and taper steroids over 1 month. May increase to 1-2mg/kg/day if no improvement.
- May resume treatment if improved to grade ≤ 1 if steroids have been tapered.

Grade 3:

- Withhold nivolumab
- Treat with 1-2mg/kg/day of prednisone (or equivalent) with a taper for at least 1 month
- Consider colonoscopy
- Steroids must be tapered and symptoms improved to grade ≤ 1to resume treatment.
- If symptoms persist > 3-5 days or recur, consider addition of a non-corticosteroid immunosuppressive agent.

Grade 4:

- Permanently discontinue nivolumab and remove patient from study therapy
- Treat with 1-2mg/kg/day of prednisone (or equivalent) with a taper for at least 1 month
- Consider colonoscopy
- If symptoms persist > 3-5 days or recur, consider addition of a non-corticosteroid immunosuppressive agent.

HEPATIC (Note discontinuation rules for hepatic toxicity documented in Section 7.3)

Grade 1:

- Continue nivolumab
- Monitor LFT's throughout treatment
- If symptoms worsen, treat as grade 2

Grade 2:

- Withhold nivolumab
- Increase frequency of monitoring to every 3 days
- Consider 0.5-1mg/kg/day prednisone or equivalent with taper over at least 1 month
- Toxicity must be returned to grade ≤ 1 after a steroid taper before restarting nivolumab

Grade 3-4:

- Permanently discontinue nivolumab and remove from study therapy
- Monitor every 1-2 days
- Consult hepatology
- Initiate 1-2mg/kg/day prednisone (or equivalent) followed by taper of at least one month
- Consider non-steroid immunosuppression if no improvement in 3-5 days

CUTANEOUS

Grade 1-2:

- Continue treatment
- Administer symptomatic treatments (ie, topical steroids)
- Consider skin biopsy and/or drug discontinuation if symptoms persist for > 1-2 weeks

Grade 3:

- Withhold nivolumab
- Consider dermatology consultation and skin biopsy
- Start 1-2mg/kg/day of prednisone or equivalent with at least a 1 month taper
- May consider resuming nivolumab if improved to grade ≤ 1 after steroid taper

Grade 4 (or confirmed SJS or TEN):

- Permanently discontinue nivolumab and remove from study therapy
- Consider dermatology consultation and skin biopsy
- Start 1-2mg/kg/day of prednisone or equivalent with at least a 1 month taper