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Nivolumab for Relapsed or Refractory Disease Post Chimeric Antigen Receptor T-cell Treatment in Patients with Hematologic Malignancies

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Supported by:
Bristol Myers Squibb

PROTOCOL SYNOPSIS

Protocol Title	**Nivolumab for Relapsed or Refractory Disease Post Chimeric Antigen Receptor T-cell Treatment in Patients with Hematologic Malignancies**
Protocol Number	BMS CA209-7CD
Protocol Sponsor	Andrew Cowan, MD, University of Washington
Trial Phase	Phase II
Trial Type	Interventional
Clinical Indication	Relapsed or Refractory Hematologic Malignancy (including B-cell NHL, CLL, multiple myeloma)
Study Objectives	**Primary Objectives** 1. To assess the efficacy of nivolumab, a PD-1 inhibitor, in subjects with hematologic malignancies with relapsed, refractory, or detectable disease after receipt of CAR T-cell therapy **Secondary Objectives** 1. To determine overall survival, progression free survival, and duration of response after treatment with nivolumab 2. To assess the safety of administering nivolumab, a PD-1 inhibitor, in subjects with hematologic malignancies with relapsed or refractory disease after receipt of CAR T-cell therapy **Exploratory Objectives** 1. To determine cytokine response after treatment with nivolumab 2. To determine correlation between PD-1 and PD-L1 expression in pre-treatment tumor biopsies and outcomes 3. To collect peripheral blood samples for future biomarker analyses
Study Design	This is a Phase II single arm, unblinded trial.
Population	Hematologic malignancy subjects with relapsed, refractory or detectable disease after CAR T cell therapy. Histologies to include: • B-Cell NHL • CLL • Multiple Myeloma

Endpoints	**Primary Endpoint**
	• Best overall response rate, as assessed by disease-specific guidelines:
	  ○ Multiple Myeloma – International Myeloma Working Group response criteria (See Appendix E)
	  ○ Non-Hodgkin Lymphoma – Response assessment will be based on the Lugano Criteria (See Appendix C)
	  ○ Chronic Lymphocytic Leukemia – Response assessment based on the IWCLL Criteria (See Appendix D)
	Secondary Endpoints
	• Overall survival
	• Progression-free survival
	• Duration of response
	• Adverse events, determined by NCI CTCAE v5.0
	Exploratory Endpoints
	• Serum inflammatory cytokines
	• Immunohistochemistry for PD-1 and PD-L1 in pre-treatment tumor biopsies
	• Peripheral blood sample for future biomarker analyses

Type of control	No treatment control
Investigation Drug	Nivolumab
Dose	480 mg IV every 4 weeks
Route of administration	Intravenous
Regimen	Single agent nivolumab
Trial Blinding	Unblinded, open label
Treatment Groups	1 group
Efficacy Assessments	Safety assessment will occur through the study and consist of continuous surveillance and recording of adverse events (AEs) and serious adverse events (SAEs). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events may be collected for 90 days after the end of treatment). Subjects may have post- treatment follow-up for disease status up to 5 years at longest, or until disease progression,

	initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. 1. Non-Hodgkin Lymphoma: PET-CT and CT (Diagnostic quality) after 2 cycles (8 weeks), then Diagnostic CT of chest, abdomen, and pelvis every 3 cycles (12 weeks) thereafter. Response assessment will be based on the Lugano Criteria[1] a. Initial response assessment after 2 cycles (8 weeks) with PET-CT and diagnostic CT of chest, abdomen, and pelvis b. Diagnostic CT of the chest, abdomen, and pelvis every 3 cycles thereafter 2. Chronic lymphocytic leukemia: PET-CT and CT (Diagnostic quality)after 2 cycles (8 weeks), then Diagnostic CT of chest, abdomen, and pelvis every 3 cycles (12 weeks) thereafter. A bone marrow aspirate +/- biopsy will only be obtained at screening and to confirm CR. Response assessment based on IWCLL criteria[2] a. Initial response assessment after 2 cycles (8 weeks) with PET-CT and diagnostic CT of chest, abdomen, and pelvis b. Diagnostic CT every 3 cycles thereafter 3. Multiple myeloma: Assessment of serum protein electrophoresis (SPEP), serum free light chains (sFLC), every 4 weeks. 24-hour urine assessment of Bence-Jones Proteinuria only in subjects who have this as sole marker of disease. Response assessment based on the IMWG[3]. A bone marrow aspirate and biopsy will be obtained at screening and to confirm CR. PET-CT only to be performed amongst subjects with plasmacytoma as the only site of measurable disease, at screening, after 2 cycles, then every 3 cycles thereafter.
Number of trial subjects	20
Estimated duration of trial	105 months (estimated time from first subject enrollment through final subject completion of study intervention, plus 5 years of follow up)
Duration of Participation	9 months Subjects will receive treatment with nivolumab until disease progression, unacceptable toxicity, or withdrawal by subject or investigator. Survival, and disease status will be followed for up to 5 years.

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1.0 INTRODUCTION

This is a phase II study to evaluate the efficacy of nivolumab, a PD-1 inhibitor, for treatment of patients with hematologic malignancies (including B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma) who either experience relapse or have persistent/detectable disease after treatment with chimeric antigen receptor (CAR) T cell therapy. This is a clinical research protocol, and the described study will be conducted in compliance with the IRB approved protocol, associated Federal regulations, and all applicable IRB requirements.

2.0 OBJECTIVES

2.1 Study Objectives

Primary Objectives

1. To assess the efficacy of nivolumab, a PD-1 inhibitor, in patients with hematologic malignancies with relapsed, refractory, or detectable disease after receipt of CAR T-cell therapy

Secondary Objectives

1. To determine overall survival, progression free survival, and duration of response after treatment with nivolumab
2. To assess the safety of administering nivolumab, a PD-1 inhibitor, in patients with hematologic malignancies with relapsed or refractory disease after receipt of CAR T-cell therapy

Exploratory Objectives

1. To determine cytokine response after treatment with nivolumab
2. To determine relationship between PD-1 and PD-L1 expression in pre-treatment tumor biopsies and outcomes
3. Residual peripheral blood specimens will be stored and used for future molecular biomarkers analyses

3.0 BACKGROUND

3.1 Relapsed/Refractory Hematologic Malignancies after CAR-T cell therapy as an Area of Unmet Medical Needs

Patients with relapsed or refractory hematologic malignancies have a poor prognosis. As an example, patients with multiple myeloma (MM) who are refractory to proteasome inhibitors and immunomodulatory agents have a median overall survival of 9 months[4]. This trend is mirrored amongst other hematologic malignancies – patients with aggressive lymphoma who fail dose adjusted R-EPOCH have a reported median overall survival of only 10 months[5]. Thus, there is a clear unmet need for effective therapies in patients with relapsed hematologic malignancies.

Despite the grim statistics, increasingly, patients with hematologic malignancies increasingly have a wide array of treatment options for relapsed disease. The use of drugs to manipulate the immune system to achieve an anti-tumor effect, or genetic modification of the immune system to target malignancy – collectively known as immunotherapy – has revolutionized the treatment options for all patients with hematologic malignancies. The malignancies that have particularly benefited from immunotherapy include B-cell lymphocytic leukemia (B-ALL), aggressive and indolent non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and MM. Monoclonal antibodies targeting immune checkpoints, such as programmed death-1 (PD-1), have been FDA approved for treatment of many solid tumors, and also shown promising results in some hematologic malignancies, such as relapsed classical Hodgkin lymphoma. Another class of immunotherapy, chimeric antigen receptor (CAR)-modified T-cells, involves generation of tumor-specific T-cells through genetic transfer of a tumor-targeting receptor. CAR T-cells are currently FDA approved for treatment of relapsed diffuse large B-cell lymphoma (DLBCL) and B-ALL in young adults, and other products are currently in evaluation for other hematologic malignancies with promising early results.

One of the first cellular immunotherapies to gain FDA approval was tisagenlecleucel, a CD19 CAR-T cell (Kymriah). Tisagenlecleucel was first studied in the single arm Phase II ELIANA trial, a global trial of CD19 CAR T-cells in patents with relapsed or refractory B-ALL. A total of 75 patients were infused with tisagenlecleucel, with a 12-month event-free survival rate of 50% (95% CI, 35-64), and 12-month overall survival of 76% (95% CI, 81 – 95)[6]. The results of this trial led to FDA approval in 2017. Concomitant studies of CD19 CAR-T cells in other hematologic malignancies with expression of tumor CD19 then followed. The landmark JULIET trial was an international phase 2 trial of tisagenlecleucel for adult patients with relapsed or refractory diffuse large B-cell lymphoma who were either ineligible for autologous stem cell transplantation (ASCT) or relapsed after ASCT[7]. This trial demonstrated a 52% overall response rate, with a 12-month relapse free survival rate of 65%. Importantly, toxicity profile was manageable, with no deaths attributable to tisagenlecleucel, cytokine release syndrome, or neurologic toxicity. Another CD19 CAR T-cell therapy also gained approval for relapsed or refractory diffuse large B-cell lymphoma, axicabtagene ciloleucel (Yescarta)[8]. The ZUMA-1 trial was a single arm multicenter Phase 1-2 trial of axicabtagene ciloleucel inpatients with refractory or relapsed disease after ASCT and included the following histologies: diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma. Long term follow-up from the ZUMA-1 trial were recently reported, and of evaluable patients, 83% had an objective response, with a median duration of response of 11.1 months, and median progression free survival of 5.9 months. The toxicity profile for ZUMA-1 showed more grade 3 or worse cytokine release syndrome (11%), and grade 3 or worse neurologic events in 32%[9].

Chimeric antigen T-cells have also been studied in multiple myeloma (MM), though there no FDA approved cellular products as of 2019. There have been several targets used in multiple myeloma, but the most promising thus far has been B cell maturation antigen (BCMA), based on its plasma cell-restricted expression profile. Several groups have studied BCMA CAR T-cells. An early effort by investigators at the National Cancer Institute (NCI) was a phase I clinical trial of BCMA CAR T-cells for relapsed or refractory MM. At the highest dose level, 9 x 10^6 CAR-BCMA T cells/kg, they found an overall response rate of 81%, and median EFS of 31 weeks, with severe cytokine release syndrome in some cases, but mostly reversible[10, 11]. At present, the most developed product is bb2121, a second-generation CAR T-cell product targeting BCMA. Updated results from the Phase 1 trial of bb2121 were presented at the American Society of Clinical Oncology (ASCO) meeting in June 2018, showing remarkable efficacy, with an overall response rate of 95.5% in the highest dose cohort of 150 x 10^6, and a median progression-free survival for patients at that dose level of 11.8 months[12].

Unfortunately, despite the initial promise from cellular immunotherapies such as CD19 and BCMA CAR-T cells, the subset of patients who either do not respond, or relapse following therapy, is poor. A recent presentation at ASH examined the outcomes of patients with CD19 expressing lymphomas who underwent CD19 specific CAR T-cell therapy who either did not respond or responded and later progressed. They reported a median OS of 5.1 months for non-responders, and 13.6 months for those who responded and later progressed[13]. These results highlighted the poor outcomes among patients who did not benefit from CD19 CAR-T cells.

3.2 Preclinical and Clinical Data for PD-1 Inhibitors with CAR T-cell Therapy

Although impressive results have been seen with CD19 CAR T-cells in patients with an otherwise grim prognosis, they have been tempered by the reality that a) even patients with initial responses can relapse, and b) the majority of patients do not respond to CD19 CAR T-cells and, as demonstrated by the data presented at ASH, have a dismal prognosis, with a median OS of only 5.1 months for non-responders. Thus, there is an unmet need to improve outcomes for this population of patients who relapse or are refractory to CAR T-cell therapy.

In thinking about the reasons that patients may not respond or may lose response to CAR T-cell therapy, two general themes emerge. One potential reason for loss of response is loss of surface antigen target from the tumor[14]. Another theory that has emerged, is that the CAR T-cells may take on a more exhausted phenotype over time. Exhausted CAR T-cells overexpress inhibitory receptors such as programmed death 1 (PD-1), with simultaneous upregulation of PD-L1 and PD-L2[15]. Pre-clinical research has shown that in a solid tumor model, in animals treated with CD28 and 4-1BB based second generation CAR T cells, PD-1 upregulation within the tumor microenvironment inhibited T cell function[16]. The CD28 CAR T-cells had less retention of cytotoxic and cytokine secretion functions, but further investigation also showed that PD-1/PD-L1 pathway interference through PD-1 antibody blockade, could restore the effector function of these CD28 CAR-T cells[16]. Another study demonstrated that tumor specific PD-L1 expression could cause second generation CD19 CAR t cells to become hypofunctional *in* vitro; using CRISPR/Cas9 mediated gene editing and lentiviral transduction to generate PD-1 deficient CD19 CAR T cells, the investigators showed that PD-1 deficient T cells allowed for clearance of the PDL1+ tumors *in vivo*[17]. Further evidence of the negative interaction from PD1/P-L1 signaling was demonstrated in a preclinical study of engineered CAR T cells secreting check point inhibition targeting PD-1 and showed that these engineered cells are more functional and had greater expansion, in addition to showing more tumor eradication than the non-modified CAR T cells[18]. Taken together, these preclinical investigations suggest a role for PD-1 or PD-L1 axis disruption as a potential target for improving the function and efficacy of tumor directed CAR T cells.

Based on these preclinical data, there have been some early published reports of the impact of checkpoint inhibition in combination with CAR T cells. An early case report of a patient with relapsed/refractory DLBCL of primary mediastinal origin who progressed early after receipt of CD19 CAR T cells, who then received a PD-1 inhibitor, resulting in a clinically significant antitumor response, expansion of CD19 CAR T cells, and decreased expression of PD-1 – suggesting a role for PD-1 blockage in at least one patient who failed to initially respond to CD19 CAR T cells[19]. In a study presented at the ASH conference in 2018, in 14 children/adolescents with refractory B-cell malignancies who had either responded transiently, or not at all, to CD19 CAR T cells, receipt of a PD-1 inhibitor helped 7/14 patients reestablish the initial response to CD19 CAR T cells[20]. Another study demonstrated that among lymphoma patients who relapsed post CAR T-cell therapy, pembrolizumab, a PD-1

inhibitor, could improve responses in 3/11 patients[21]. Although these studies did not demonstrate a routinely high response rate, it is perhaps not surprising that only a subset showed clinical benefit, in keeping with the multifactorial reasons for relapse after receipt of CAR T-cells. Together, these studies do suggest an early signal of benefit for a subset of hematologic malignancy patients who fail to benefit from CAR T-cells, or respond and have later relapse.

3.3 Rationale for Dose Selection

Nivolumab is FDA approved as a 240 mg intravenous infusion (IV) every 2 weeks, or 480 mg IV every 4 weeks, for a variety of different indications, including metastatic melanoma, adjuvant treatment of melanoma, metastatic non-small cell lung cancer, advanced renal cell carcinoma, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial carcinoma, and hepatocellular carcinoma (approved indications are detailed in the FDA-approved package insert for Opdivo [nivolumab]). Based on the ease of administration to this patient population, we have chosen the FDA approved dosing of 480 mg IV infusion every 4 weeks, which has shown to be safe in multiple different patient populations, both solid tumor and hematologic malignancy.

3.4 Research Hypothesis

The addition of nivolumab, a PD-1 inhibitor, administered to patients who have evidence of persistent or recurrent disease after CAR T-cell therapy will be safe and may augment T-cell function and response to CAR T-cells.

4.0 DRUG INFORMATION

4.1 Study Agent

Nivolumab – also referred to as BMS-936558 or MDX1106, and commercially marketed by BMS as Opdivo – is a fully human monoclonal IgG4 antibody, which binds to PD-1 receptors on T-cells and prevents the binding of its ligands, PD-L1 and PD-L2. Activated T and B lymphocytes express PD-1, which is a negative regulatory molecule. When PD-1 binds to its ligands PD-L1 and PDL2, it results in reduction in T-cell proliferation, cytokine synthesis, and cytotoxic activity[22]. PD-1 inhibitors such as nivolumab, inhibit the interaction between PD-1 and its ligands, thereby promoting immune responses, and antigen-specific T-cell responses to antigens.

Nivolumab is expressed in Chinese hamster ovary cells and produced using mammalian cultivation and purified using chromatographic techniques. The clinical trial product is a sterile solution for parenteral administration. Nivolumab (nivolumab is approved for use in multiple countries, including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014) (Ref: BMS IB for Nivolumab, 2016). See Investigator Brochure for Nivolumab.

Clinical supplies will be provided by BMS as summarized in Table 1.

Table 1.

Product Name & Potency	Dosage Form
Nivolumab 100 mg/10 mL	Solution for injection

4.2 Packaging and Labeling Information

Clinical supplies will be affixed with IND labeling in accordance with regulatory requirements, as specific in 21 CFR 312.6.

4.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-Investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

4.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

An authorized person at the trial site must record receipt and dispensing of trial medication.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

The site will destroy unused IP per their SOPs. A copy of the drug destruction certificate must be retained for submission to BMS at the end of the study.

4.5 Timing and Administration of nivolumab

Trial treatment should be administered on Day 1 (+/- 3 days) of each cycle after all procedures/assessments have been completed as detailed on the Study Calendar (Appendix A). All trial treatments will be administered on an outpatient basis.

Nivolumab at a dose of 480 mg IV will be administered as a 30 minute IV (-5min/+10 min) infusion every 4 weeks. Every effort should be made to target infusion timing to be as close to 30 minutes as possible.

4.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.7 Effects in Humans and Clinical Efficacy

Nivolumab has clinical activity in a wide range of human malignancies, including NSCLC, melanoma, RCC, SCCHN, Hodgkin's lymphoma, and other tumor subtypes as monotherapy or in combination with other checkpoint inhibitors. The majority of responses in studies were durable, in excess of 6 months. The PK, clinical activity, and safety of nivolumab have been assessed in over 70 clinical trials sponsored by BMS. Across those studies, approximately 16,900 subjects have received nivolumab monotherapy in single or multiple dose studies, or in combination with other therapies. Please see Investigator Brochure for Nivolumab for further details.

4.8 Clinical Safety

Nivolumab monotherapy has a consistent AE profile across multiple tumor types in clinical trials, with no maximum tolerated dose reached at any monotherapy dose up to 10 mg/kg. Across all studies, nivolumab-related AEs include pulmonary toxicity, kidney toxicity, endocrine abnormalities, GI toxicities, dermatologic toxicity, and hepatotoxicity. For nivolumab monotherapy, the majority of these AEs have been managed successfully with supportive care, or in more severe cases, dose delay, discontinuation, or use of glucocorticoids or hormone replacement therapy. See Investigator Brochure for Nivolumab for more details and also section 9.5.

4.8.1.1 Nivolumab – Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to nivolumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

4.8.1.2 Infusion Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of nivolumab.

Table 5. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of nivolumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.8.1.3 Precautions for Women of Childbearing Potential

The nonclinical findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy. However, cases of human in-utero exposure to nivolumab (involving the fetuses of female subjects receiving nivolumab) were reported. Given the potential risk suggested by preliminary data from nonclinical and clinical data, dosing during pregnancy will continue to be prohibited. In addition, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. WOCBP also must not donate eggs while on treatment or for 5 months after the last dose of nivolumab.

These durations have been calculated using the upper limit of the half-life for nivolumab (~25 days) and are based on the recommendation that WOCBP use contraception for 5 half-lives after the last dose of nivolumab. Females should not breastfeed while receiving nivolumab and for any subsequent protocol-specified period.

Female subjects should start using birth control from study Visit 1 throughout the study period up to 5 months after the last dose of study therapy.

Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 14 days prior to the start of study drug. Women must not be breastfeeding. Females of nonchildbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Females of childbearing potential must agree to use 2 effective contraceptive methods during the study and for 5 months following the last dose of nivolumab.

4.8.1.4 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with nivolumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to BMS without delay and within 24 hours to the Sponsor-Investigator and

within 2 business days of investigator knowledge if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to BMS. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to BMS and followed as described above.

4.9 Risk / Benefit of PD-1 Inhibitors in Multiple Myeloma

Checkpoint inhibitors – principally PD-1 and PD-L1 inhibitors – have been studied extensively in multiple myeloma. Studies of PD-1 inhibitors as a monotherapy did not show substantial anti-tumor activity, but also did not have any concerning safety signals. A Phase 1b study of nivolumab, an anti-PD-1 antibody, in patients with relapsed or refractory hematologic malignancy patients, included 27 patients with MM[23]. With respect to safety, the MM cohort appeared to have a decreased risk of any grade adverse event (AE) as compared with the B-Cell NHL and T-CELL NHL patients (52% compared with 71% and 74%, respectively), and a decreased rate of grade ≥ 3 AEs (19% vs 26% and 22%, respectively). The study also showed minimal single agent efficacy, with an overall response rate (ORR) of 4% (1 complete response), with all other patients having stable disease. The KEYNOTE-013 trial was a multi-center Phase 1b study of pembrolizumab, a PD-1 antibody, in patients with hematologic malignancies[24]. The study accrued 30 patients with MM; 40% of patients had any treatment-related AE (TRAE), and only 1 patient experienced a grade ≥ 3 AE (3.3%). There were no grade 4 or 5 TRAEs. The study did not show evidence for anti-tumor activity, with an ORR of 0%; the majority of patients had stable disease (56.7%). Taken together, phase 1 studies of PD-1 inhibitors in MM show an acceptable safety profile in line with that seen in other cancers, but little evidence for single agent activity.

Despite the discouraging results seen with PD-1 inhibitor monotherapy in MM, there was some theoretical evidence that combination of immunomodulatory agents (IMiDs) such as lenalidomide or pomalidomide with PD-1 inhibition may be synergistic, leading to the development of several phase 3 trials. However, these trials were all put on hold in 2017 due to an interim analysis that showed an increased risk of death in MM patients on the experimental arm of these trials. KEYNOTE-185 was a randomized phase 3 trial comparing pembrolizumab, lenalidomide, and dexamethasone, to lenalidomide and dexamethasone for patients with newly diagnosed MM[25]. On July 3, 2017, the FDA halted the trial due to an imbalance in deaths in the experimental arm – with 6 treatment related deaths in the experimental arm, and 2 in the control arm. The KEYNOTE-183 trial was a randomized study in relapsed/refractory MM, comparing pomalidomide, pembrolizumab, and dexamethasone, to pomalidomide and dexamethasone[26]. This trial was also halted early due to an imbalance of deaths, with 4 treatment-related deaths in the study arm, and no deaths in the control arm. Taken together, these trials suggest an adverse risk benefit ratio for combining PD-1 inhibitors with IMiDs in patients with MM.

Despite these findings, there is still good rationale for novel combinations of PD-1 inhibitors with other immunotherapy based approaches. An example of an unmet need where PD-1 inhibitors could be considered is in CAR T cell therapy. The phase 1 study of bb2121, a CAR T cell therapy targeting BCMA in MM, showed a median progression-free survival of 11.8 months; CAR T cell expansion and persistence was associated with responses[27]. Inevitably, however, all patients will relapse, and potentially using a PD-1 inhibitor for patients who relapse could result in responses due to persistent circulating CAR T cells, as has been seen in other hematologic malignancies. Thus, there is good

rationale for using PD-1 inhibition as a monotherapy in this setting for MM patients, given that there were no adverse safety signals with PD-1 inhibitors seen when given as monotherapy.

5.0 OVERVIEW OF CLINICAL TRIAL

5.1 Study Design

This is a pilot study of nivolumab, 480 mg IV every 4 weeks, for patients with relapsed or persistent disease after treatment with CAR T-cell therapies.

5.2 Primary Endpoint

- Best overall response rate, as assessed by disease-specific guidelines:
  - Multiple Myeloma – International Myeloma Working Group response criteria (See Appendix F)
  - Non-Hodgkin Lymphoma – Response assessment will be based on the Lugano Criteria (See Appendix D)
  - Chronic Lymphocytic Leukemia – Response assessment based on the IWCLL Criteria (See Appendix E)

5.3 Secondary Endpoints

- Overall survival
- Progression-free survival
- Duration of response
- Adverse events, determined by NCI CTCAE v5.0

5.4 Exploratory Endpoints

- Serum inflammatory cytokines
- PD-1 and PD-L1 expression in pre-treatment tumor biopsy by immunohistochemistry
- Peripheral blood may be used for future studies, such as molecular biomarker analyses

5.5 Estimated Accrual

Estimated accrual for this trial is 20 subjects with hematologic malignancies over 36 months

5.6 Name of Funding Source

Bristol Myers Squibb

6.0 SAFETY CONSIDERATIONS

6.1 Stopping Rules

In the event of a death on study that is deemed to be possibly, probably, or definitely attributable to the drug, further infusions will be suspended pending review by the DMC and consultation with the FDA. To further protect the safety of subjects, the study incorporates a stopping rule if the lower bound of a 1-sided 80% exact binomial confidence interval of the discontinuation rate due to medically significant Grade 3 or greater events that are possibly, probably, or definitely attributable to the drug is > 20%. Operationally, any of the following would trigger such as rule: 2 out of the first $\leq$6 subjects or 3 out of the first $\leq$9 subjects or 4 out of the first $\leq$13 or 5 out of the first $\leq$16 or 6 out of the first $\leq$20 subjects have unacceptable toxicity or $\geq$Grade 3 AEs that are possible, probably, or definitely attributable to drug. If the true probability of $\geq$Grade 3 AE is 2.5%, the probability of study suspension under the above rule is approximately 0.01; if the true probability is 40%, the probability of suspension is approximately 0.91 (probabilities estimated from 5,000 simulations).

If this rule is met, further treatment for all subjects enrolled will be immediately halted. A safety evaluation will be performed and reviewed with the FDA and DMC prior to resuming any drug.

7.0 SUBJECT ELIGIBLITY

7.1 Inclusion Criteria

1. Male and female patients
2. Diagnosis of the following tumor types
    a. Non Hodgkin-Lymphoma, including:
        i. Diffuse large B-cell lymphoma: Histopathologic confirmation
        ii. Mantle cell lymphoma: Histopathologic confirmation
        iii. Follicular lymphoma, all grades: Histopathologic confirmation
        iv. Marginal zone lymphoma: Histopathologic confirmation
    b. Chronic lymphocytic leukemia: Histopathologic or flow cytometric confirmation:
    c. Multiple myeloma: Histopathologic or flow confirmation
3. Relapsed, refractory, or detectable disease after treatment with chimeric antigen receptor T-cells
    a. Multiple Myeloma: patients must have exhausted all treatment options known to provide clinical benefit, and are refractory to a minimum of 3 prior lines of therapy (including an IMiD, PI, or anti-CD38 monoclonal antibody).
4. Have measurable disease, defined by histology:
    a. Non-Hodgkin's Lymphoma, based on presence of lesions $\geq$1.5 cm that can be accurately measured in 2 dimensions by CT (preferred) or MRI, and are not included in any prior field of radiation therapy
    b. Chronic lymphocytic leukemia: circulating lymphocytes $\geq$5,000 / mm^3
    c. Multiple Myeloma, based on the International Myeloma Working Group (IMWG) criteria of having one or more of the following findings:
        i. Serum M protein $\geq$1.0 g/dL

ii. Urine M protein ≥200 mg/24 hours
iii. Involved serum free light chain level ≥10 mg/dL with abnormal κ/λ ratio
iv. Measurable biopsy-proven plasmacytomas (≥1 lesion has a single diameter ≥2 cm)
v. Bone marrow plasma cells ≥30%

5. Age 18 years and older, and have the capacity to give informed consent
6. Anticipated survival of > 3 months
7. ECOG performance status of 0-2 (See Appendix B)
8. Post CAR T cell receipt of intervening palliative radiation therapy is allowed
9. Adequate organ function, as defined by:
    a. eGFR ≥ 20 ml/min
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN and total bilirubin ≤ 2 x ULN
    c. ANC ≥ 1,000/µL
    d. Platelets ≥ 50,000/µL
    e. Hemoglobin ≥ 8 g/dL

7.2 Exclusion Criteria

1. Receipt of intervening systemic therapy after CAR T-cell infusion
2. History of another primary malignancy that has not been in remission for at least 1 year (with the exception of non-melanoma skin cancer, curatively treated localized prostate cancer, curatively treated superficial bladder cancer and cervical carcinoma in site on biopsy or a squamous intraepithelial lesion on PAP smear)
3. Active hepatitis B, hepatitis C at time of screening
4. Known (HIV) seropositivity
5. Subjects with uncontrolled infection
6. Concurrent use of other anticancer agents or experimental treatments
7. Active autoimmune disease requiring immunosuppressive therapy with the exception of vitiligo and autoimmune alopecia
8. Known active CNS involvement
9. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses are permitted in absence of active autoimmune disease
10. Known history of any active infectious pneumonitis
11. Presence of acute or chronic graft-versus-host disease (GVHD) requiring active treatment unless limited to skin involvement and managed with topical steroid therapy alone
12. Has active cytokine release syndrome
13. Pregnancy or breastfeeding: Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 14 days of the first dose of study drug.

Women must not be breastfeeding. Females of nonchildbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraceptive methods during the study and for 8months following the last dose of nivolumab.

7.3 Criteria for Removal/Withdrawal from Treatment

Subjects may be removed from this study at any time at their discretion. Subjects may also be removed from this protocol if they develop any untoward side effects from the study medications. In addition, there are stopping rules in place for lack of efficacy and excessive toxicity as detailed in the statistical section.

If a subject withdraws consent to participate in the study or aspects of the study, attempts should be made to obtain permission to record survival data up to the protocol-described end of the subject follow-up period. Survival data are important to the integrity of the final study analysis. Documentation in the medical record should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

7.4 Patient Evaluation and Counseling

Patients will be seen at the Fred Hutchinson Cancer Center (FHCC) for consideration of treatment options for their disease. The protocol will be discussed thoroughly with the patient and other family members if appropriate, and all known and potential risks to the patient will be described. The procedure and alternative forms of therapy will be presented as objectively as possible, and the risks and hazards of the procedure explained to the patient. Signed consent will be obtained from the patient using forms approved by the FHCRC IRB. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

8.0 SUBJECT REGISTRATION

Subjects will be registered by the Study Coordinator and entered into the Clinical Trial Management System (CTMS), OnCore. A complete, signed, study consent and HIPAA authorization, in addition to a completed eligibility checklist signed by the PI or authorized sub-investigator are required for registration.

9.0 STUDY INTERVENTIONS

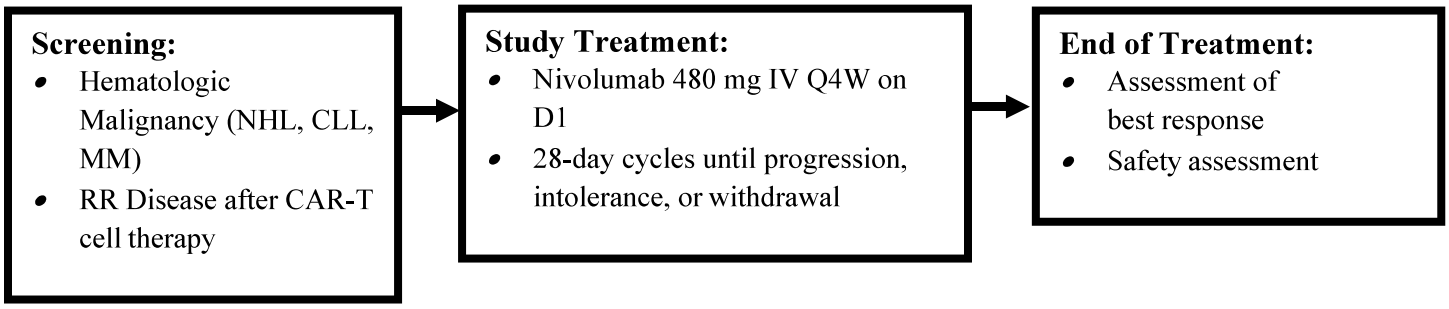
This is a single arm, unblinded phase II trial of nivolumab, a PD-1 inhibitor, for treatment of patients with hematologic malignancies (including B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma) who either experience relapse or have persistent disease after treated with CAR T-cell therapy.

Approximately 20 subjects will be enrolled on this study, which will include a screening phase, an active treatment phase, and a follow-up phase. Before any study-related procedure can be performed, all

subjects must sign an informed consent form (ICF). Subjects will be evaluated for eligibility at screening.

The active treatment phase will extend from cycle 1, day 1, until study treatment discontinuation due to disease progression, initiation of subsequent anti-cancer therapy, unacceptable toxicity, withdrawal, or completion of study treatment. A study schema is depicted in figure 1.

Figure 1. Study Design



The study will be conducted as a single arm phase II trial. After 2 cycles, an interim response assessment will be conducted to evaluate for early progression. Subjects with disease progression at that assessment will be discontinued from study treatment. Subjects will undergo disease-specific monitoring for response, as outlined in Section 9.5, during treatment on study.

9.1 Administration of Nivolumab

For treatment related questions, please contact Dr. Cowan at (206) 606-7348.

Nivolumab will be administered as a 30-minute IV infusion on Day 1 of each 28-day cycle.

The nivolumab dose is fixed at 480 mg. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Refer to section 4.0 for further information on administration.

Management and dose delays associated with nivolumab AEs can be managed by referring to Section 4.8, or Section 9.5.

9.2 Concomitant Medication and Supportive Care Guidelines

Medications used during the course of the clinical trial should be documented.

<u>Prohibited Concomitant Therapy During Active Study Treatment</u>

- The administration of concurrent medications intended to treat the primary cancer is not allowed during protocol therapy. This includes chemotherapy, investigational agent, biologic agent, or other anti-tumor agents. Radiation therapy is also prohibited
- Immunosuppressive agents (except to treat a drug-related adverse event)

- Topical and inhaled corticosteroids to treat other medical conditions are allowed. Immunosuppressive doses of corticosteroids are not permitted (> 10 mg daily prednisone or equivalent), except to treat a drug-related adverse event or for treatment of adrenal insufficiency. Intermittent corticosteroid usage to treat infusion reactions is allowed

Subjects should be discouraged from taking any alternative or naturopathic medications since these agents may interact with study therapy. Any use of these medications should be at the judgment of the treating physician and documented in the subject's medical record.

9.3 Duration of Therapy

Study participation may conclude when any of the following events occur:

- Participant withdrawal
- At the discretion of the investigator
- Disease progression
- Intolerance of therapy or unacceptable toxicity

The reason for discontinuation and effective date should be documented. The PI should be promptly notified of the change in participant status.

9.4 Study Response Assessments

Safety assessment will occur through the study and consist of continuous surveillance and recording of adverse events (AEs) and serious adverse events (SAEs).

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events may be collected for 90 days after the end of treatment). Subjects may have post-treatment follow-up for disease status up to 5 years, or until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.

4. Non-Hodgkin Lymphoma: PET-CT and CT (Diagnostic quality) after 2 cycles (8 weeks), then Diagnostic CT of chest, abdomen, and pelvis every 3 cycles (12 weeks) thereafter. Response assessment will be based on the Lugano Criteria[1]
    a. Initial response assessment after 2 cycles (8 weeks) with PET-CT and diagnostic CT
    b. Diagnostic CT every 3 cycles thereafter
5. Chronic lymphocytic leukemia: PET-CT and CT (Diagnostic quality) after 2 cycles (8 weeks), then Diagnostic CT every 3 cycles (12 weeks) thereafter. A bone marrow aspirate +/- biopsy will be obtained at screening and to confirm CR. Response assessment based on IWCLL criteria[2]
    a. Initial response assessment after 2 cycles (8 weeks) with PET-CT and diagnostic CT
    b. Diagnostic CT every 3 cycles (12 weeks) thereafter
6. Multiple myeloma: Assessment of serum protein electrophoresis (SPEP), serum free light chains (sFLC), every 4 weeks. 24-hour urine assessment of Bence-Jones Proteinuria only in subject who have this as sole marker of disease. Response assessment based on the IMWG[3]. A bone marrow aspirate and biopsy will be obtained at screening and to confirm CR. PET-CT only to be performed for subjects with plasmacytoma as the only site of measurable disease at screening, after 2 cycles, then every 3 cycles (12 weeks) thereafter.

9.5 Nivolumab – Dosing Delays and Modifications

Adverse events (both non-serious and serious) associated with nivolumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. The dose of nivolumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 5 below:

Table 2. Recommended Dose Modifications for Nivolumab-Related Adverse Events

Adverse Reaction	Severity (CTCAE v.5.0)	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose*
	Grade 3 diarrhea or colitis	Withhold dose*
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose*
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose*
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose*
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose*
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose*
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose*
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose*
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose* Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue

	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Resume treatment when adverse reaction improves to Grade 0 or 1.

9.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator for significant subject noncompliance with protocol requirements, or for administrative and/or other safety reasons. Subjects who require cessation of study therapy but do not withdraw consent may remain in standard follow-up for up to 5 years.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Appendix A (Study Calendar) and Section 11.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event and 90 days for serious adverse event monitoring. Subjects may have post-treatment follow-up up to 5 years per routine standard of care for survival and disease status.

10.0 CLINICAL AND LABORATORY EVALUATIONS

10.1 Schedule/Timing of Events (See Appendix A, Study Calendar)

10.1.1 Screening Evaluations (Day -28 to Day -1)

- Research Consent, HIPAA
- Medical History, Including:
  - Hematologic, cytogenetic, flow cytometric, and histologic findings at time of diagnosis and at time of enrollment on the study
  - Prior therapies and response to therapies
- Physical Examination
- ECOG Performance Status (See Appendix B)

- Chemistries, Hematology
    - CBD (to include: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophils, lymphocytes, monocytes, eosinophils, basophils, immature granulocytes)
    - Renal/Hepatic Function Panel (to include: sodium, potassium, chloride, total carbon dioxide, anion gap, glucose, urea nitrogen, creatinine, total protein, albumin, total bilirubin, direct bilirubin, calcium, phosphate, AST (GOT), Alkaline phosphatase, ALT (GPT), eGFR)
    - Magnesium, Lactate Dehydrogenase
- C-reactive Protein (CRP), Ferritin
- Uric Acid
- Serum or urine HCG within 14 days of cycle 1, day 1
- Coagulation Panel (To include INR, PT, PTT)
- Urinalysis
- T3, FT4, TSH
- Archival pre-treatment tumor biopsy (if available)
- Disease Specific:
    - Multiple Myeloma
        - Serum free light chain (SFLC) Assessment to include kappa to lambda ratio
        - SPEP with immunofixation
        - Bence Jones quantification, only in subjects for whom urinary Bence Jones quantitation represents best marker of disease
        - PET/CT (only amongst patients in whom plasmacytoma is the only measurable site of disease)
        - Bone marrow aspirate and biopsy, to include: histopathology, flow cytometry, FISH, and conventional cytogenetics
    - Non-Hodgkin Lymphoma, CLL
        - PET/CT and Diagnostic CT of the chest, abdomen, and pelvis. Diagnostic CT of neck only if palpable lymphadenopathy present
        - CLL Only: Bone marrow aspirate and biopsy, to include morphology, flow cytometry, FISH, cytogenetics

10.2 On Study Evaluations, Cycle 1

- Days 1
    - History and Physical Exam
    - Performance Status
    - Vital Signs (Including Temperature, Blood Pressure, Heart Rate, Oxygen Saturation)
    - Chemistry/Hematology
        - CBD
        - Renal/Hepatic Function Panel
        - Magnesium and LDH
    - CRP, Ferritin
    - Uric Acid

- Coagulation Panel
- T3, FT4, TSH
- Research Samples
  - Blood
    - Cytokines
    - Exploratory laboratory specimen
- Disease Specific:
  - Multiple Myeloma
    - SFLC, SPEP with immunofixation, Bence Jones Proteinuria (only ifneeded)

- Days 8, 15, 22
  - Chemistry/Hematology
    - CBD
    - Renal/Hepatic Function Panel
    - Magnesium and LDH
  - CRP, Ferritin
  - Uric Acid
  - Coagulation Panel
  - Research Samples
    - Blood
      - Cytokines
      - Exploratory laboratory specimen
- If subjects become febrile or develop symptoms of cytokine release syndrome, or tumor lysis during cycle 1, we may measure serum ferritin, CRP, coagulation panel, and tumor lysis markers at different time points outside those specified in the protocol, at discretion of the PI or treating provider.

10.3 On Study Evaluations, Cycle 2

- Day 1
  - History and Physical Exam
  - Performance Status
  - Vital Signs (Including Temperature, Blood Pressure, Heart Rate, Oxygen Saturation)
  - Chemistry/Hematology
    - CBD
    - Renal/Hepatic Function Panel
    - Magnesium and LDH
  - CRP, Ferritin
  - Uric Acid
  - Coagulation Panel
  - Research Samples
    - Blood
      - Cytokines
      - Exploratory laboratory specimen

- Disease Specific
  - Multiple Myeloma
    - SFLC, SPEP with immunofixation, Bence Jones Proteinuria (only if needed)

- Day 22 +/- 3 days
  - PET/CT and Diagnostic Quality CT of chest, abdomen, pelvis (Lymphoma)
  - PET/CT (Myeloma, only if measurable disease consists solely of plasmacytoma)

10.4 On Study Evaluations, Cycles 3-6

- Day 1
  - History and Physical Exam
  - Performance Status
  - Vital Signs (Including Temperature, Blood Pressure, Heart Rate, Oxygen Saturation)
  - Chemistry/Hematology
    - CBD
    - Renal/Hepatic Function Panel
    - Magnesium and LDH
  - CRP
  - T3, FT4, TSH
  - Research Samples
    - Blood
      - Cytokines
      - Exploratory laboratory specimen
  - Disease Specific
    - Multiple Myeloma
      - SFLC, SPEP with immunofixation, Bence Jones (only if needed)
      - PET/CT (Myeloma, only if measurable disease consists solely of plasmacytoma)
    - Lymphoma / CLL
      - Diagnostic Quality CT of chest, abdomen, pelvis – to be performed every 3 cycles

10.5 On Study Evaluations, Cycles 7 and Beyond

- Day 1
  - History and Physical Exam
  - Performance Status
  - Vital Signs (Including Temperature, Blood Pressure, Heart Rate, Oxygen Saturation)
  - Chemistry/Hematology
    - CBD
    - Renal/Hepatic Function Panel
    - Magnesium and LDH
  - Disease Specific

- Multiple Myeloma
  - SFLC, SPEP with immunofixation, Bence Jones (only if needed)
- Lymphoma / CLL
  - Diagnostic Quality CT of chest, abdomen, pelvis – to be performed every 3 cycles

10.6 End of Treatment (EOT) Visit Schedule and Procedures

EOT Visits for all subjects who discontinue from the study should occur at least 7 days, but ≤ 30 days, after the last dose of study drug and prior to beginning other treatment (+/- 14 days). Procedures to be performed during the EOT Visit include:

- Physical Exam
- Vital Signs
- Performance Status
- Labs:
  - CBC and Differential
  - Blood Chemistry - Comprehensive metabolic panel, including electrolyte balance, and hepatic and renal functions
- AE Assessment
- Concomitant Medication

11.0 STUDY PROCEDURES

11.1 Study Procedures

The Study Calendar in Appendix A summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and/or BMS for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

11.1.1 Administrative Procedures

11.1.1.1 Informed Consent

The investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

11.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements and applicable laws and regulations.

11.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed and signed off by the investigator or qualified designee to ensure that the subject qualifies for the trial.

11.1.1.3 Medical History

A medical history will be obtainedand will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

11.1.1.4 Prior and Concomitant Medications Review

11.1.1.4.1 Prior Medications

Prior medication taken by the subject within 28 days before starting study treatment will be reviewed and current medications taken by the subject at the time of screening will be recorded.

11.1.1.4.2 Concomitant Medications

Medication, if any, taken by the subject during the trial will be recorded. All medications related to reportable SAEs should be recorded as defined in Section 11.2.

11.1.1.5 Disease Details and Treatments

11.1.1.5.1 Disease Details

Prior and current details regarding disease status will be obtained.

11.1.1.5.2 Subsequent Anti-Cancer Therapy Status

All new anti-neoplastic therapy initiated after the last dose of trial treatment will be obtained.

11.1.2 Clinical Procedures/Assessments

11.1.2.1 Adverse Event (AE) Monitoring

Each subject will be assessed to evaluate for potential new or worsening AEs as specified in the Study Calendar and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and for 30 days after the last dose of study drug according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, expectedness, and action taken with regard to trial treatment.

For subjects receiving treatment with nivolumab all AEs of unknown etiology associated with nivolumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

11.1.2.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.

11.1.2.3 Vital Signs

Vital signs will be taken at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Study Calendar (Appendix A). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

11.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix B) at screening, prior to the administration of trial treatment, and after discontinuation of trial treatment as specified in the Study Calendar (Appendix A).

11.1.2.5 Tumor Imaging and Assessment of Disease

FDG-PET and diagnostic CT imaging will be required during study screening and 8 weeks after initiation of study drug for subjectsubjects with non-Hodgkin malignant lymphoma and CLL and FDG PET will be necessary for some subjects with multiple myeloma whose only disease is measured by that modality. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis alone will be performed at each tumor assessment thereafter; neck CT is only necessary for those subjects with palpable neck lymphadenopathy. For measurement of response, 2014 criteria as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" will be used for NHL, and the IWCLL response criteria for CLL[1, 2] (see Appendix D & E).

All CT scans should be performed with IV contrast unless contraindicated, and abdominal and pelvis scans should be performed with oral contrast.

11.1.2.6 Bone marrow aspirate and biopsy

A bone marrow aspirate and biopsy will be obtained before the first dose of study drug for subjects with multiple myeloma and CLL, and for confirmation of CR when indicated in MM and CLL. The Sponsor-Investigator or sub-Investigator may waive bone marrow aspirate and biopsy requirements. These samples will be evaluated locally.

11.1.2.7 Correlative Studies Blood Sampling

Peripheral blood exploratory correlative study samples will be collected during screening, weekly during cycle 1, and every cycle from cycles 3-6 (see Section 10).

11.1.2 Archival Pre-Treatment Tumor Biopsy

Archival pre-treatment tumor biopsy, if available, will be accessioned from pathology for testing with PD-1 and PD-L1 immunohistochemistry.

11.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided in Section 10. All chemistry and hematology studies may be performed within 3 days of nivolumab dosing prior to day 1 of each cycle.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Appendix A. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

11.1.4 Other Procedures

11.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section 11.2 - Assessing and Recording Adverse Events.

11.1.5 Visit Requirements

Visit requirements are outlined in Appendix A – Study Calendar. Specific procedure-related details are provided above in Section 11.1 - Trial Procedures.

11.1.5.1 Screening

11.1.5.1.1 Screening Period

The screening period begins upon signing consent and includes evaluations as described in the Study Calendar. The screening period may last up to 28 days.

11.1.5.2 Treatment Period

The treatment period includes the window phase during which nivolumab is administered every 28 (+/- 3) days.

11.1.5.3 End-of-treatment Visit

EOT Visits for all subjects who discontinue from the study should occur at least 7 days, but ≤ 30 days, after the last dose of IP and prior to beginning other treatment (+/- 14 days).

The off-study visit will include laboratory studies, medical history, physical exam, remission status, concomitant medications, adverse events, and documentation of any ECI and subsequent management, as in the Study Calendar. All AEs that occur prior to the end-of-treatment visit should be recorded. Subjects with an AE of Grade > 1 will be followed for 30 days. SAEs that occur within 90 days of the end of treatment should also be followed and recorded.

After the end-of-study visit, additional follow-up will be conducted as per routine standard of care for up to 5 years unless other criteria for withdrawal are met. Long-term follow-up may be performed at subjects' local physician's offices. Long-term follow-up will assess survival and disease progression; for clarification, subjects may be contacted by the study team until death, subject withdrawal of consent, lost to follow-up, or study termination, whichever occurs first.

12.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

Subjects may be removed from this study at any time at their discretion. Subjects may also be removed from this protocol if they develop any untoward side effects from the study medications. In addition, there are stopping rules in place for lack of efficacy and excessive toxicity as detailed in the statistical section.

If a subject withdraws consent to participate in the study or aspects of the study, attempts should be made to obtain permission to record survival data up to the protocol-described end of the subject follow-up period. Survival data are important to the integrity of the final study analysis. Documentation in the medical record should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

An explanation for discontinuing treatment is recorded for each subject discontinuing treatment on the appropriate CRF/eCRF. The Sponsor-Investigator of the study, Dr. Andrew Cowan, must be notified immediately if a subject discontinues treatment. All subjects, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- if the Sponsor decides to stop the study;
- at Investigator's discretion;
- at the subject's request;
- if the subject enrolls in a trial of another investigational agent;
- for disease progression;
- Grade 4 or life-threatening toxicity (See Section 11, Adverse Events and section 9.5 (Table 2)) attributable to study agent;

- pregnancy;

13.0 ADVERSE EVENTS

13.1 Adverse Event

According to ICH guidelines (Federal Register. 1997; 62(90):25691-25709) and 21 CFR 312.32, IND Safety Reports, and ICH *E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:*

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an adverse event unless an intervention is required (repeat testing to confirm the abnormality is not considered intervention), the laboratory abnormality results in a serious adverse event or the adverse event results in study termination or interruption/discontinuation of study treatment.

Adverse events and Serious Adverse Events are collected from the time of screening until day 30 (AEs), and day 90 (SAEs).

13.2 Serious Adverse Event

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal	Adverse event results in death.
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	It required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	Resulted in a substantial and permanent disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or treatment plan regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

13.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

13.4 Monitoring and Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug, a study procedure, or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

13.5 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

13.6 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

- Definite: The event follows a reasonable temporal sequence from exposure to the investigational agent, has been previously described in association with the investigational agent, and cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational agent and/or re-appears on re-exposure (e.g., in the event of an infusion reaction).
- Probable: The event follows a reasonable temporal sequence from exposure to the investigational agent and has been previously been described in association with the investigational agent OR cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Possible: The event follows a reasonable temporal sequence from exposure to the investigational agent but could be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unlikely: Toxicity is doubtfully related to the investigational agent(s). The event may be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.

- Unrelated: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

13.7 Adverse Event Reporting Requirements

13.7.1 Reporting to BMS

Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether or not related to the BMS product associated with this study, must be collected, including those thought to be associated with protocol-specified procedures. CIOMS, MedWatch 3500A, or site approved form and reported to BMS within **24 hours \ 1 business day** to comply with regulatory requirements.

Either the CIOMS, MedWatch 3500, or approved site SAE form should be completed for any event where doubt exists regarding its status of seriousness. Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

Investigators should report to the responsible regulatory authority as appropriate.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to the below email address and the BMS Protocol number must be included on the SAE form or on the cover sheet with the SAE form transmission

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1-609-818-3804

If only limited information is initially available, follow-up reports may be required.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If it is discovered a subject is pregnant or may have been pregnant at the time of exposure to the BMS product associated with this study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be reported and submitted to BMS on a BMS Pregnancy Surveillance Form **or** the MedWatch, CIOMS, or approved site SAE form, and reported to BMS within 24 hours/1 business day by confirmed fax or reported via electronic mail to: Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. Your original forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Pregnancies must be reported and submitted to BMS on a BMS Pregnancy Surveillance Form **or** the MedWatch, CIOMS, or approved site SAE form.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. Non-serious AE information should also be collected from the start of the observational period intended to establish a baseline status for the subjects.

Non-serious adverse events must be recorded on the Non-interventional Research AE/SAE Form and individually reported to BMS annually to comply with regulatory requirements.

All non-serious AEs must be reported by confirmed fax transmission or reported via electronic mail to:

Non-serious AE Email Address: Worldwide.Safety@BMS.com

Non-serious AE Facsimile Number: +1-609-818-3804

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 the BMS product associated with this study and for those present at the end of the study, as appropriate. The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

- The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report to verify and confirm all AE and SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

13.8 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

13.9 Sponsor-Investigator Responsibility for Reporting Adverse Events

13.9.1 IRB Reporting Requirements

The investigator or designee must report events to the FHCRC IRB in accordance with the policies of the IRB.

13.9.2 FDA (IND) Reporting Requirements

The sponsor assumes responsibility for IND safety reporting to the FDA and participating investigators, in accordance with regulations under 21 CFR 312.32.

For determination of IND safety reporting, AE attribution will be assessed according to the suspected adverse reaction definition described in 21 CRF 312.32 as an AE for which there is a reasonable possibility that the drug caused the adverse event where "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reactions that are serious, related, and unexpected will be reported to the FDA as an IND safety report, in accordance with regulations under 21 CFR 312.32.

14.0 CRITERIA FOR ENDPOINT EVALUATIONS

14.1 Criteria for Evaluation and Endpoints – Lymphoid Malignancies

Responses will be based on the standard criteria for lymphoid malignancies – including the Lugano criteria and the iwCLL response criteria[1, 2] (See Appendix C, D).

14.1.1 Selection of Target Lesions

Up to six of the largest dominant nodes or tumor masses selected according to each of the following:

- Clearly measurable in at least two perpendicular dimensions
- Abnormal lymph nodes are those that are either
  - >15 mm in the greatest transverse diameter (GTD) regardless of the short axis diameter, or
  - >10 mm in the short axis diameter regardless of long axis
- If possible, they should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least must be at least 1.0 cm in two perpendicular dimensions

14.1.2 PET Scans

Visual assessment currently is considered adequate for determining whether a PET scan is positive. A Deauville score should be reported. In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology.

14.1.3 Response Criteria

For measurement of response, standard 2014 criteria as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" will be used, and for CLL, the iwCLL response criteria[1, 2].

14.2 Criteria for Endpoint Evaluation – Multiple Myeloma

Responses will be based on the International Myeloma Working Group criteria for response in multiple myeloma[3] (Appendix E).

14.3 Progression-Free Survival

PFS will be measured as time from first study drug administration to the first occurrence of disease progression or death from any cause. Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy. The estimates will be formed using the all treated population. Progression-free survival will be calculated using assessments by investigators. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median).

14.4 Overall Survival

Overall survival (OS) will be measured as the time from the first study drug administration to death from any cause.

Data for subjects without death will be censored at the date of the last tumor assessment. Kaplan-Meier methodology will be used to estimate the event-free curves.

15.0 BIOMARKER ANALYSES

15.1 Peripheral Blood Biomarker Correlative Studies

15.1.1 Serum Cytokines

Serum cytokines will be measured in the Immune Monitoring Laboratory (IML), Fred Hutch. Cytokines to be measured include IFN-γ, TNF-α, GM-CSF, and IL-6 by Luminex bead assay.

15.1.2 Collection of specimen(s)

Whole blood will be collected into one 10 mL serum separator tube.

15.1.2.1 Handling of specimen(s)

Specimens will be collected at room temperature.

15.1.2.2 Shipping of specimen(s)

Specimens will be shipped at ambient room temperature to the IML, Fred Hutch.

15.1.2.3 Site performing correlative study

The serum cytokine assay will be performed by the IML, Fred Hutch.

15.1.3 Peripheral blood for storage

In addition to samples collected above, up to 40 mL of additional peripheral blood will be collected prior to cycle 1 day 1 of study drug, and weekly thereafter for 4 weeks, then every cycle for cycles 2-6. This will be stored for future analyses of biomarkers or other molecular correlates, to be determined.

15.1.3.1 Collection of specimen(s)

Whole blood will be collected into up to four 10 cc EDTA tubes.

15.1.3.2 Handling of specimen(s)

Samples will be collected at room temperature, followed by Ficoll separation and frozen storage of PBMCs and serum.

15.2 Archival Tumor Biopsy for PD-1 and PD-L1 IHC

Expression of PD-1 and PD-L1 in a pre-treatment tumor biopsy will be assessed using immunohistochemistry for PD-1 and PD-L1, to be performed internally at the Fred Hutchinson Cancer Center. This will be evaluated for correlation with outcomes.

15.2.1 Collection of specimen(s)

Samples of pre-treatment tumor biopsies will be requested from pathology internally, if available.

15.2.2 Handling of specimen(s)

Samples will be collected at room temperature and sent to the Experimental Histopathology resource at the Fred Hutchinson Cancer Center.

16.0 STATISTICAL CONSIDERATIONS

16.1 Study Design

The primary objective of the study is to determine the efficacy of nivolumab as measured by the overall response rate (ORR), in subjects with hematologic malignancies with relapsed or refractory disease after receipt of CAR T-cell therapy. ORR will be estimated, and its corresponding 95% exact binomial CI will be provided. The analyses of time-to event endpoints (DOR, PFS, and OS) will follow standard methodology by employing Kaplan-Meier and Cox proportional hazard model methodology.
Safety data will be summarized descriptively. Adverse events will be summarized by severity, seriousness, and relationship to study drug. Laboratory data will be compared to baseline values.
Additional exploratory data analyses will be conducted as appropriate.

The primary objective will be investigated by assessing if the true ORR is at least above some desirable target level following therapy with nivolumab. A subject is classified as response evaluable if they have at least one response assessment or if they discontinue from treatment due to death from any cause prior to obtaining at least one response assessment.

Based on the observations in Ansell 2018, the ORRs were low, e.g., 10% and 3% in the auto-HCT-failed and auto-HCT-ineligible, respectively[28]. The desire is therefore to rule out a 5% ORR which will require around 25% ORR. If the sample size is 20, the study will have 85% power to detect the difference between the Null hypothesis of 5% ORR and the Alternative of 25% ORR, with a 1-sided alpha of 0.05.

16.2 Objectives

Primary Objectives

- To assess the efficacy of nivolumab, a PD-1 inhibitor, in subjects with hematologic malignancies with relapsed, refractory, or detectable disease after receipt of CAR T-cell therapy
- To assess the safety of administering nivolumab, a PD-1 inhibitor, in subjects with hematologic malignancies with relapsed or refractory disease after receipt of CAR T-cell therapy

Secondary Objectives

- To determine overall survival, progression free survival, and duration of response after treatment with nivolumab

Exploratory Objectives

- To determine cytokine response after treatment with nivolumab
- To determine PD1 and PD-L1 expression patterns in pre-treatment tumor biopsy and correlate with response
- To collect peripheral blood samples for future biomarker analyses

16.3 Statistical Consideration

Descriptive statistics, such as mean, standard deviation, and range for continuous variables, and percent and number for categorical variables, will be summarized for baseline information and demographic information. The statistical test for primary efficacy endpoint ORR will be performed using an exact binomial test for single proportion at the 5% one-sided significance level if appropriated.

16.4 Stopping rules for toxicity and futility

In the event of a death on study that is deemed to be possibly, probably, or definitely attributable to the drug, further infusions will be suspended pending review by the DMC and consultation with the FDA. To further protect the safety of subjects, the study incorporates a stopping rule if the lower bound of a 1-sided 80% exact binomial confidence interval of the discontinuation rate due to medically significant Grade 3 or greater events that are possibly, probably, or definitely attributable to the drug is > 20%. Operationally, any of the following would trigger such as rule: 2 out of the first $\leq$6 subjects or 3 out of the first $\leq$9 subjects or 4 out of the first $\leq$13 or 5 out of the first $\leq$16 or 6 out of the first $\leq$20 subjects have unacceptable toxicity or $\geq$ Grade 3 AEs that are possible, probably, or definitely attributable to

drug. If the true probability of ≥Grade 3 AE is 2.5%, the probability of study suspension under the above rule is approximately 0.01; if the true probability is 40%, the probability of suspension is approximately 0.91 (probabilities estimated from 5,000 simulations).

If this rule is met, further treatment for all subjects enrolled will be immediately halted. A safety evaluation will be performed and reviewed with the FDA and DMC prior to resuming any drug.

We are using a Simon's two-stage design (Simon, 1989) to stop early for futility. Based on the null hypothesis of 6% ORR and alternative hypothesis of 26% ORR, with a 1-sided alpha of 0.05, in the first stage, 12 subjects will be accrued. If there are 0 responses in these 12 subjects, then study will be stopped for futility. Otherwise, 8 or more additional subjects will be accrued for a total of 20 subjects. The null hypothesis will be rejected if 4 or more responses are observed in 20 subjects. This design (minimax) yields a type I error rate of 0.05 (one-sided) and power of 80%.

16.5 Ethnic and Gender Distribution Chart

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	8	10	18
Ethnic Category Total of All Subjects*	9	11	20
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific	0	0	0
Black or African American	0	0	0
White	8	9	17
More Than One Race	0	0	0
Racial Categories: Total of All	9	11	20

17.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures (see Appendix A).

18.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

18.1 Pre-Study Documentation

The following documentation required by the FDA must be completed prior to initiation of the trial: FDA Form 1572; curricula vitae of the PI and all Sub-Investigators; copy of the correspondence from the IRB indicating approval of the protocol and Informed Consent Forms, signed by the IRB chairperson or designee; copy of the Informed Consent Forms that were reviewed and approved by the IRB.

18.2 Study Site Training

Before initiation of the study, the Sponsor-Investigator, or its designated representatives will review and discuss the following items with the Investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol.

18.3 Documentation

The PI and study staff has responsibility for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the Sponsor, the FDA, and/or other applicable regulatory agencies/competent authorities at any time, and should consist of the following elements: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the Competent Authorities, IRB/EC, site, and Sponsor); and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

18.4 Data Collection

Case report forms must be completed and submitted for each subject enrolled in the study. Any changes or corrections made to the CRF/eCRF must be subsequently reviewed and signed by the PI. All data fields in the CRF/eCRF must be completed to avoid queries.

18.5 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB/EC and relevant Competent Authorities approval. The Sponsor is responsible for submitting protocol amendments to the FDA as described in 21 CFR § 312.30 (Protocol Amendments) and other regulatory agencies according to national, state or local requirements. The Sponsor, or its designee, is always available to answer protocol- or subject-related questions.

18.6 Study Monitoring and Data Collection

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the

study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

18.7 Disclosure of Data/Publication

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by the FDA or other regulatory agencies, the Sponsor or its designee and by the IRB/EC.
It is anticipated that the final results of this study will be submitted to a peer-reviewed scientific journal. Authorship on such a paper will be acknowledged with customary scientific practice. As such, without the expressed permission of the Sponsor, only clinical Study data relating the Study as a whole will be published.

18.8 Ethical Considerations

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

18.9 Informed Consent

The PI or qualified designee assumes the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or parents/legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The Sponsor or designee will review the

informed consent prior to submission to the IRB/EC. The form is to be signed and dated by the subject or subject's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the Sponsor or designee and approved by the IRB/EC prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

18.10 Institutional Review Board/Ethics Committee

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval. A photocopy of the IRB/EC notification of approval must be forwarded to the Sponsor or its designee before any investigational supplies will be shipped to the PI.

The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior Sponsor and IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Copies of all study-related correspondence between the Investigator and the IRB/EC must be provided to the Sponsor, or its designee, by the Investigator. The PI or designee must promptly notify the IRB/EC of any SAE occurring at the site and of any safety reports (e.g., IND Safety Reports) received from the Sponsor, or its designee, and must copy the Sponsor, or its designee on that correspondence.

The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

18.11 Subject Privacy

The Sponsor-Investigator affirm and uphold the principle of the subject's right to privacy. The Sponsor-Investigator and its designees and the Investigator shall comply with applicable national and local privacy laws.

19.0 APPENDICES

Appendix A: Study Calendar
Appendix B: ECOG Performance Status Scale
Appendix C: Lugano Criteria
Appendix D: IWCLL Criteria
Appendix E: IMWG Criteria

19.1 Appendix A: Study Calendar

Required Studies	Screening Period	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 Day 1	C2D22	Cycles 3-6 Day 1	Cycle 7 + Day 1	Post Therapy	Long-term Follow-up[7]
Scheduling and Timing	-28 to -1d	+/- 3d	+/- 3d	+/- 3d	+/- 3d	+/- 3d	+/- 3d	+/- 3d	**+/- 3 days**	+/- 14 days	
Informed consent	X										
Inclusion/Exclusion criteria	X										
AE Assessment[1]	X	X				X		X	X	X	
Medical history	X										
Medication review (prior and concomitant)	X	X				X		X	X	X	
Trial treatment administration		X				X		X	X		
Post-study anticancer therapy status											X
Survival status											X
Vital signs	X	X				X		X	X	X	
Physical exam	X	X				X		X	X	X	
ECOG performance status	X	X				X		X	X	X	
Labs											
CBC and differential	X	X	X	X	X	X		X	X	X	
Comprehensive metabolic panel including LDH, Mg, Phosphate, and direct bilirubin[9]	X	X	X	X	X	X		X	X	X	
CRP	X	X	X	X	X	X		X			
Ferritin	X	X	X	X	X	X					
Uric acid	X	X	X	X	X	X					
Coagulation panel	X	X	X	X	X	X					
Serum free light chain[2]	X	X						X	X	X	
SPEP[2]	X	X						X	X	X	
Urinalysis	X										
T3, FT4, and TSH	X	X						X		X	
Bone marrow studies[2,3]	X							X			
Pregnancy test[4]	X										
Tumor assessment[5]	X						X	X	X	X	
Correlative studies blood draw[6]	X	X	X	X	X	X		X			
Cytokine Panel		X	X	X	X	X		X			
Pre-Treatment Archival Tumor Biopsy[8]	X										

[1]Adverse events will be recorded from the time of a subject signing consent up until 30 days after the last dose of nivolumab, or 90 days after the last dose of nivolumab in the case of serious adverse events.
[2]For subjects with multiple myeloma only.
[3]The Sponsor-Investigator or sub-Investigator may waive screening bone marrow aspirate and biopsy requirements. For subjects with CLL/SLL and MM, repeat bone marrow biopsy only to be done after screening to confirm CR
[4] Pregnancy test is only required in women of childbearing potential. Verbal report of pregnancy will be reported during conduct of the trial.
[5]Tumor assessment imaging (see section 11.1.2.5) will be performed prior to cycle 3 (within 7 days of scheduled treatment dose) and every 3 cycles thereafter. Tumor assessment labs and/or imaging will also be performed as indicated per clinical standard of care (e.g. as appropriate for disease, to evaluate clinical suspicion of disease progression). Screening PET-CT and diagnostic CT done prior to screening up to day -42 may

be used for screening assessment. PET-CT and diagnostic CT will be performed at screening, then after 2 cycles on cycle 2 day 22. Thereafter, tumor assessment will comprise diagnostic CT of chest, abdomen, pelvis every 3 months. For multiple myeloma only, PET-CT should only be done amongst subjects in whom the only measurable disease is by imaging criteria – both at screening and for follow-up.

[5]End of treatment evaluations should be done within 30 days (+/- 14 days) of the last dose of nivolumab or prior to the start of a new anti-cancer drug, whichever is first.

[6]Correlative studies to include peripheral blood for storage for future biomarker analyses. Please see section 15 for details on blood collection and storage.

[7]Long-term follow-up should be done according to the subject's physician standard of care. This may be performed at subjects' local physician's offices. Long-term follow-up will assess survival and disease progression. Subjects may be contacted by the study team until death, subject withdrawal of consent, lost to follow-up, or study termination, whichever occurs first

[8]If available, will be tested for PD-1 and PD-L1 IHC

[9] The use of growth factors or transfusions to meet hematologic eligibility criteria is allowed

19.2 APPENDIX B: ECOG Performance Status Scale

ECOG Performance Status Scale

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

19.3 APPENDIX C: Lugano Classification

Lugano Classification

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	Complete radiologic response (all of the following)
	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
Lymph nodes and extralymphatic sites	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal	Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
	response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (egg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

- Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

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

19.4 Appendix D: CLL Response Criteria

Adapted from the iwCLL response Criteria (REF).

Group	Parameter	CR	PR	PD	SD
	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
A	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
B	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete remission (response); CRi, CR with incomplete bone marrow recovery; CT, computed tomography; PD, disease progression; PR, partial remission (response); SD, stable disease.

19.5 APPENDIX E: Multiple Myeloma Definitions of Response and Progression (MODIFIED IMWG)

Response Subcategory	Response Criteria
Stringent Complete Response (sCR)	CR, as defined below, plus the following: Normal FLC ratio[b] and absence of clonal cells[c] in bone marrow by immunohistochemistry or immunofluorescence.
Complete Response (CR)[b]	Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow.
Very Good Partial Response (VGPR)[b]	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein level plus urine M-protein level < 100 mg per 24 hour.
Partial Response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hour. If serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. In addition to the above criteria, if present at baseline, > 50% reduction in the size of soft tissue plasmacytomas is also required
Minor (Minimal) Response (MR)	25-49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50-89%, which still exceeds 200 mg per 24 hours. In addition, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. No in- crease in the size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progression. Revised
Progressive Disease (PD)	Any of the following: Increase of 25% from lowest response value in any one or more of the following: 1. Serum M-component (absolute increase must be ≥0.5 g/dL (5g/L))[d] and/or 2. Urine M-component (absolute increase must be ≥ 200 mg (0.2g) per 24 h) and/or 3. Only in subjectsubjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL (100mg/L)) 4. Bone marrow plasma cell percentage (absolute % must be ≥ 10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or Development of hyper-calcemia (corrected serum calcium > 11.5 mg/100 mL) that can be attributed solely to the plasma cell proliferative disorder.

[a] All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

[b] Note clarification to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects is defined as a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such subjects is defined as a > 90% decrease in the difference between involved and uninvolved FLC levels.

[c] Presence or absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] For progressive disease, serum M-component increase of ≥ 1 g/dL (10g/L) is sufficient to define progression if starting M-component is ≥ 5 g/dL (50 g/L).

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