

MC1681
CA209-522

Mayo Clinic Cancer Center

MC1681: Phase 2 Single-Arm, Open-Label Study of Nivolumab in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

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Drug Company Supplied: Nivolumab (Opdivo®)

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Protocol Resources

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*No waivers of eligibility allowed

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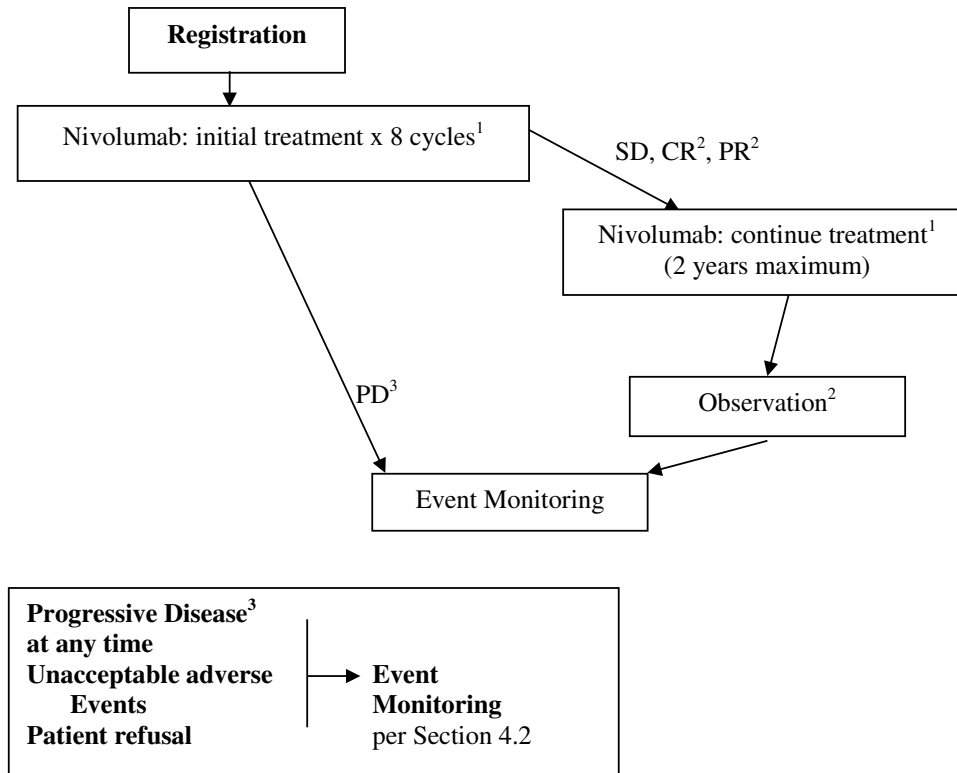
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Schema



¹ Cycle length initial treatment (first 8 cycles): 14 days

Cycle length continuation treatment (beginning with Cycle 9): 28 days

²PET-CT based response criteria: Stable Disease (SD), CR – complete response, PR – partial response
 (See [Section 11.0](#))

³PET-CT based response criteria. Progressive disease (PD) (See [Section 11.0](#)). PET confirmation of PD is per physician discretion.

Generic name: Nivolumab
 Brand name(s): Opdivo®
 Mayo Abbreviation: BMS936558
 Availability: Mayo Cancer Center Pharmacy

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1.0 Background

1.1 Disease Background

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment. Like Hodgkin's lymphoma (HL), NHL usually originates in lymphoid tissues and can spread to other organs. NHL, however, is much less predictable than HL and has a far greater predilection to disseminate to extranodal sites. The prognosis depends on the histologic type, stage, and treatment. The NHLs can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. In Western populations the majority of NHL (~85%) are of B-cell origin.

Approximately 12-15% of the NHL that are not classified as B-cell in origin are T-cell and natural killer (NK) cell in origin. Within these malignancies, two broad groups can be defined, the precursor or pre-thymic lymphomas (e.g. lymphoblastic lymphoma) and the post-thymic lymphomas or peripheral NK/T-cell lymphomas (PTCLs). In the World Health Organization (WHO) Classification, the PTCLs can be further subdivided into predominantly leukemic, extranodal, and nodal types. Studies in recent years have confirmed that lymphomas of the T-cell phenotype have a poorer prognosis than do B-cell lymphomas (Vose, Armitage et al. 2008).

To date, CHOP or CHOP-like chemotherapy has constituted the most prevalent approach to the treatment of PTCLs. However, except for ALK-positive ALCL, this approach has been disappointing both in terms of the response rate and the durability of response. More intensive chemotherapy regimens and stem cell transplantation have been studied, however patient numbers have been small and the populations heterogeneous; none of these approaches have been confirmed to improve outcome in PTCL patients (O'Connor, Bhagat et al. 2014).

In the relapsed and refractory setting, Gemcitabine has been explored both as a single agent and in combination. As a single agent in the relapsed setting, it was associated with a 51% overall response rate (ORR) with 23% complete responses (CR) (Zinzani, Venturini et al. 2010). Bendamustine, as a single agent, was associated with a similar ORR (50%) and CR (28%) with short duration of response (DOR) at 3.5 months and overall survival (OS) of only 6.2 months (Damaj, Gressin et al. 2013). Despite reasonable response rates, the duration of benefit with traditional chemotherapy has been short.

A number of novel approaches to the treatment of PTCL have recently been reported, including treatment with nucleoside analogues, histone deacetylase (HDAC) inhibitors, novel anti-folates and immunotherapy. Pralatrexate, a novel anti-folate, has been reported to produce durable complete remissions in patients with PTCL. An ORR of 29% was observed in patients with relapsed/refractory T-cell lymphomas enrolled in the PROPEL Phase II trial (O'Connor, Pro et al. 2011), with 11% CR. Though the median progression free survival (PFS) was short (3.5 months), the median DOR was prolonged at 10.1 months. A similar overall response rate of 25% has been reported with single agent treatment with the HDAC inhibitor, romidepsin, in patients with relapsed PTCL. The CR rate was 15% with prolonged median DOR of 17 months (Coiffier, Pro et al. 2012). Similar results were seen with belinostat, another HDAC inhibitor (O'Connor, Horwitz et al. 2015). Pralatrexate, romidepsin and belinostat have received FDA approval for the treatment of PTCL in the relapsed/refractory setting. Multiple combination trials are ongoing.

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Immunotherapy with alemtuzumab has shown activity in relapsed/refractory PTCL and early results of studies of alemtuzumab reported with ORR of 35% with 14% CR in a small study. Immunotoxin therapy with denileukin difitox has also shown promise with a reported ORR of 48% with 22% CRs (Lunning, Moskowitz et al. 2013). Despite the initial promise of these novel approaches, the duration of clinical benefit has been short and the outlook for patients with PTCL remains grim. There is therefore clearly a need for additional novel approaches. Emerging data with different checkpoint inhibitors, particularly PD-1 blockers, in various hematologic malignancies showed activity, which was particularly impressive in HL (Berger, Rotem-Yehudar et al. 2008; Ansell, Lesokhin et al. 2015). In a small number of PTCL patients treated with PD-1 blockade, responses were seen.

Hematologic malignancies are unique in that the tumor is itself constituted by cells of the immune system. They are attractive targets for immune checkpoint blockade given the demonstrated curative potential of other adoptive immune strategies, such as allogeneic stem cell transplant. Lymphoid malignancies have previously demonstrated significant responsiveness to immunologic manipulations.

The tumor microenvironment in lymphoid malignancies is characterized by a vast inflammatory cell infiltrate consisting of both T helper and regulatory cells. Despite this immune cell infiltrate, there is lack of host mediated antitumor effect. Program death ligands (PDL) 1 and 2 inhibit T cell activity by interacting with program death receptor 1 (PD-1) on T cells, which provides lymphoma cells a mechanism to evade immune surveillance. Nivolumab, a fully human IgG4 monoclonal antibody which blocks PD-1 receptor restoring the cancer fighting ability of T cells, was first approved by the FDA in metastatic or unresectable melanoma. In a phase I study of 23 heavily pretreated patients with relapsed/refractory HL, nivolumab demonstrated promising activity: ORR 87%, CR 17%, and 24-month PFS of 86%. The most common toxicities included rash (22%), thrombocytopenia (17%), stomatitis (13%), increased serum lipase (13%) and lymphopenia (13%), which were all manageable without any reports of grade 4 or 5 events (Ansell, Lesokhin et al. 2015).

To assess the effect of PD-1 blockade in hematologic malignancies other than cHL, a phase 1 dose escalation study of nivolumab in patients with relapsed or refractory lymphoid malignancies has been completed and was recently presented. The patients included 27 patients with multiple myeloma, 29 with B-cell non-Hodgkin lymphoma (13 with DLBCL/PMBCL, 10 with FL, 8 other B cell NHL), 23 patients with T-cell lymphoma (13 with mycosis fungoides, 5 with peripheral T-cell lymphoma NOS and 5 with other T cell lymphomas), and 1 patient with chronic myelogenous leukemia (CML). Responses were seen in 4 of 10 DLBCL patients (including 1 CR), and 4 of 10 FL patients (including the other CR of the study). The only other responses seen were PR in 2 of 13 (15%) patients with mycosis fungoides and 2 of 5 (40%) patients with PTCL NOS (Lesokhin, Ansell et al. 2014). Due to this signal of activity in PTCL, we propose to study the efficacy of nivolumab in relapsed and refractory PTCL patients in the current study.

1.2 Treatment

1.21 Nivolumab Background and Associated Known Toxicities

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by

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activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab was expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. Nivolumab is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

1.22 *Nonclinical Studies*

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family(Wang, Thudium et al. 2014). Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN- γ) release in vitro(McDermott and Atkins 2013). Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1(Wang, Thudium et al. 2014). In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN- γ release(Wang, Thudium et al. 2014). In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents(Wang, Thudium et al. 2014).

In addition, an enhanced pre- and postnatal development (ePPND) study, nivolumab was administered twice weekly at 10 or 50 mg/kg to pregnant cynomolgus monkeys from gestational day (GD) 20 to 22 until parturition. Nivolumab was well tolerated at both doses, and there were no nivolumab-related effects on viability, clinical signs, food consumption, body weights, immunological endpoints, or clinical/anatomic pathology parameters in these females throughout the study. However, in the offspring, maternal nivolumab administration at both doses was associated with fetal/neonatal mortality characterized by: 1) dose-dependent increases in third trimester fetal losses (12.5% and 33.3% at 10 and 50 mg/kg, respectively, relative to 7.1% in controls), which occurred predominantly after GD 120; and 2) increased neonatal mortality at 10 mg/kg, which was noted in 3 infants with extreme prematurity during the first 2 postnatal weeks. The cause(s) of these fetal losses and infant prematurity could not be determined. There were no premonitory signs of pregnancy complications or developmental abnormalities observed in affected dams or their offspring. Although infants were exposed to nivolumab at levels similar to their mothers, there were no gross or microscopic lesions clearly attributable to nivolumab. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance is consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice(Habicht, Dada et al. 2007). In these models, maternal regulatory T cells are thought to be the principal mediators of fetal tolerance via suppression of autoimmune reactions directed towards the fetus. PD-1 signaling can support placental expansion of regulatory T cells and/or suppress effector T cell function.

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Abrogation of PD-1 signaling (eg, PD-L1 knockout, nivolumab administration, etc) may eliminate the suppressive activity of regulatory T cells in the placenta, resulting in increased inflammatory reactions towards the fetus and associated decreased fetal survival rates (Habicht, Dada et al. 2007).

1.23 *Effects in Humans*

The PK, clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, and clear-cell renal cell carcinoma (RCC) in addition to other tumor types. Clinical activity and safety information was obtained from Phase 2/3 studies (CA209063, CA209017, CA209057, ONO-4538-05, and ONO-4538-06) in subjects with advanced or metastatic squamous (SQ) and nonsquamous (NSQ) NSCLC, Phase 2/3 studies (CA209037, CA209066, CA209067, and CA209069) in subjects with unresectable or metastatic melanoma, and a Phase 2 study (CA209010) in subjects with advanced or metastatic clear-cell RCC. Data are also provided from Phase 1 studies MDX1106-03, CA209012, CA209016, and CA209039 and from Phase 1 safety cohort of CA209143. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

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

1.24 *Clinical Pharmacokinetics*

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (V_{ss}) was 8.0 L (30.4%), and geometric mean elimination half-life (t_{1/2}) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

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

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The regimen of nivolumab 480 mg Q4W, either as the starting therapy or as maintenance treatment following nivolumab 240 mg Q2W, is currently being evaluated in multiple clinical studies. As of Sep 2016, 4 patients in the nivolumab clinical development programs have received nivolumab 480 mg Q4W for at least 1 dose. There have been no new safety signals identified during routine clinical and pharmacovigilance monitoring of these studies. Clinical evaluation of this dose regimen is in its early stages, as such PK, immunogenicity or summary of safety information are not currently available.

In study CA209522, nivolumab 480 mg Q4W is to be administered in the maintenance phase following nivolumab 240 mg Q2W for 8 dose as a more convenient dosing schedule for patients without compromising safety or efficacy. Nivolumab 480 mg Q4W has been selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer, and renal cell carcinoma). Using an updated PPK model that incorporated a time-varying clearance, nivolumab 480 mg Q4W is predicted to provide average steady state concentrations (Cavgss) similar to nivolumab 3 mg/kg Q2W. Nivolumab 480 mg Q4W is predicted to provide greater (approximately 40%) maximum steady state concentrations (Cmaxss) and lower (approximately 20%) trough steady state concentrations (Cminss). Nivolumab has been shown to be safe and well tolerated up to doses of 10 mg/kg Q2W and has not demonstrated a clear dose response or exposure-response relationships. Based on these safety findings, the predicted Cmaxss at 480 mg Q4W (Figure 1) are not considered to put subjects at increased risk for AEs, because they are predicted to be lower and within the exposure ranges observed following nivolumab 10 mg/kg Q2W. The approved dose of 3 mg/kg Q2W has shown survival benefit across multiple tumor types compared to respective standards of care. Nivolumab exposure was not a predictor of survival in exposure-response analyses conducted for multiple tumor types. The Cminss values following nivolumab 480 mg Q4W are predicted to be in the range of those on the flat part of the exposure-response curves, and are not expected to impact efficacy.

Based on these data, administration of nivolumab 480 mg Q4W in the maintenance phase of study CA209522 is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.

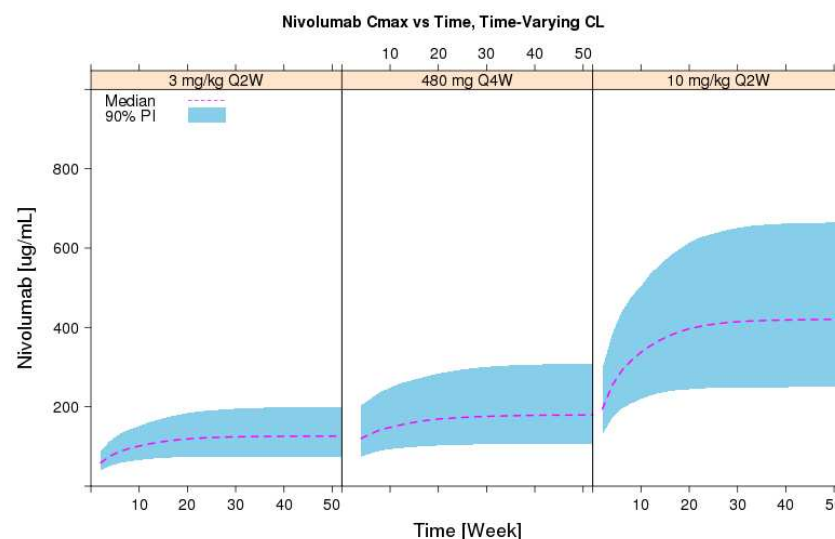
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Figure 1: Predicted Nivolumab Cmax vs Time, by Dosing Regimen



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1.25 *Clinical Efficacy*

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

1.26 *Safety in Subjects with Relapsed or Refractory Hematologic Malignancies*

Nivolumab, at 1 or 3 mg/kg, has an acceptable safety profile in subjects with relapsed or refractory hematologic malignancy, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The following were the key safety findings for 105 subjects treated with nivolumab monotherapy in CA209039 as of 15-Apr-2015:

- The most frequently reported drug-related AEs (>10% of subjects) were fatigue (16.2%) and rash (10.5%). The majority were Grade 1-2 in severity.
- The most frequently reported drug-related SAE was pneumonitis (4.8%).
- Drug-related AEs leading to discontinuation were reported for 14.3% of subjects. The most frequently reported AE leading to discontinuation were pneumonitis (2.9%).
- The most frequently reported drug-related select AE categories were skin (19.0%), GI (9.5%), and pulmonary (9.5%). The most frequently reported (>5% of total treated subjects) drug-related select AEs were rash (10.5%), pneumonitis (9.5%), pruritus (9.5%), and diarrhea (8.6%). Drug-related select AEs were mostly Grade 1-2 in all categories.
- Most deaths were due to disease progression. One death was reported due to study drug toxicity (The subject with NHL [small lymphocytic lymphoma] in

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the 3 mg/kg treatment group died due to Grade 5 pneumonitis with onset 10 days after the subject received the only dose of nivolumab).

1.27 *Clinical Activity of Nivolumab in Lymphoma*

In a broad phase I study, Ansell et al treated 23 patients with classical HL who had been heavily pretreated (Ansell, Lesokhin et al. 2015). Nivolumab at a dose of 3 mg/kg was administered q 2 weeks until tumor progression, or toxicity. Of these, 78% had progressed following a prior autologous stem cell transplant, and 78% following brentuximab vedotin. An objective response was achieved in 87%, including 17% with a CR. The rate of progression-free survival at 24 weeks was 86%. Therapy was discontinued in 6 patients to go to stem cell transplantation, with disease progression in 4, and toxicity in 2.

From the same study Lesokin et al (Lesokhin, Ansell et al. 2014) reported 29 patients with a variety of histologies of NHL with responses in 36% of diffuse large B-cell NHL (9% CR), 40% of follicular NHL (10% CR). In patients with T-NHL, ORR was 17% (no CR). When mycosis fungoides was excluded from the analysis, an ORR of 40% in the 5 patients with PTCL was seen.

1.3 Rationale

Given the observed activity of nivolumab in patients with relapsed and refractory PTCL in a small cohort of patients, the lack of significant toxicities, and since there is a need for newer non-cytotoxic therapies for the relapsed/refractory PTCL subgroup, we will explore the efficacy of nivolumab in the relapsed/refractory setting. Correlative studies will help further help us understand predictors of response or non-response to nivolumab.

2.0 Goals

2.1 Primary

To assess the clinical benefit of nivolumab in T-cell lymphomas, as measured by objective response rate (ORR) within 12 cycles according to the Lugano Classification Response Criteria (2014) ([Section 11.0](#))

2.2 Secondary

2.21 To assess safety and tolerability of the regimen in this patient population

2.22 To assess progression-free survival (PFS)

2.23 To assess duration of response (DOR)

2.24 To assess overall survival (OS)

2.3 Correlative Research

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

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- 2.32 To evaluate intratumoral Biomarkers- intratumoral cell populations and distribution, genetic variability, mutational burden and T-cell activation will be evaluated to identify potential biomarkers that correlate with response to therapy. This goal will also be exploratory in nature
- 2.33 To assess the potential association between PD-L1/PD-1/PD-L2 expression on tumor and T cells and/or PD-L1 soluble levels in plasma with clinical efficacy of PD-1 blockade.

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3.0 Patient Eligibility

3.1 Inclusion Criteria

- 3.11 Age ≥ 18 years.
- 3.12 Relapsed or refractory T-cell lymphoma (TCL) biopsy-proven ≤ 6 months prior to registration, including the following subtypes:
- Peripheral T-cell lymphoma, not otherwise specified
 - Anaplastic large cell lymphoma, ALK negative, primary systemic type
 - Angioimmunoblastic T-cell lymphoma
 - Extranodal NK/T-cell lymphoma, nasal type
 -
 - Blastic NK-cell lymphoma
 - Enteropathy-associated T-cell lymphoma
 - Hepatosplenic gamma delta T-cell lymphoma
 - Transformed mycosis fungoides
 - T/NK-cell lymphoma, unclassifiable
- 3.13 Measurable disease: Subjects must have at least one lesion that is >15 mm (1.5 cm) in the longest diameter on cross-sectional imaging and measurable in two perpendicular dimensions per computed tomography (spiral CT) or MRI.
- 3.14 After failure of ASCT or after failure of frontline therapy in subjects who declined or are not ASCT candidates
- 3.15 ECOG Performance Status (PS) 0, 1 or 2 ([Appendix I](#))
- 3.16 The following laboratory values obtained ≤ 7 days prior to registration.
- White blood cell (WBC) $\geq 3000/\text{mm}^3$
 - Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Hemoglobin >9.0 g/dL
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) unless elevation due to Gilbert's Syndrome
 - Aspartate transaminase (AST) ≤ 2.5 x ULN
 - Creatinine ≤ 2.0 mg/dL
 - Calculated creatinine clearance must be ≥ 45 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

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

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

- 3.17 Negative serum or urine pregnancy test done ≤ 7 days prior to registration, for persons of childbearing potential only.

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Note: Persons of child-bearing potential (POCBP) must use appropriate method(s) of contraception. POCPB should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

Men who are sexually active with POCPB must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with POCPB will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. Persons who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception. Should a person become pregnant or suspect being pregnant while participating in this study, the person should inform the treating physician immediately.

3.18 Provide written informed consent.

3.19a Willing to return to enrolling institution for follow-up during the Active Monitoring Phase of the study.

Note: The **Active Monitoring** Phase of a study includes active treatment and observation.

3.19b Willing to provide tissue and blood samples for correlative research purposes (see [Sections 6.2](#), [14.0](#) and [17.0](#)).

3.2 Exclusion Criteria

3.21 All primary cutaneous T-cell lymphomas and Adult T-cell lymphoma/leukemia (HTLV1+)

3.22 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

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

3.24 Active, known or suspected autoimmune disease.

Note: Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment

3.25 Use of systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications <14 days of registration. Note: Inhaled or topical steroids are permitted. >10 mg daily prednisone equivalents are permitted only in adrenal insufficiency in the absence of active autoimmune disease.

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- 3.26 Prohibited Treatments and or Therapies
- a) Autologous Stem Cell Transplant (ASCT) ≤ 12 weeks prior to first dose of the study drug.
 - b) Prior treatments (window prior to registration):
 - chemotherapy ≤ 2 weeks
 - nitrosureas ≤ 6 weeks
 - therapeutic anticancer antibodies ≤ 4 weeks
 - radio- or toxin immunoconjugates ≤ 10 weeks
 - radiation therapy ≤ 3 weeks
 - or major surgery ≤ 2 weeks
 - c) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways
 - d) Prior treatment with PD1 and PD-L1 inhibiting therapy
 - e) Prior allogeneic SCT
 - f) Chest radiation ≤ 24 weeks prior to registration
- 3.27 Immunocompromised patients, patients with known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) and currently receiving antiretroviral therapy, active Hepatitis B virus surface antigen (HBV sAg+), active Hepatitis C (if Ab+ then PCR+) indicating acute or chronic infection
- 3.28 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.29a Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.
- 3.29b Other active malignancy ≤ 3 years prior to registration.
EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.
NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer.
- 3.29c Active CNS involvement or leptomeningeal involvement
- 3.29d History of pancreatitis.

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4.0 Test Schedule

4.1 Study Calendar

Tests and procedures window	Baseline			Active Monitoring Phase			
	≤14 days prior to Registration	≤7 days prior to Registration	Cycle 1 Day 1 prior to treatment	End of each cycle ±3 days	Restaging End of Cycles 4, 8, and 12 ±7 days	End of Treatment ¹ ±7 days	Observation Post-treatment followup ² ±14 days
History and exam, ECOG PS, Weight	X			X ³	X	X	X
Height	X						
Adverse event assessment	X			X	X	X	X
Pregnancy Test ⁴		X	X	X	X	X	X
B Symptoms ⁵	X						
Hematology: CBC with 5 part differential		X		X	X	X	X
Comprehensive metabolic panel: ALT, AST, total bilirubin, alkaline phosphatase, BUN or serum urea, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, albumin, bicarbonate		X		X	X	X	X
Uric Acid		X					
Erythrocyte sedimentation rate	X						
HBV sAg and HCV Ab or HCV RNA	X						
TSH (with Free T4 and Free T3)		X		X ⁶	X	X	X
ECG	X						

¹ At PD or PMD, withdrawal, removal, or completion of protocol therapy

² Four visits: 1) 35±7 days after last treatment 2) 100-120 days post treatment 3) 230-250 days post treatment 4) 330-390 days post treatment

³ If on physical exam there are any palpable lymph nodes present: Tumor (bidimensional)-measurements by physical exam to be done at end of every cycle, prior to next cycle.

⁴ For persons of childbearing potential only: Serum pregnancy testing is required ≤7 days prior to registration and again ≤24 hrs prior to the first infusion, and then every 28 days (±7 days) during the study therapy period regardless of dosing schedule. After discontinuation from nivolumab, these tests should be repeated at approximately 30 days and approximately 70 days [or more frequently if required by local standard].

⁵ Unexplained persistent fever >38° C (or >100.4° F) in previous month, recurring drenching night sweats during the previous month, and/or unexplained weight loss >10% of body weight in the previous six months.

⁶ Thyroid function testing should be done every third month (±3 days).

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Tests and procedures	Baseline			Active Monitoring Phase			
	≤14 days prior to Registration	≤7 days prior to Registration	Cycle 1 Day 1 prior to treatment	End of each cycle	Restaging End of Cycles 4, 8, and 12	End of Treatment ¹	Observation Post-treatment followup ²
window				±3 days	±7 days	±7 days	±14 days
PET-CT ⁷	X				X	X	
CT scan Chest/Abd/Pelvis					X ⁸		X
Mandatory research blood/bone marrow samples (See Section 14.0) ^{R,9}			X ^R	X ^R	X ^R	X ^R	X ^{R,10}
Mandatory tissue sample (See Section 17.0) ^{R,11}	X ^R						X ^R

Cycle = 14 days during initial therapy (Cycles 1-8)

Cycle = 28 days during continuation therapy (beginning with Cycle 9)

R Research funded (see Section 19.0)

⁷ Baseline ≤28 days prior to registration, then End of Cycle 4 (≤5 days prior to Cycle 5), end of Cycle 8, and end of Cycle 12

⁸ CT scans after the 12th cycle will be done every 16 weeks as long as treatment continues. Then every 3 months during the first year of observation, then as clinically indicated.

⁹ Must be drawn on Day 1 of each cycle before treatment Cycles 1-4, at restaging post Cycle 12, end of treatment for any reason, and at time of PD or PMD.

¹⁰ Only at time of PD or PMD.

¹¹ Baseline sample to be submitted ≤14 days prior to Registration; see [Section 17.0](#)

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4.2 Event Monitoring

CRF	Event Monitoring Phase ¹				
	q. 3 months until PD	At PD ²	After PD q. 6 mos.	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression by uploading it into the Supporting Documentation form in the Rave system.

5.0 Stratification Factors: None

6.0 Registration Procedures

6.1 Registering a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (<http://ccswww.mayo.edu/training/>) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19b, 14.0 and 17.0).

6.3 Documentation required

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

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When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Verification

Prior to accepting the registration, registration application will verify the following:

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

6.5 Correlative research options

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

- Patient has/has not given permission to store and use his/her sample(s) for future research of lymphoma at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.6 Treatment start

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

6.7 Pretreatment tests/procedures

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

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9a Treatment location

Treatment on this protocol must commence at Mayo Clinic Rochester, Mayo Clinic Arizona, or Mayo Clinic Florida institutions under the supervision of a hematologist.

6.9b Study drug availability

Study drug is available on site for this patient

6.9c Blood draw kits

Blood draw kit is available on site for this patient (not applicable to MCR).

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7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Treatment Schedule

Agent	Dose Level	Route	Day	Cycle Length
Nivolumab	240mg	IV	Cycles 1-8 Day 1	Every 14 days for 8 cycles
	480 mg	IV	Beginning Cycle 9, Day 1	Every 28 days for a maximum of 24 cycles (Total of 32 cycles)

No routine premedications are needed with nivolumab administration.

7.2 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 14 days during initial treatment and every 28 days during continuation therapy.

After therapy discontinuation, the patient must return to the institution for four visits: 1) 35±7 days after last treatment; 2) 100-120 days post treatment; 3) 230-250 days post treatment; and 4) 330-390 days post treatment, during observation (Active Monitoring Phase) until the patient goes to event monitoring per Section 13.0.

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8.0 Dose Delay Criteria Based on Adverse Events

For events with an attribution of possibly, probably or definitely related to study medication, strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

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

8.1 No dose reductions or escalations are allowed for nivolumab.

8.2 Dose Delay Criteria for Nivolumab

See Management Algorithms ([Appendix II](#))

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	Event	Agent	Action
Investigations	Alanine aminotransferase increased, Aspartate aminotransferase increased, and/or Blood bilirubin increased	Nivolumab	<p>If a patient has a baseline AST/ALT that is within the normal limits, delay dosing for nivolumab-related \geqGrade 2 (>3-5 x ULN) elevations and start corticosteroids at 0.5 to 1 mg/kg/day prednisone equivalents. Nivolumab may be resumed if the value improves to Grade 1 (≤ 3 x ULN) or better.</p> <p>If a patient has a baseline AST/ALT in the Grade 1 range (ULN to ≤ 3 x ULN), delay dosing for nivolumab-related \geqGrade 3 (>5 to 8 x ULN) elevations and start corticosteroids at 1 to 2 mg/kg/day prednisone equivalents. Nivolumab may be resumed if the value improves to Grade 2 (>3 to 5 x ULN) or better.</p> <p>If a patient has a baseline total bilirubin that is within normal limits, delay dosing for nivolumab-related Grade 2 elevations (>1.5-3 x ULN) and start corticosteroids at 0.5 to 1 mg/kg/day prednisone equivalents. Nivolumab may be resumed if the bilirubin improves to Grade 1 (≤ 1.5 x ULN) or better.</p> <p>If a patient has a baseline total bilirubin that is in the Grade 1 range (ULN to ≤ 1.5 x ULN), delay dosing for nivolumab-related Grade 3 elevations (>3-5 x ULN) and start corticosteroids at 1 to 2 mg/kg/day prednisone equivalents.</p>

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CTCAE System/Organ/Class (SOC)	Event	Agent	Action
			<p>Nivolumab may be resumed if the total bilirubin improves to Grade 2 (≤ 3 x ULN) or better.</p> <p>Doses of nivolumab should be discontinued permanently for the following LFT abnormalities: AST or ALT >8 x ULN (Grade 3) or drug-induced liver injury (DILI); Total bilirubin >5 x ULN (Grade 3) or DIL; concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN. Administer corticosteroids 1 to 2 mg/kg/day prednisone equivalents.</p> <p>Subjects with combined Grade 2 AST/ALT meeting discontinuation parameters: go to event monitoring per Section 4.2.</p>
Gastrointestinal disorders	Pancreatitis	Nivolumab	<p>Grade 2: Hold nivolumab until resolution, maximum 3 weeks.</p> <p>If >3 weeks, discontinue nivolumab and patient goes to event monitoring.</p> <p>Grade 3 or Grade 4, hold nivolumab until Grade 2 or better then reintroduce</p> <p>If it recurs, the drug is discontinued and patient goes to event monitoring</p> <p>Any \geqGrade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay</p> <p>The PI should be consulted for \geqGrade 3 amylase or lipase abnormalities</p>
Gastrointestinal disorders	Diarrhea	Nivolumab	<p>Grade ≥ 2 despite maximal supportive care: Hold drug until resolution to baseline grade. If suspicious and clinically indicated, initiate work up to rule out infectious causes and colitis</p> <p>Grade 3 or 4 despite maximal supportive care: Discontinue drug and start corticosteroids until resolution to baseline and patient goes to event monitoring. If suspicious and clinically indicated, initiate work up to rule out infectious causes and colitis</p>
	Colitis	Nivolumab	<p>Grade ≥ 2: Hold drug until resolution to baseline grade</p> <p>Grade ≥ 3: Discontinue drug and start</p>

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CTCAE System/Organ/Class (SOC)	Event	Agent	Action
			corticosteroids until resolution to baseline grade and patient goes to event monitoring
General disorders and administration site conditions	Fatigue	Nivolumab	Grade 3: Hold drug until Grade 2 or better
Metabolism and nutrition disorders	Hyperglycemia	Nivolumab	Grade 4: Permanently discontinue nivolumab
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Nivolumab	Grade ≥ 2 : Hold drug and start corticosteroids until resolution to baseline grade Grade ≥ 3 : Discontinue nivolumab and initiate treatment with high doses of corticosteroids and patient goes to event monitoring
	Cough	Nivolumab	Grade ≥ 2 : Hold drug and start corticosteroids until resolution to baseline grade Grade ≥ 3 : Discontinue nivolumab and initiate treatment with high doses of corticosteroids and patient goes to event monitoring
	Dyspnea	Nivolumab	Grade ≥ 2 : Hold drug until resolution to baseline grade
All other hematologic and non-hematologic	All other hematologic and non-hematologic	Nivolumab	Grade ≥ 2 : Hold nivolumab until resolution to Grade 1 or baseline, except for lymphopenia and leukopenia NOTE: Grade 3 lymphopenia or leukopenia do not require dose delay

8.3 Discontinuation Criteria for Nivolumab

Treatment should be permanently discontinued for the following:

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

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- Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
 - AST or ALT >8 x ULN
 - Total bilirubin >5 x ULN
 - Concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
 - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
 - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
 - Grade 4 lymphopenia or leucopenia
 - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator [as allowed by protocol]
- Any dosing interruption lasting >6 weeks with the following exceptions:
 - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
 - Dosing interruptions or delays lasting >6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

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9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

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

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

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

9.4 Diarrhea

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

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

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

If suspicious and clinically indicated, initiate work up to rule out infectious causes and colitis at treating physician's discretion.

9.5 Hepatotoxicity

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

9.6 Additional adverse events

Please refer to [Appendix II](#) for additional Adverse Event Management Algorithms excerpted from the investigator's brochure for nivolumab (version 15).

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10.0 Adverse Event (AE) Reporting and Monitoring

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

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

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

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Global Pharmacovigilance & Epidemiology Bristol-Myers Squibb Company Fax Number: 609-818-3804 Email: Worldwide.safety@bms.com Mayo Sites – attach to MCCC Electronic SAE Reporting Form
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Global Pharmacovigilance & Epidemiology Bristol-Myers Squibb Company Fax Number: 609-818-3804 Email: Worldwide.safety@bms.com Will automatically be sent to CANCERCROSAFETYIN@mayo.edu

Definitions*Adverse Event*

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

Suspected Adverse Reaction

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

Expedited Reporting

Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

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Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

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

10.1 Adverse Event Characteristics

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

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

- a. Identify the grade and severity of the event using the CTCAE version 4.0.
- b. Determine whether the event is expected or unexpected (see Section 10.2).
- c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
- d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
- e. Determine if other reporting is required (see Section 10.5).
- f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

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

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

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

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

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

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10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

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

10.31 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. If patient is hospitalized, please follow normal reporting criteria. These events must still be reported via Routine Reporting (see Section 10.6). *

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

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

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not require expedited reporting ¹
Blood and lymphatic system disorders	Anemia	≤Grade 4
Investigations	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood count	≤Grade 4
	Lymphocyte count decreased	≤Grade 4

¹ These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

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

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.]

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10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1,2}

<p>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) NOTE: Investigators MUST immediately report to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64) An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 		
<p>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.</p>		
Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	
<p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> ○ "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report. ○ "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE. 		
<p>¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: Expedited 24-hour notification followed by complete report within 3 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 3, 4, and Grade 5 AEs <p>Expedited 7 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 AEs resulting in hospitalization or prolongation of hospitalization <p>² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.</p> <p>Effective Date: May 5, 2011</p>		

NOTE: Refer to Section 10.31 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Clinic Cancer Center Expedited Event Report form
<http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158->

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[56/Processes/MC4158-56-Process.MC4158-56](#) and attach MedWatch 3500A.

Submit to BMS:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table 10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

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

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO complete the Mayo Clinic Cancer Center Expedited Event Report form online at <http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56> and attach appropriate documentation. The system will automatically forward to CANCERCROSAFETYIN@mayo.edu. The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

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

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

Reportable categories of Death

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

10.53 Secondary Malignancy

- A **secondary malignancy** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
 - Myelodysplastic syndrome (MDS)
 - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

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

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10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

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

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

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10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.

Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal disorders	Number of stools at baseline	X	
	Diarrhea		X
Respiratory, thoracic and mediastinal disorders	Pneumonitis	X	X
	Dyspnea	X	X
Skin and subcutaneous tissue disorders	Rash acneiform	X	X
	Rash maculo-papular	X	X

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

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

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

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

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

10.8 BMS Additional Event Reporting Instructions

10.81 Adverse event reporting is required as per the Study Agreement.

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety.
- For subjects randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization

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- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e. CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. For drugs with potential for delayed SAEs (e.g., delayed excretion of the parent or active metabolites), a longer follow-up period may be warranted to allow collection of these SAEs, laboratory tests, and other assessments.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
 - Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
 - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
 - In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

10.82 Serious Adverse Event Collection and Reporting

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Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study including periodic reconciliation.

10.83 For studies conducted under an Investigator IND in the US

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: <http://www.accessdata.fda.gov/scripts/medwatch/>.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
<http://www.accessdata.fda.gov/scripts/medwatch/>

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804

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Email: Worldwide.safety@bms.com

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

10.84 DEFINITIONS

SERIOUS ADVERSE EVENTS

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

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

NOTE: (PI- determines if this information should be included. This is provided as supplemental information that is included in BMS-

sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

ADVERSE EVENTS

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

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

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

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

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

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

NONSERIOUS ADVERSE EVENT

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

baseline status for the subjects.

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

Nonserious Adverse Event Collection and Reporting

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

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

Laboratory Test Abnormalities

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

The following laboratory abnormalities should be documented and reported appropriately:

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

10.85 Potential Drug Induced Liver Injury (DILI)

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

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

AND

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

AND

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

10.86 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently

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discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

10.87 Overdose

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

10.88 Other Safety Considerations

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

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11.0 Treatment Evaluation

Lugano Classification Response Criteria

11.1 Response Considerations

Schedule of Evaluations: PET/CT scans are required at baseline for all patients. In addition to a baseline PET/CT scan, confirmatory scans should also be obtained post Cycle 4, 8, and 12 of chemotherapy, then a CT scan every 16 weeks thereafter. During observation, CT scan should be obtained every 3 months during the first year to evaluate for disease progression.

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

Response is based on PET/CT based on the revised 2014 Lugano Classification. (Cheson et al, 2014).

Progressive disease is based on either PET-CT based (PMD) or CT based (PD) response criteria. PET confirmation of progressive disease is per physician discretion.

11.2 Pseudoprogression

Some therapeutic agents, particularly immunotherapeutics, display different patterns of anti-tumor response, which may include a period of increasing tumor burden followed by a response, stable disease followed by slow decline in tumor burden, or even a response in the presence of new lesions (Chow, 2013; Wolchok et al., 2009). Immune-mediated responses may take longer to manifest than those from cytotoxic agents. In other cancer settings, a phenomenon called "tumor flare" or pseudoprogression has also been described, in which increased metabolic activity in FDG-PET is observed on posttreatment PET-CT which represents a biologic effect on the tumor and its microenvironment. (REF)

In order to avoid falsely assigning disease progression during the the study, a subject whose radiologic disease assessment is indicative of progression may, at the discretion of the Investigator, continue on treatment pending a repeat scan, if all of the following criteria are met:

- absence of symptomatic or clinical progression
- stable performance status
- adequate tolerance to nivolumab
- treating beyond progression does not delay an intervention felt to be in the patient's best interest

If the second confirmatory scan indicates unequivocal disease progression, the

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subject will be discontinued from treatment. The date of the first scan indicating progression will be used for analysis purposes. If however the second scan indicates a reduction in tumor burden or stable disease from the baseline scan, the subject may continue on treatment in the absence of unacceptable toxicity or other reason for treatment discontinuation.

Notwithstanding, the Investigator is free to remove the patient from treatment at any time during the study if it is felt to be in the patient's best interest.

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

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

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

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

12.0 Descriptive Factors

- 12.1 Histologic subtype: Peripherheral T-Cell Lymphoma NOS vs. Other
- 12.2 Prior ASCT vs No ASCT

13.0 Treatment/Follow-up Decision at Evaluation of Patient

- 13.1 Criteria for continuation of treatment
 - Patients who are CR/CMR, PR/PMR, or SD will continue treatment per protocol.
- 13.2 Progressive Disease (PD)
 - Patients who develop PD while receiving therapy will go to the event-monitoring phase.
- 13.3 Off protocol for reasons other than PD
 - Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.
- 13.4 Observation
 - If the patient has achieved CR/CMR, PR/PMR, or SD, the patient will be observed for

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four visits: 1) 35±7 days after last treatment; 2) 100-120 days post treatment; 3) 230-250 days post treatment; and 4) 330-390 days post treatment, during observation (Active Monitoring Phase) until the patient goes to event monitoring for up to 5 years from time of registration (see [Section 4.2](#)).

13.5 Maximum cycles for patients who achieve CR/CMR

Patients who achieve a CR/CMR will receive a maximum total of 32 cycles (i.e 2 years of therapy). After 2 years, they should be observed (see Section 13.4 above).

13.6 Continuation of therapy after PR/PMR or SD

Patients who are in PR/PMR or SD will continue on therapy for a total of 2 years. After 2 years, they should be observed (see Section 13.4 above) until PD and then they will go to event monitoring (see Section 13.5 above). Subsequent treatment is at the discretion of their attending physician.

13.7 Definition of Ineligible

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

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

13.8 Definition of Major Violation

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

13.9 Definition of Cancel

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

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14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol (see Appendix III for handling)

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Cycles 1-4 Day 1 Pre- treatment	End of Cycle 12	End of treatment ²	At time of PMD or PD ²	
Tumor biopsy or bone marrow aspirate ¹	Mandatory	Tumor or bone marrow	ACD (yellow top)	6 mL (1 tube)	X					
Peripheral blood	Mandatory	Whole Blood	EDTA (purple top)	10 mL (4 tubes)		X	X	X	X	
Peripheral blood	Mandatory	Whole Blood	No anticoagulant (red top)	10 mL (1 tube)		X	X	X	X	

¹ Only obtained when a clinical biopsy/bone marrow is needed. Biopsies and bone marrow samples can be collected ≤90 days prior to registration provided there is no intervening treatment. If a biopsy or bone marrow was performed prior to consenting the patient for this study, a repeat biopsy or bone marrow is not required to obtain the research aspirate sample at baseline.

² Samples are required, however there is no protocol violation if sample is not obtained.

NOTE: All samples will be sent to Predolin Biobank Stable 613 (See Section 14.33)

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14.2 Collection and Processing

14.21 Processing for the Blood, tumor and Marrow samples

Collection tube description and/or additive (color of tube top)	Component Available	Cell Surface Markers (Flow Cytometry)	DNA	Banking
EDTA (purple)	Plasma			X
EDTA (purple)	DNA		X	X
Serum -No anticoagulant (red)	Serum			X
ACD (yellow)	Tumor cells	X		X

14.22 Note: All collection tubes need to be labeled with the protocol number, patient initials (last, first middle), study patient ID number (if available), specimen type (bone marrow or peripheral blood) and date of collection.

14.3 Shipping and Handling

14.31 Kits

Kits will be provided for the samples collected in Section 14.1. The kit contains supplies and instructions for collecting, processing, and shipping specimens.

Participating Mayo sites may obtain kits by e-mailing Kim Henderson at henderson.kimberly@mayo.edu. E-mail requests should include the site address, contact information and number of kits being requested.

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

Label specimen tubes with the protocol number, patient initials (last name, first name), study patient ID number (if available), specimen type (bone marrow or peripheral blood) and date of collection, as well as the arm of the study (A or B or C)

14.32 Collect all specimens according to instructions in Appendix III and table above.

14.33 Shipping Specimens

Specimens must be shipped the same day they are drawn.

Ship the bone marrow and peripheral blood tubes in the kit provided. No cold pack is required. The Fed Ex air bill is pre-addressed and provided in the kit.

Ship specimens via Priority Overnight service on Monday – Thursday Preferred (Friday only if you must) directly to:

Predolin Biobank
Attn: Kim Henderson
Mayo Foundation
221 4th Avenue SW 613 Stabile
Rochester, MN 55905

Please email henderson.kimberly@mayo.edu or call Kim Henderson at (507) 284-3805 to notify the laboratory when specimens are being shipped. The message should include the study name, sample type, Fed Ex air bill tracking number, contact name and telephone number.

Shipping costs will be covered by the study if these kits and Fed Ex air bills are used for shipping specimens. Each kit contains the required tubes.

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- 14.41 Blood/blood product samples will be collected for the following research
- 14.411 DNA extraction and storage of DNA for future pharmacogenetic assays (e.g., for genetic polymorphisms, neoantigens and mutational burden that may correlate with treatment efficacy). Dr. Stephen Ansell's laboratory Stable 6-28 will initially analyze a portion of the DNA using standard laboratory protocols. Remaining DNA will be stored frozen at -70°C by Dr. Stephen Ansell's Lab, according to patient consent information) until specific analyses are identified. As protocols are developed, they will be presented for IRB review and approval.
- 14.412 A portion of the serum/plasma/PBMCs will initially be analyzed for the presence of Cytokines and T-cell activation in Dr. Stephen Ansell's laboratory using standard laboratory protocols. According to patient consent information remaining serum/plasma will be stored frozen at -70°C by Dr. Stephen Ansell's Lab, until specific analyses are identified. As protocols are developed, they will be presented for IRB review and approval.
- Serum cytokine analysis: Samples will be subjected to multiplex ELISA (Invitrogen, Camarillo, CA) to measure 30 serum cytokines in pre-treatment and subsequent blood samples. Luminex-200 system version 1.7 will be used for reading plates and MasterPlex QT1.0 system (MiraiBio) will be used to analyze data. Cytokines will include epidermal growth factor (EGF), eotaxin, basic fibroblast growth factor (FGF-b), granulocyte macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), IFN- α , IFN- γ , interleukin 1 receptor antagonist (IL-1RA), IL-1 β , IL-2, IL-2R, IL-4, 5, 6, 7, 8, 10, 12, 13, 15, 17, Inducible protein-10 (IP10/CXCL10), monocyte chemotactic protein 1 (MCP-1), monokine induced by interferon γ , (MIG/CXCL9), MIP-1 α (CCL3), MIP1 β (CCL4), regulated on activation normal T-cell expressed and secreted (RANTES), TNF- α and vascular endothelial growth factor (VEGF). Internal control serum will be included in all assays to control for interassay variation.
- Flow cytometry: To define changes in peripheral blood cell populations (Activated vs, exhausted T-cells, Treg cells, monocytes and MDSCs) after treatment with nivolumab, peripheral blood mononuclear cells will be stained with fluorochrome-conjugated antibodies to human CD69 (R&D Systems), CD3 (clone HIT3a), CD19 (clone 4G7), PD1 (clone EH12.1), CD14 (clone M5E2), CD163 (clone GH1/61), CD21 (clone B-ly4), CD273 (clone M1H18), CD274 (clone M1H1), TIM3 (clone 344823), and CD23 (clone EBVCS-5; all obtained from BD Biosciences) and the data will be analyzed using CellQuest software (Becton Dickinson).
- 14.413 We will collect serum/plasma for future research studies, according to patient consent information on molecular determinants of efficacy and tolerability. Samples will be stored frozen at -70°C by Dr. Stephen Ansell's Lab until specific analyses are identified. As protocols are developed, they will be presented for IRB review and approval.

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15.0 Drug Information

15.1 Nivolumab (Opdivo®, BMS-936558)

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

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

15.13 **Preparation and storage:** Appropriate dose/required volume should be added to an IV container of either 0.9% Sodium Chloride or 5% Dextrose in Water with a final concentration of 0.35 mg/ml to 10 mg/ml. Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials. Store at room temperature for no more than 8 hours (includes time of administration) or under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation. Protect from light and freezing.

15.14 **Administration:** Administer over 60 minutes through a line with a sterile, nonpyrogenic, low protein binding 0.2 to 1.2 micrometer in-line filter. Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. It cannot be administered as an IV push or bolus injection. Do not administer other medications through the same IV line. Flush IV line at the end of the infusion.

15.15 **Pharmacokinetic information:**

Distribution: Vd: 8 L

Half-life elimination: ~27days

Renal Impairment: No clinically important differences in the clearance of nivolumab were found between subjects with mild or moderate renal impairment and subjects with normal renal function. Data from subjects with severe renal impairment are too limited to draw conclusions on this population.

Hepatic Impairment: No clinically important differences in the clearance of nivolumab were found between subjects with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in subjects with moderate (total bilirubin >1.5 to 3 times ULN and any AST) or severe hepatic impairment (total bilirubin >3 times ULN and any AST).

15.16 **Potential Drug Interactions:** No formal pharmacokinetic drug-drug interaction studies have been conducted.

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

Very common known potential toxicities, ≥10%:

Gastrointestinal: Diarrhea

General: Fatigue

Less common known potential toxicities, 1% - 10%:

Endocrine: Hypothyroidism, hyperthyroidism, hyperglycemia

Gastrointestinal: Nausea, vomiting, constipation, abdominal pain, stomatitis, dry

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mouth, colitis,
General: Pyrexia, asthenia, peripheral edema, chills,
Immune system: infusion related reaction
Investigations: Increased AST/ALT, increased lipase, increased alkaline phosphatase, increased creatinine, increased amylase, increased thyroid stimulating hormone
Metabolism and nutrition disorders: Decreased appetite, hyponatremia
Musculoskeletal: Arthralgia, myalgia, back pain, pain in extremities
Nervous system: Headache, dizziness
Respiratory: Pneumonitis, dyspnea, cough
Skin and subcutaneous tissue disorders: Pruritis, rash, dry skin, maculopapular rash, vitiligo, erythema, generalized pruritus

Uncommon known potential toxicities, 0.1% - <1%:

Cardiac: Tachycardia, atrial fibrillation
Ear: Vertigo
Endocrine and metabolic: Adrenal insufficiency, thyroiditis, hypophysitis, diabetes mellitus, hypopituitarism, autoimmune thyroiditis
Eye: Dry eye, blurred vision, uveitis
Gastrointestinal: Pancreatitis, gastritis
General: Mucosal inflammation, edema, face edema, localized edema, peripheral swelling, swelling face
Hepatic: Hepatitis, autoimmune hepatitis,
Immune system: Hypersensitivity,
Infections: Upper respiratory tract infection, bronchitis
Investigations: increased bilirubin
Musculoskeletal: Musculoskeletal pain, arthritis, musculoskeletal chest pain, neck pain, polyarthritis, bones pain
Nervous system: Peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy
Renal and urinary: Acute kidney injury; renal failure, tubulointerstitial nephritis
Respiratory: Respiratory failure, interstitial lung disease, lung infiltration
Skin and subcutaneous tissue disorders: Alopecia, dermatitis acneiform, urticaria, psoriasis, dermatitis, rash (pruritic, macular, erythematous, generalized, popular, pustular), drug eruption
Vascular: Hypotension, hypertension

Rare known potential toxicities, < 0.1% (Limited to life-threatening):

Cardiac: Arrhythmia, ventricular arrhythmia
Endocrine: Diabetic ketoacidosis, autoimmune hypothyroidism
Eye disorders: iridocyclitis
Gastrointestinal: Autoimmune colitis, acute pancreatitis
Hepatic: Acute hepatitis
Immune system: Anaphylactic reaction, sarcoidosis
Musculoskeletal: Myositis, myocarditis, polymyalgia rheumatic, polymyositis, rhabdomyolysis
Nervous system: Polyneuropathy, encephalitis, Myasthenia gravis, Guillain-Barre syndrome, demyelinating polyneuropathy, demyelination, myasthenic syndrome
Renal: Nephritis, autoimmune nephritis

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Respiratory: Pneumonia, acute respiratory distress syndrome
Skin and subcutaneous tissue disorders: Erythema multiforme, Stevens
Johnson syndrome, toxic epidermal necrolysis
Other: Solid organ and tissue transplant rejection, graft versus host disease,
increased risk of transplant-related complications

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

15.19 **Nursing Guidelines**

- 15.191 Nivolumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids. Additionally combination therapy (with ipilimumab) tends to have a higher rate of immune mediated side effects.
- 15.192 Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- 15.193 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.
- 15.194 Monitor LFTs closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- 15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- 15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, new onset diabetes, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and “not feeling well.” Additional symptoms may be that of nausea, sweating, headache and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- 15.197 Pancreatitis is possible with nivolumab. Instruct patients to report abdominal pain, nausea and vomiting to the study team.
- 15.198 Patients who are started on steroid therapy for any side effects of nivolumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

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- 15.199a Monitor renal functions as patients may experience acute interstitial nephritis. Report any increase of levels to the study team.
- 15.199b Patients who have previously undergone a solid organ or tissue transplant and subsequently undergo therapy with nivolumab are at increased risk of organ/tissue rejection. Instruct patients that it is crucial that they stay in touch with their transplant team during treatment.
- 15.199c Patients who have undergone allogeneic BMT are at higher risk of GVHD and death when receiving nivolumab. Monitor patients closely for GVHD symptoms and instruct patients to report these symptoms to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This is a phase II study of Nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). It will use a one-stage design with an interim analysis based on a Simon optimal design to assess efficacy.

- 16.11 Endpoint: The primary endpoint in this trial is the proportion of objective responses (either a CR or PR according to the revised Lugano Classification Response criteria (Cheson et al, 2014)). For the primary endpoint, CR or PR will be considered synonymous with “success”, unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.2 Statistical Design

16.21 Decision Rule

In a previous phase II single arm trial of 130 confirmed PTCL patients receiving Romidepsin (14 mg/m² as a 4 hour transfusion on Days 1, 8 and 15 of 28 day cycles), 25% achieved a response (CR/CRu + PR). The CR/CRu rate was 15%. A second phase II single arm study of 111 treated PTCL patients receiving Pralatrexate (30 mg/m²/wk intravenously for 6 weeks in 7-week cycles) showed a 29% response rate (CR + PR) with 11% having CR. This study will include patients with histologically proven TCL who will be receiving nivolumab (240mg every 2 weeks for 4 months, then 480mg every 4 weeks). It is expected that this dose will have a complete response rate similar to those presented above. The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. This design uses 35 evaluable patients to test the null hypothesis that the true complete response rate is at most 10%.

- 16.211 Interim Analysis: Enter 12 evaluable patients into the study. If there are one or no successes observed in the first 12 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 2, we will continue accrual.
- 16.212 Final Decision Rule: If 5 or fewer successes are observed in the first 35 evaluable patients, we will consider this regimen ineffective in this

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patient population. If 6 or more successes are observed in the first 35 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

- 16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.34.
- 16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 12 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.
- 16.22 Sample Size: This study is expected to require a minimum of 12 and a maximum of 35 evaluable patients. We anticipate accruing 4 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the study is expected to accrue a maximum of 39 patients overall.
- 16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 10 evaluable patients per year. Therefore, the accrual period is expected to be 3 years. The primary endpoint will be evaluated approximately 3.5 years after the trial opens, or after the last patient accrued has been observed for at least 6 months and data collection for the induction phase is complete. The total study duration is expected to be approximately 5.5 years, or until all patients have completed all cycles of treatment.
- 16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions and the probability of stopping accrual after the interim analysis can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.10	0.15	0.20	0.25	0.30
Then the probability of declaring that the regimen warrants further study is...	0.098	0.337	0.604	0.795	0.901
and the probability of stopping after the interim analysis is ...	0.659	0.444	0.275	0.158	0.085

- 16.25 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study
- 16.3 Analysis Plan
- 16.31 Primary Outcome Analyses:

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- 16.311 Definition: The primary endpoint of this trial is the proportion of complete or partial responses to therapy. A success is defined as a CR or PR as the objective status during therapy. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.
- 16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated.
- 16.32 Secondary Outcome Analyses: These analyses will include all patients meeting the eligibility criteria who have signed a consent form and have begun treatment, including patients who fail to achieve a complete response.
- 16.321 Response: Response rates will be estimated using complete and partial metabolic responses (CMR or PMR) divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. These rates will be compared to the primary endpoint to explore any differences in the measurement method.
- 16.322 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.
- 16.323 Progression free survival time is defined for all evaluable patients who have achieved a CR/CMR or PR/PMR as the time from registration to relapse or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier. In addition, the progression-free survival rate at 5 years after registration will be reported.
- 16.324 Duration of response is defined for all evaluable patients who have achieved a CR/CMR or PR/PMR as the date at which the patient's objective status is first noted to be a CR/CMR or PR/PMR to the earliest date relapse is documented. The distribution of duration of complete response will be estimated using the method of Kaplan-Meier
- 16.325 Overall survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958). In addition, the overall survival rate at 2 years after registration will be reported.
- 16.33 Correlative Analyses
- 16.331 Correlative analyses will be exploratory in nature and will include evaluation of T-cell activation, cytokine up regulation, biomarker activity with respect to response to therapy (intratumoral cell populations, genetic variability, serum cytokines, T-cell activation), and PD-L1/PD-1/PD-L2 expression. These factors will be summarized and used to help characterize the types of patients accrued to this trial. In addition, we will explore differences in the distributions of these

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risk factors by clinical outcome (progression-free survival status at 5 years and whether the patient remains in sustained CR/CMR/PR/PMR). Nonparametric quantitative comparisons by group will be made as appropriate (Fisher's exact or Wilcoxon rank sum). Kaplan-Meier methods and log-rank statistics will be used to compare between groups for time-to-event measures. Given the limited number of patients, the difference in risk factor distribution by outcome will be largely exploratory.

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

16.4 Data & Safety Monitoring:

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

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

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

- if 4 or more patients in the first 10 treated patients (40%) experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 10 patients have been treated, 40% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

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

16.5 Results Reporting on ClinicalTrials.gov:

At study activation, this study will have been registered within the "ClinicalTrials.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is

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5.5 years after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time the last patient registered has been followed for at least 2 months.

16.6 Inclusion of Women and Minorities

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

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

The diagnosis is more common in men, as the male:female ratio is approximately 2:1 (Weisenburger, Savage et al. 2011)

16.63 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 30% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			Total
	Females	Males	Unknown	
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	13	25	0	38
Ethnic Category: Total of all subjects	13	26	0	39
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	1	1	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	12	25	0	37
Racial Category: Total of all subjects	13	26	0	39

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

Not Hispanic or Latino

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

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

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

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

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

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17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Baseline	At Progression	Specific Details for submission
Pathology review – confirm diagnosis	Mandatory for diagnoses made at non-Mayo sites	H & E, stained slides	All H&E stained diagnostic slides	X		17.2
Correlative studies	Mandatory	Paraffin sections	Tissue block (preferred) or unstained slides (10 slides), 4-5 microns each	X	X ¹	17.3

1. Samples are required, however there is no protocol violation if sample is not obtained.

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

17.21 Central pathology review is not required as long as the tissue diagnosis of lymphoma was confirmed by a Mayo pathologist. If the tissue diagnosis is not confirmed by a Mayo pathologist, the slides will need to be reviewed to confirm the diagnosis. Completion of central pathology review is not required prior to registration; however materials for central review must be reviewed within 42 days after registration.

17.22 Central pathology review will be conducted as needed for confirmation of diagnosis by Dr. Andrew Feldman and colleagues at Mayo Clinic Rochester if the initial tissue biopsy was not performed and evaluated at Mayo Clinic.

17.23 Required materials:

- Lymphoma Pathology Reporting Form (Complete Section I only)
- Tissue Submission Form
- Tumor tissue pathology report

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- Paraffin block containing tumor tissue from the most recent tumor tissue biopsy is preferred, not bone marrow or peripheral blood. If the institution is unwilling to release a block, 18 unstained, charged slides cut at 4-5 microns should be submitted. Slides should be placed in appropriate slide container.
- All tumor tissue diagnostic H&E stained slides
- Tumor tissue immunochemistry or immunophenotyping by flow cytometry report (if available)

After central review is completed, the pathologist will return all diagnostic slides to the submitting outside institution. In addition, the pathologist will also forward the completed Lymphoma Pathology Reporting Form and accompanying reports to the study QAS for scanning and data entry purposes to the following:

QAS for MC1681
Mayo Clinic
NW Clinic 3-24
200 First Street SW
Rochester, MN 55905
Phone: 507-284-4642

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue

17.321 Paraffin embedded tissue block will be used to generate tumor derived genomic DNA for the correlative studies as described in section 17.4.

17.322 If tissue block is not available, then Ten (10) 4-5 micron paraffin embedded tissue slides will be collected for DNA isolation and sequencing.

17.323 Eight (8) 4-5 micron paraffin embedded tissue slides will be collected for staining cell specific markers for T cells, T cell subsets, tumors and PD-1, PD-L1, etc. other related co-stimulatory or inhibitory markers.

17.324 Shipping

Specimens need to be labeled with patient initials and study ID number, sex, age and specific diagnosis for the trial enrollment.

Ship specimens via Priority Overnight service on Monday – Thursday Preferred (Friday only if you must) directly to:

Predolin Biobank Attn: Kim Henderson
613 Stabile
Mayo Foundation
221 4th Avenue SW
Rochester, MN 55905

Please email henderson.kimberly@mayo.edu or call Kim Henderson at (507) 284-3805 to notify the laboratory when specimens are being shipped. The message should include the study name, sample type, Fed Ex air bill tracking number, contact name and telephone number.

Shipping costs will be covered by the study.

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17.4 Background and Methodology

Background: Accumulating evidence has shown that clinical responses to checkpoint inhibitor is likely associated with tumor PD-L1 overexpression as well as tumor exomic mutation burden. Therefore, we plan to test the spectrum of tumor mutations using WES/targeted sequencing as well as measure tumor PD-L1 and other marker staining with immunohistochemistry analysis

- 17.41 Sequencing: Genomic DNA will be extracted from formalin-fixed, paraffin-embedded tissue blocks. H&E-stained sections from each case will be reviewed by an expert hematopathologist and representative blocks with at least 30% tumor cells will be selected. 10 x 5-micron sections will be cut from blocks in the Mayo Clinic Pathology Research Core (based on tissue area of 25 mm²). DNA will be extracted in the Mayo Clinic Biospecimens Accessioning and Processing Core using the Qiagen FFPE DNA extraction kit. DNA quantitation will be performed using a Qubit fluorometer prior to sequencing.
- 17.42 Immunohistochemistry (IHC): Expression of PD-L1 has been demonstrated to associate with clinical response of cancer patients treated with nivolumab. It is also established that CD8+ cytotoxic T cell response is critical to mediate anti-tumor immunity. Therefore, multiple markers including T cell, tumor cells, as well as related co-stimulatory and inhibitory markers will be stained to identify if there is any association of expression of these markers with clinical response. Serial 5- μ m paraffin-embedded sections will be used for IHC. The tissue will be deparaffinized with three changes of xylene and cleared through graded series of ethanol. Endogenous peroxidase will be quenched by incubation in 50% methanol/H₂O₂ and after rinsing with tap water; all sections will be pretreated for 30 minutes with 50 mmol/L EDTA using a steamer and cooled for additional 5 minutes. All staining will be done automatically on DAKO Autostainer using the following antibodies to CD11c (Leica Microsystems 5D11), CD14 (Cell Marque EPR 3653), CD163 (DAKO 1F8), CD68 (DAKO PG-M1), CXCL13 (R&D Systems 53610), FOXP3 (Abcam 236AE/7), CD3 (R&D Systems), PD-L1 (405.9A11), PD-L2 (366C.9E5) and PD-1 (Abcam NAT). The sections will be viewed with an Olympus BXFA51 microscope and pictures taken with an Olympus DP71 camera.
- 17.43 Fluorescence in situ hybridization (FISH): PD-L1 overexpression is commonly due to genetic mutations of the PD-L1 locus. FISH will therefore be performed to assess copy number at chromosome 9p24.1. The bacterial artificial chromosome probes (CHORI; www.chori.org) RP11-599H2O, which maps to 9p24.1 and includes CD274 (encoding PD-L1, labeled with Spectrum Orange), and RP11-635N21, which also maps to 9p24.1 and includes PDCD1LG2 (encoding PD-L2, labeled with Spectrum Green), will be cohybridized. A control centromeric probe, Spectrum Aqua-labeled CEP9 (Abbott Molecular) that maps to 9p11-q11, will be hybridized according to the manufacturer's recommendations. Nuclei with a target:control probe ratio of at least 3:1 will be classified as amplified, those with a probe ratio of more than 1:1 but less than 3:1 will be classified as relative copy gain, and those with a probe ratio of 1:1 but with more than two copies of each probe will be classified as polysomic for chromosome 9p.

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18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring

See [Section 4.0](#) and Data Submission Schedule for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy.

Supporting documentation for diagnosis will include a pathology report from the most recent tumor tissue biopsy, most recent bone marrow biopsy report, and baseline imaging report. These reports should be uploaded into the Supporting Documentation: Baseline form in the Medidata Rave system ≤ 14 days after registration.

For response to treatment, supporting documentation includes an imaging report and, if applicable, a Bone Marrow Biopsy report..

For patients who progress after study therapy, supporting documentation may include an imaging report, bone marrow biopsy report, or pathology report.

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

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19.0 Budget

19.1 Costs charged to patient

All routine clinical care. The participant will be billed for pharmacy and administration charges and other ancillary expenses such as any oral medications prescribed at the time of discharge.

19.2 Tests to be research funded

Correlative studies described in Sections 14.0 and 17.0.

19.3 Other budget concerns

Nivolumab will be supplied by Bristol-Myers Squibb.

Protocol administration, study coordinator time, data management, and statistical analysis efforts will be funded by a grant from Bristol-Myers Squibb.

T-Cell Leukemia Lymphoma Foundation will provide funding for investigator effort.

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20.0 References

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on 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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

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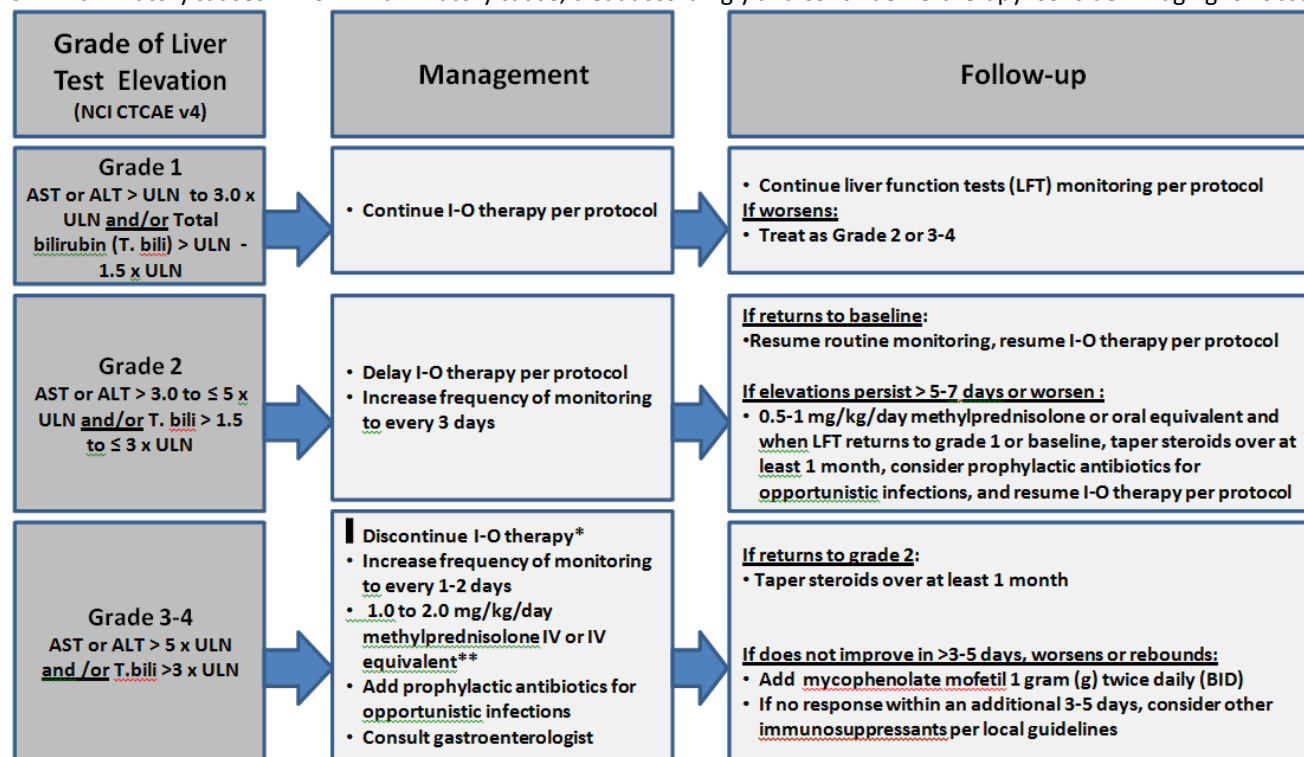
MCCC Add 5

Appendix II Adverse Event Management Algorithms

(excerpted from Nivolumab Investigator Brochure version 15, June 2016)

Hepatic Adverse Event Management Algorithm

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



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

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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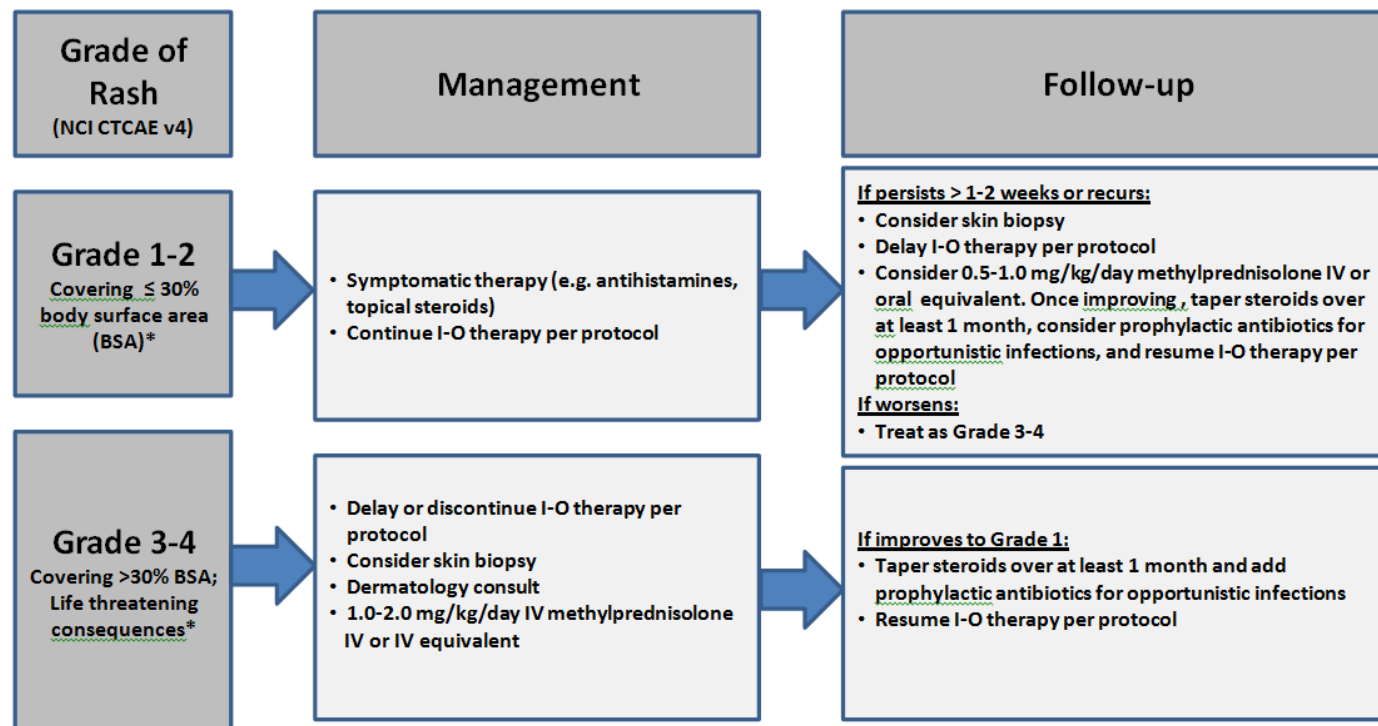
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MCCC Add 5

Skin Adverse Event Management Algorithm

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



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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

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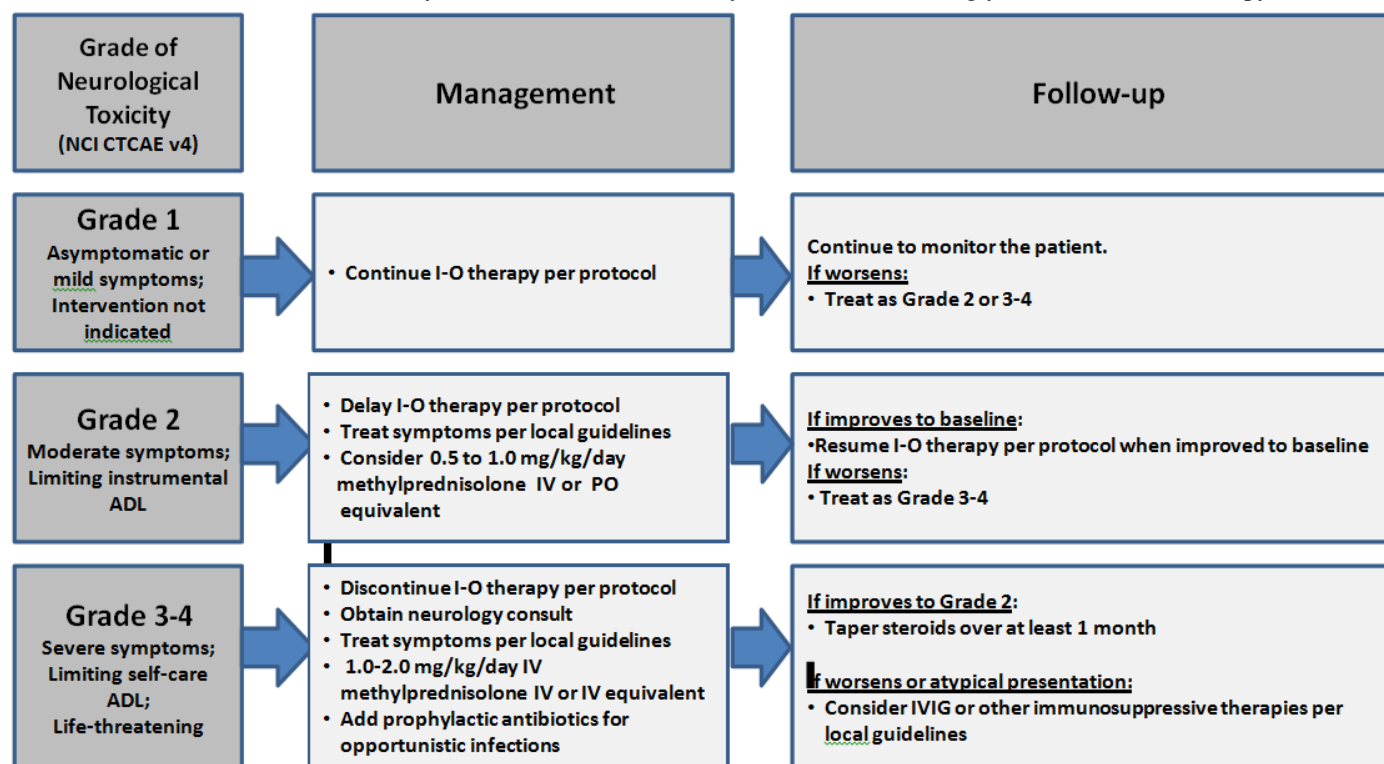
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MCCC Add 5

Neurological Adverse Event Management Algorithm

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



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

Version date: 24Jul2018

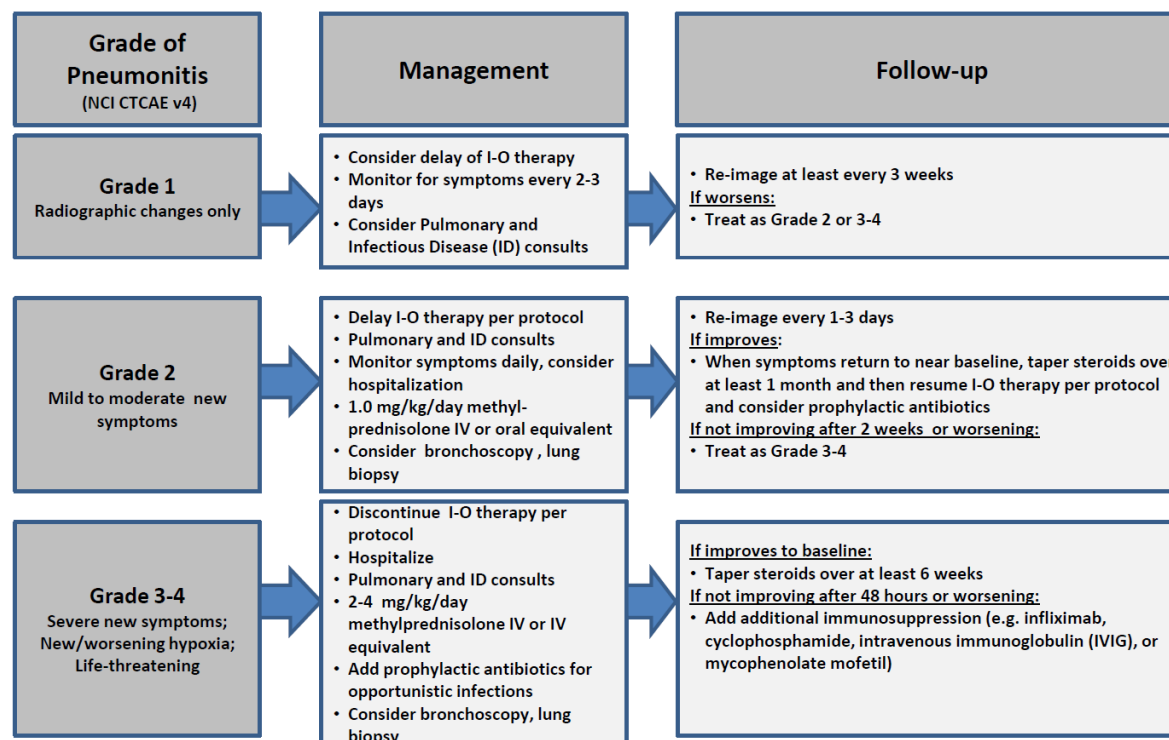
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MCCC Add 5

Pulmonary Adverse Event Management Algorithm

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



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

Version date: 24Jul2018

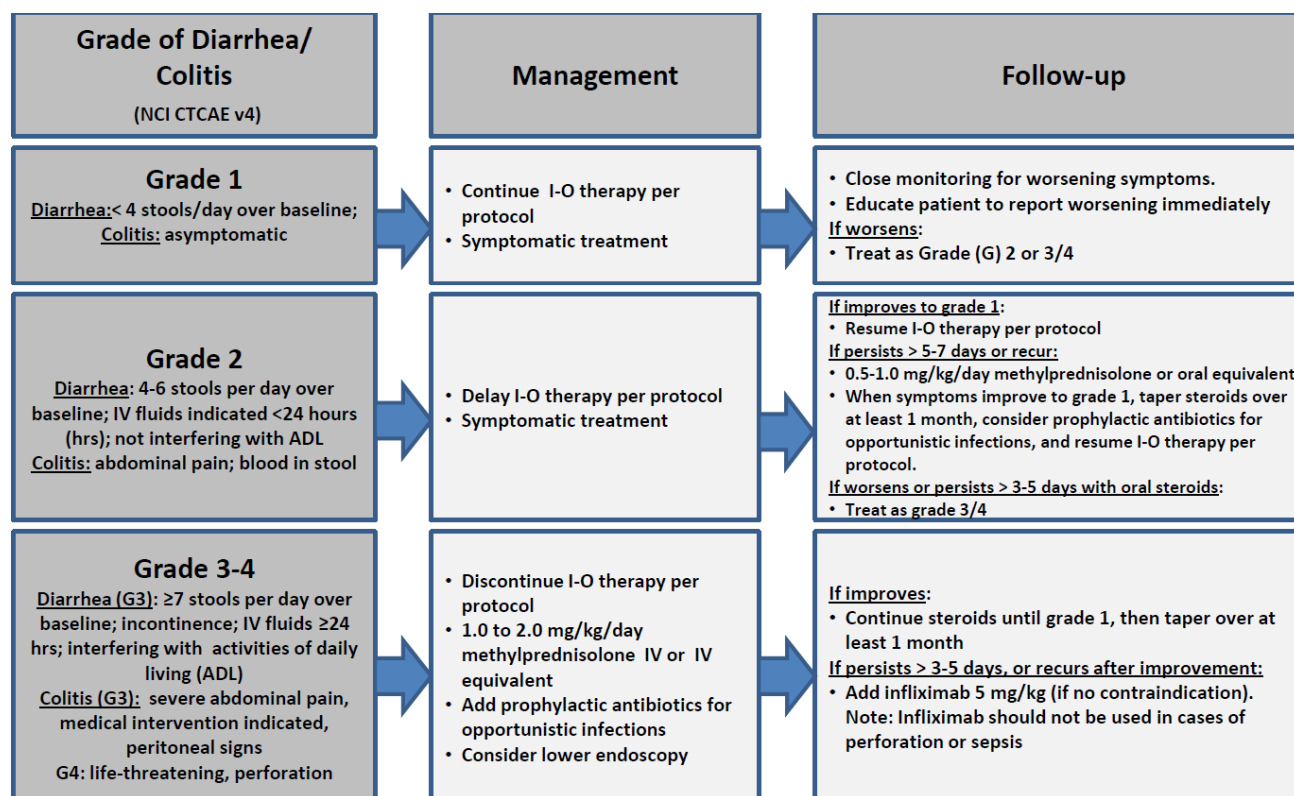
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MCCC Add 5

GI Adverse Event Management Algorithm

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



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

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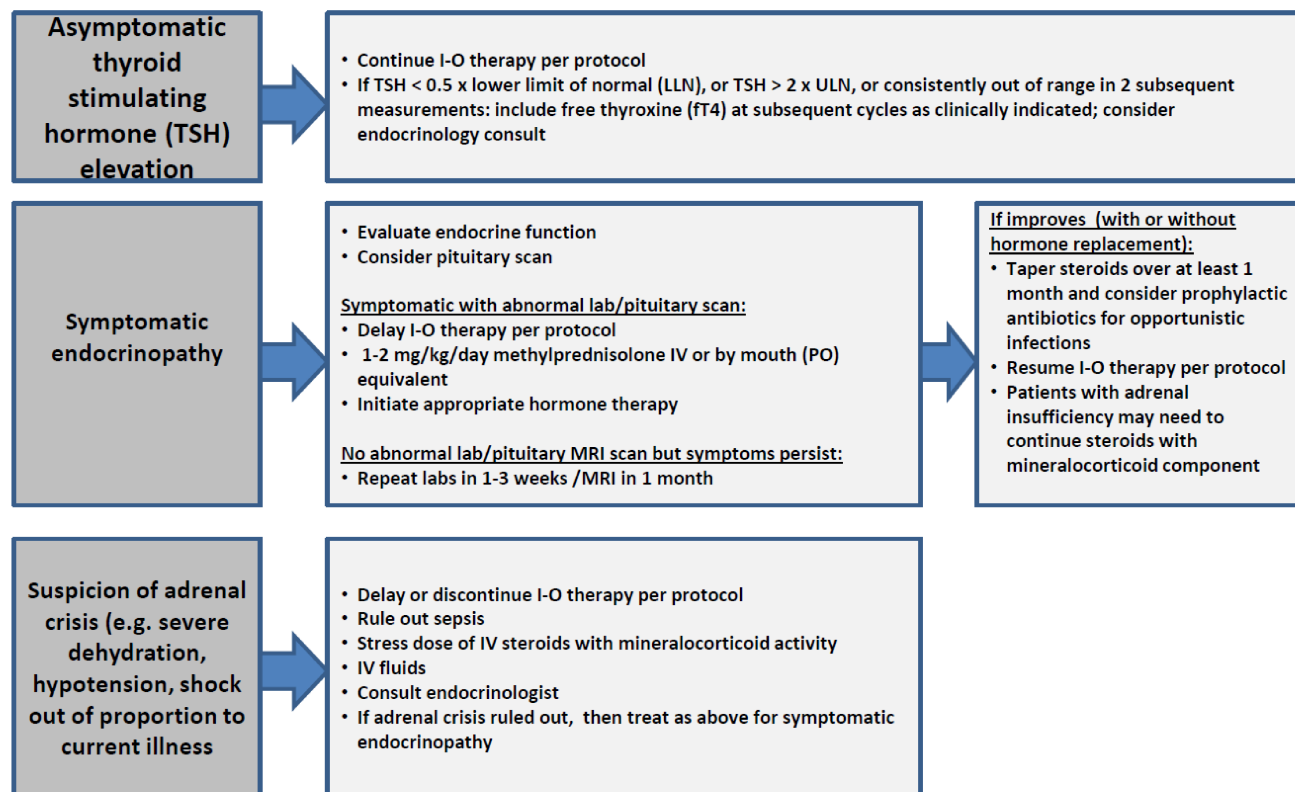
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MCCC Add 5

Endocrinopathy Adverse Event Management Algorithm

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



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

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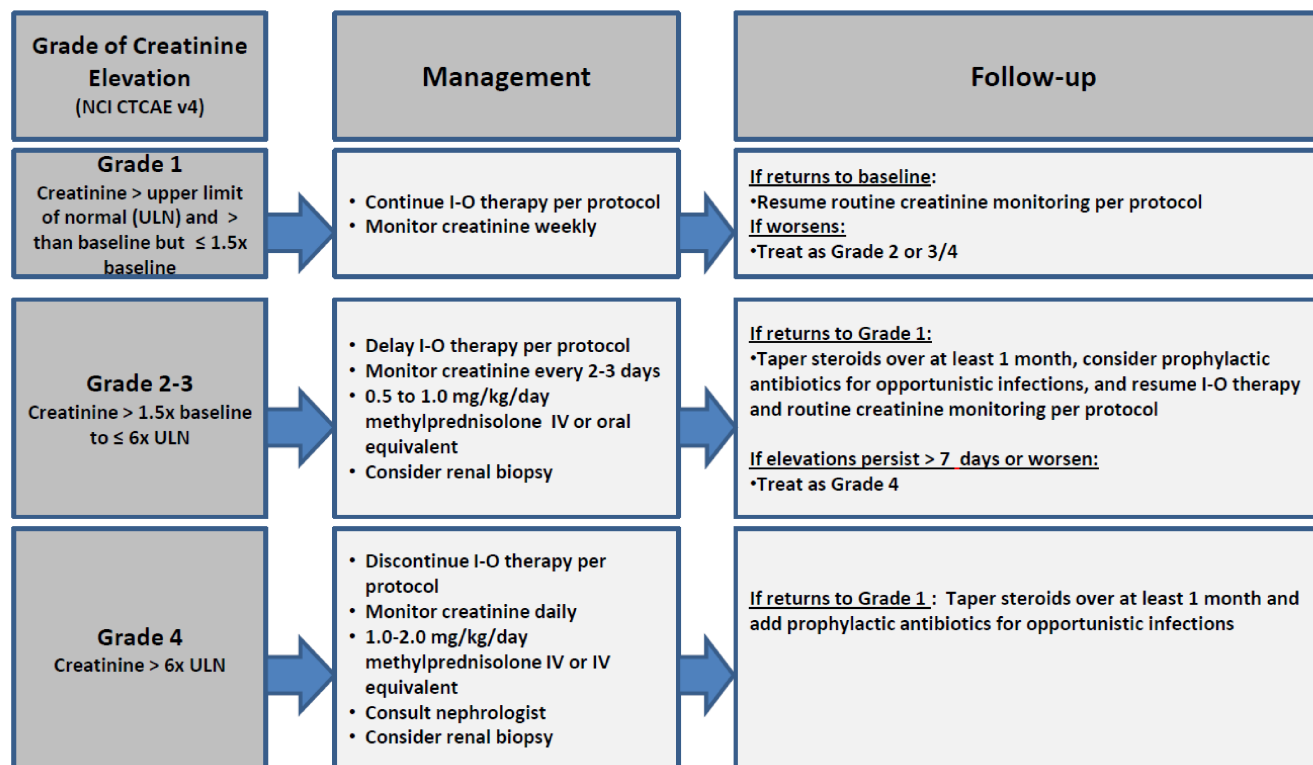
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MCCC Add 5

Renal Adverse Event Management Algorithm

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



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

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Appendix III Specimen Checklist and Shipping Instructions

Blood Collection Kit Predolin Biobank

MC1681: Phase 2 Single-Arm, Open-Label Study of Nivolumab in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- One 6ml ACD (yellow) collection tube
- One 10ml EDTA (purple) collection tube
- One 10ml Red Top collection tube
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following specimens:
 - Bone marrow – 6ml in one (1) ACD tube (Collected at Baseline only)
 - Peripheral blood – Draw:
 - 10ml in one (4) EDTA tube
 - 10ml in one (1) Red top tube
2. All specimens are to be clearly labeled with the protocol number MC1681, the patient's initials (last, first, middle), study patient ID (if available), type of sample (bone marrow or peripheral blood), and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and the Patient Information form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Adhere the Fed Ex Airbill to the exterior of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Please email Kim Henderson at Henderson.kimberly@mayo.edu or call 507-284-3805 to notify the laboratory when samples are being shipped. Indicate the protocol number MC1681, the Fed Ex tracking number, name and phone number of the contact person. The samples in prepared kits should be shipped to the following:

Predolin Biobank Attn: Kim Henderson
Mayo Foundation
221 4th Avenue SW 613 Stable
Rochester, MN 55905

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